ATF Form 4473 (OMB No. 1140-0020)
Comments Responses April 2016

Date of Submission	Name of Respondent	Contact Information	Comment	Response	Response Completed Date
4/7/2016	Joel VanderHoek Borderview International	joel@borderview.com	I hope you are well. Per the FR notice (81 FR 20424), I am requesting a copy of the proposed 4473 form with instructions.	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 (5300.9) is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/7/2016	Ben Hubbard All Things Projectile, LLC	allthingsprojectile@gmail.com	I would like a copy of the proposed 5300.9 form.	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 (5300.9) is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/6/2016	John Rives	john@therives.net	Could you provide me with a copy of the revised Form 4473 information collection?	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/7/2016	Marc Want Business Control Systems, Corp.	mwant@businesscontrol.com	I would like to obtain the details for the new proposed form 4473. Business Control Systems Corp. is a supplier of Point of Sale and Distribution systems to the licensed FFLs. I would like to review the proposed changes for ease of use and transactional integration with existing automation systems.	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/7/2016	Teresa Ficaretta Reeves & Dola, LLP	tficaretta@reevesdola.com	I would like to obtain a copy of the revised Form 4473 that was announced in today's Federal Register. Thank you.	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/7/2016	Christopher Zealand NRA-ILA Research & Information Division	CZealand@nrahq.org	Would you please send me a copy of the proposed revised Form 4473 so I could see what changes are being made?	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/8/2016	Bill Mauer	IAGolem@comcast.net	I am opposed to this proposal. Thank you for your attention.	Thank you for your interest in this information collection. Your comment has been noted.	4/11/2016
4/8/2016	James Baker	arcanus@cragvale.com	Last I checked, Federal LAW strictly prohibits the Federal Government and any agency thereof from creating or maintaining a database of 4473 forms or data. Federal Law 18 U.S.C. 926 No such rule or regulation prescribed [by the Attorney General] after the date of the enactment of the Firearms Owners Protection Act may require that records required to be maintained under this chapter or any portion of the contents of such records, be recorded at or transferred to a facility owned, managed, or controlled by the United States or any State or any political subdivision thereof, nor that any system of registration of firearms, firearms owners, or firearms transactions or disposition be established. What you are proposing is clearly illegal.	Thank you for your interest in this information collection. As stated in the Federal Register, the ATF Form 4473 allows for Federal firarms licensees (FFLs) to determine the eligibililty of persons purchasing firarms. It also alerts buyers to certain restrictions on the receipt and ppossession of firearms. The Forms 4473 must be maintained at the licensed premises of the FFLs for not less than 20 years. This information collection does not create a database of Forms 4473 or database of information recorded on the Forms 4473.	4/11/2016
4/8/2016	Kevin Dent	fortean@rocketmail.com	Please provide me with a copy of your agency's proposed information collection instrument, Firearms Transaction Record (ATF Form 4473, F 5300.9), with instructions, as identified in the notice published on April 7, 2016 at 81 FR 20424. I would prefer an electronic copy sent to this email address; if it must be sent in hard copy, please let me know and I will provide a mailing address.	Thank you for your interest in this information collection. A copy of the revised ATF Form 4473 is available online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/8/2016	Greg D Griffin ATF	greg.griffin@atf.gov	Hello Carolyn King of the FIPB, soon to be Area Supervisor in the Tampa FD. Hope all is well with you and your family! About 3 weeks ago I sent an e-mail to my Area Sup asking her to forward a suggestion to re-word block # 26 from "Manufacturer and / or Importer" to "Manufacturer and Importer if any" to match regulation 478.124(c)(4). She's been so busy with her Domain Assessment she hasn't forwarded it. When I saw the daily broadcast for today I thought I would send it to you for consideration. Below is my e-mail that explains it better. As you are aware, there has recently been confusion as whether or not too cite licensees who are not complying with regulation 478.125(e), in recording in their A&D log the "manufacturer and importer if any". We are aware of the regulations requiring both if both are listed on the gun but the example of the A&D log in the regulation book is incorrect. I've also noticed that the ATF Form 4473 is also incorrect or in the least confusing as to what is required. Since it's about time for a revision to the 4473 I thought I would make this suggestion: Box 26. Of Section D states the "Manufacturer and/or Importer (if the manufacturer and importer are different the FFL should include both)" This is inconsistent with regulation 478.124(c)(4) that states that "…the name of the manufacturer and importer (if any)…" shall be recorded. Box 26. Of Section D of the 4473 should be changed to be consistent with the regulations as follows: Manufacturer and/or Importer if any (if the manufacturer and importer are different the FFL should shall include both)" Please forward to the appropriate section or person responsible for considering these changes	Thank you for your interest in this information collection. Item 26 has been revised. The revised ATF Form 4473 is available for review online at https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download.	4/11/2016
4/8/2016	Kenny Moore	moore-kenneth@comcast.net	As to the following question, Agency Information Collection Activities; Proposed eCollection eComments Requested; Firearms Transaction Record (ATF Form 4473 (5300.9). Comments should address one or more of the following four points: • Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; Collection of information is not necessary for functional use of this agency. Would be a burden of use and increase federal spending for not use or ATF form 4473 that is now collected at FFL Dealers across the nation. 18 U.S. Code § 926 - Rules and regulations. Quoted as per 18 U.S. code, "No such rule or regulation prescribed after the date of the enactment of the Firearms Owners' Protection Act may require that records required to be maintained under this chapter or any portion of the contents of such records, be recorded at or transferred to a facility owned, managed, or controlled by the United States or any State or any political subdivision thereof, nor that any system of registration of firearms, firearms owners, or firearms transactions or dispositions be established. Nothing in this section expands or restricts the Secretary's [1] authority to inquire into the disposition of any firearm in the course of a criminal investigation."	Thank you for your interest in this information collection. As stated in the Federal Register, the ATF Form 4473 allows for Federal firearms licensees (FFLs) to determine the eligibility of persons purchasing firearms. It also alerts buyers to certain restrictions on the receipt and possession of firearms. The Forms 4473 must be maintained at the licensed premises of the FFLs for not less than 20 years. This information collection does not create a database of Forms 4473 or database of information recorded on the Forms 4473.	4/11/2016
4/9/2016	Coby (No Last Name)	coby17@verizon.net	I vigorously oppose the proposed rule. It says quite clearly "…shall not be infringed…". Tell the Director to stand up to the Administration…for a change.	Thank you for your interest in this information collection. As stated in the Federal Register the ATF Form 4473 allows for Federal firearms licensees to determine the eligibility of persons purchasing firearms. It also alerts buyers to certain restrictions on the receipt and possession of firearms. This is a revision of a currently approved information collection.	4/11/2016

4/12/2016	Marc Want Business Control Systems, Corp.	mwant@businesscontrol.com	In examining the new 4473 I am disappointed that as stated in the initial header " All entries must be handwritten in ink". This eliminates any use of automated processes in creating and managing the form thus eliminating all modern technology from use with this process. Technology can be employed in this process to have the form completed on digital media and digitally signed and stored would significantly reduce the labor, physical space and errors related to completing the form. I have visited a number of clients and can attest to the fact that after the completion of the sales process a significant amount of cost is still associated with the physical management of the form. In addition, if a search of a form has to be done that is a few years old it is not easily accessible as there may be boxes on top of boxes storing the forms resulting in difficulties in timely retrieving the form. It would be of tremendous benefit to have the form available in digital format with digital signatures, and a digital filing process with specified backup. First, this process could greatly benefit the seller in complying with regulations as it could cross check items to make certain that certain type of weapons are not sold to out an of state customer, or prematurely released. Second, scanned serial numbers can be printed as part of the completion process eliminating written errors. Third, the forms would be clear and legible. Fourth, being able to store the form as a PDF file would make it easily searchable and available at a moment's notice.	Thank you for your interest in this information collection. Federal regulation does not require Federal firearms licensees (FFLs) to complete the form electronically. Should the FFL choose to use the paper form it must be handwritten in ink. However, an FFL may complete the Form 4473 electronically under the provisions of ATF Ruling 2008-3. A copy of this ruling is available online at https://www.atf.gov/firearms/docs/2008-3-electronic-version-form-4473/download. Additionally, FFLs may request a variance to use electronic signatures and electric population of NICS or state point-of-contact background information. At this time ATF does not allow the completed Forms 4473 to be stored electronically.	4/13/2016
4/14/2016	David Noice	davenoice@gmail.com	The certification statement for questions 34-37 (33-36 on current form) requires that the FFL employee rely on "the current ATF publication 'State Laws and Published Ordinances'". The current version of that publication (31st Edition 2010-2011) only contained ordinances in effect through January 2011. Just in my state of Ohio, there have been numerous changes to state law and local ordinances that would affect an FFL employee. One quick example of a change since the 31st edition was published would be the magazine capacity limit in the city of Cincinnati. That ordinance was repealed Without an immediate update to the ATF publication "State Laws and Published Ordinances", an FFL employee would not be able to truthfully certify to that statement. It's been more than 5 years since an update has been published for what should be an annual publication. I would like to suggest that the ATF publication "State Laws and Published Ordinances" be updated and provided to FFL holders BEFORE or AT THE SAME TIME the updated 4473 is published.	Thank you for your interest in this information collection. Your comment has been noted.	4/14/2016
4/13/2016	Nick Madole The Gun Store/Elysium Armament	nick@migunstore.com	Here is my input on the proposed changes to the 4473: I currently utilize a Electronic 4473 program; it would appear that the statement at the top of the proposed form would eliminate this "All entries must be handwritten in ink". I would be very displeased if I could no longer use the e4473. It is much "cleaner" and reduces the possibilities of errors. I hope this is changed.	Thank you for your interest in this information collection. Federal regulation does not require Federal firearms licensees (FFLs) to complete the form electronically. Should the FFL choose to use the paper form it must be handwritten in ink. However, an FFL may complete the Form 4473 electronically under the provisions of ATF Ruling 2008-3. A copy of this ruling is available online at https://www.atf.gov/firearms/docs/2008-3-electronic-version-form-4473/download. Additionally, FFLs may request a variance to use electronic signatures and electric population of NICS or state point-of-contact background information. At this time ATF does not allow the completed Forms 4473 to be stored electronically.	4/14/2016
4/13/2016	David Daniely	d.daniely@gmail.com	Remove 10 a and 10 b. Those seem unnecessary and archaic. At least put a "Decline to State" option. Why does it matter if a white guy, black guy, or Hispanic is buying the gun?	Thank you for your interest in this information collection. Federal regulations, 27 CFR 478.124(c)(1), require licensees to obtain the race of the trasferee/buyer. The purpose for requiring this information is to better enable Fderal firearms licenses to help identify the transferee/buyer during the background check of a firearms transaction and aid law enforcement in accurately tracing firearms found in crimes. Pursuant to Office of Management and Budget (OMB), effective January 1, 2003, all Federal agencies requiring collection of race and ethnicity information on administrative forms and records, were required to collect this information in a standard format. The standard OMB format consists of two categories for data on ethinicity and five categories for data on race, as reflected in questions 10.a. and 10.b. on the ATF Form 4473.	4/14/2016
4/13/2016	Scott Burris Lone Star Tactical Supply	ScottB@lonestar.supply	The proposed changes to the 4473 form are fine, but do not go far enough in my opinion. Question 10, parts A and B, should be removed. This question frequently offends our customers, regardless of their ethnicity or race. Question 10 is of dubious value, for any agency purpose, and I'm certain that the form space could be put to better use. Thank you for considering my comment.	Thank you for your interest in this information collection. Federal regulations, 27 CFR 478.124(c)(1), require licensees to obtain the race of the trasferee/buyer. The purpose for requiring this information is to better enable Fderal firearms licenses to help identify the transferee/buyer during the background check of a firearms transaction and aid law enforcement in accurately tracing firearms found in crimes. Pursuant to Office of Management and Budget (OMB), effective January 1, 2003, all Federal agencies requiring collection of race and ethnicity information on administrative forms and records, were required to collect this information in a standard format. The standard OMB format consists of two categories for data on ethinicity and five categories for data on race, as reflected in questions 10.a. and 10.b. on the ATF Form 4473.	4/14/2016
4/13/2016	Adam Keeling ATF	Adam.Keeling@atf.gov	After reviewing the proposed ATF F 4473, I have found one section that may need further revision. Block 19.d. "The following response(s) was/were later received from NICS or the appropriate State agency:" with responses listed as "Proceed", "Denied", "Cancelled" "No response was provided within 3 business days", and "Overturned." The response "No response was provided within 3 business days" is a source of confusion for FFL's in states that have longer periods for a response to be received. As is the case in Washington State, FFL's must wait 10 full business days after initiating a NICS check or submitting the paperwork to the state before the firearm may be transferred to the individual. Please see Washington RCW 9.41.092, as linked here: http://app.leg.wa.gov/RCW/default.aspx?cite=9.41.092. The response currently on ATF F 4473 in block 21d and also on the proposed ATF F 4473 in block 19.d do not take into account state requirements that may differ from Federal law and regulations. A number of FFL's mistakenly believe that since the ATF F 4473 says that the firearm can be transferred after "3 business days" that they can do so, even contrary to state law. Modifying Block 19.d to include language allowing for longer state periods would be helpful in eliminating confusion for FFL's in those states.	Modifying Block 19.d to include language allowing for longer state periods would be helpful in eliminating confusion for FFL's in those states.	4/20/2016
4/14/2016	David Daniely	d.daniely@gmail.com	"...and aid law enforcement in accurately tracing firearms found in crimes" How? How does the race of the person that bought the gun help with tracing firearms found in crimes?	Thank you for your interest in this information collection. In instances were two persons have the same or similar names, race may be used to determine if the person possessing the firearm is the same person who purchased the firearm.	4/20/2016

4/17/2016	David Bradford	davidbradford510@comcast.net	Regarding the proposed new ATF Form 4473 Instructions to Question 11.f "Adjudicated as a mental defective or committed to a mental institution" - **EXCEPTION.** The new form excludes a portion of the NICS Improvement Amendment Act of 2007. Specifically this language, in bold, has been left out: (C) the adjudication or commitment, respectively, is based solely on a medical finding of disability, without an opportunity for a hearing by a court, board, commission, or other lawful authority, and the person has not been adjudicated as a mental defective consistent with section 922(g)(4) of title 18, United States Code, except that nothing in this section or any other provision of law shall prevent a Federal department or agency from providing to the Attorney General any record demonstrating that a person was adjudicated to be not guilty by reason of insanity, or based on lack of mental responsibility, or found incompetent to stand trial, in any criminal case or under the Uniform Code of Military Justice.	Thank you for your interest in this information collection. The error has been noted and will be corrected on the fo	4/20/2016
4/19/2016	Ryszard Wikar	rwscorpion11@gmail.com	My name is Ryszard Wikar, and I have been in this Country (USA) legally W/O any collision with the law about 35 Years, this year I "refuse to be a victim" of the corporation, governing this nation, and I renounced my US Citizenship,=(employee) and I decided, and I am accepted by Tribal Native American, as an Indigenous People, having Native Naturalization Certificate with U.S. Dept. State Authentic number, and United Nations number, My question is; Do you have another type of application "firearm transaction" so I can filed up and present in gun sale store, so we can finalized transaction, Present application #4473, I can't finish, Half of the questions are irrelevant. Back round was check, and is "Clear" only this application serves one type of people, "citizens" and stores owners or employee can't disbursed any w/o full filed up application.	Thank you for your interest in this information collection. There is no other Federal form that may be used to determine if a purchaser is eligible to receive a firearm purchased from a Federal firearms licensee.	4/20/2016
4/20/2016	Ryszard Wikar	rwscorpion11@gmail.com	Thank you for your respond, very clever, avoiding facts presented, which next door I should knock on? any suggestion?	Thank you for your interest in this information collection. The ATF Form 4473 is the only form approved by the Office of Management and Budget to be used by Federal firearms licensees to determine if he or she may lawfully sell or deliver a firearm to the person identified in Section A of the form. Citizens of other countries may purchase firearms in the United States if they meet certain restrictions. However they are still required to complete the ATF Form 4473 so the Federal firearms licensee can determine if the transferee/buyer may lawfull receive the firearm.	4/20/2016
4/23/2016	Keith E Turner	keitheturner@keitheturner.com	Remove questions 10a and 10b as they are irrelevant and should have no bearing on considerration for approval of a background check.	Thank you for your interest in this information collection. Federal regulations (27 CFR 478.124(c)(1)) requir licensees to obtain the race of the transferee/buyer. This informaiton helps the FBI and/or State Point-of-Contact make or rule out potential matches during the background process and can assist with criminal investigations.	4/25/2016
4/25/2016	Kevin Dent	fortean@rocketmail.com	See attached (6 pages)	Thank you for your interest in this information collection. Comments regarding changes to the form instructions will be taken into consideration. Comments regarding changes to Federal regulation will not be addressed in this information collection.	4/28/2016
4/29/2016	Nathan House Arkansas Armory	Nathan.house@arkansasarmory.com	I have several suggestions on changes to the 4473, based on the most recent draft copy. This isn't a complete list, but I wanted to make a couple of requests. First, and most importantly, can you increase the size of the box for the firearm model number and shrink the size of the box for serial number? I find myself and my employees struggling to get a long model number (I.e. "XDS-45ACP 3.3") into that box and I almost always have plenty of left over room in the serial number box. Second, on the instructions at the top of the form, it says "handwritten in ink". Can it instead say "handwritten or typed in ink"? I'm trying to figure out a way to account for the e4473 systems that are in place to help fill these forms out (including the ATF's own system). People's handwriting (print) is often horrible. Some, bless their heart, are suffering from tremors and while they are capable of filling out the form, the results aren't pretty.	Thank you for your interest in this information collection. Your comment on a increasing the amount of space to record the model will be taken into consideration. The use of electronic Forms 4473 is allowed by ATF Ruling 2016-2 which may be found online at https://www.atf.gov/firearms/docs/ruling/2016-2-%E2%80%93-electronic-atf-form-4473/download.	5/10/2016
5/10/2016	Nathalie Day Cervelle Software	nat@cervelleSoftware.com	If computerized solutions for filling out the 4473 are going to be allowed, then why does the actual form still say: "All entries must be handwritten in ink. " "PLEASE PRINT". That one line seems to disallow any computerized 4473 software as it says that entries must be handwritten. If a store is being audited, and that store does use a computerized 4473, then an IOI could at any time point to this line on the form and technically find fault with a non-handwritten form. And technically, an FFL would be at fault because it is clearly printed on the form that it should be handwritten. Are there any plans to remove that line or modify it? "All entries must be handwritten in ink or filled in via software"... or something like that?	Thank you for your interest in this information collection. Federal regulation does not require Federal firearms licensees (FFLs) to complete the form electronically. Should the FFL choose to use the paper form it must be handwritten in ink. However, an FFL may complete the Form 4473 electronically under the provisions of ATF Ruling 2016-2. A copy of this ruling is available online via https://www.atf.gov/firearms/docs/ruling/2016-2-%E2%80%93-electronic-atf-form-4473/download.	5/12/2016
5/12/2016	Alexis Rimes EZ Corp	Alexis_Rimes@ezcorp.com	(From attached list) Section A: WARNING ("All entries must be handwritten in ink." Change to "All entries must be provided in ink; electronic or handwritten is permitted.". Section A: Question 2 (Bold the word "County"). Section A: Question 12.c. (Bold the word "unlawfully"). Section A: Question 12.d.2. (no instruction reference - Add "See Instructions for Question 12.a.-12.d."). Section D: Question 37 (Change "Date Transferred" to "Date Transferred (if any)").	Thank you for your interest in this information collection. Your comments have been noted.	5/12/2016
5/12/2016	Karen Blevins ATF	Karen.Blevins@atf.gov	The new form's wording "REMINDER-Complete ATF Form 3310.4 For Multiple Purchases of Handguns Within 5 Consecutive Business Days" is confusing. It could be interpreted that the report itself must be submitted within 5 consecutive business days. As a possible suggestion for additional clarity, reword the statement as: "REMINDER-Complete ATF Form 3310.4 For Multiple Purchases of Handguns That Occur Within 5 Consecutive Business Days" or "REMINDER-By The Close of Business, Complete ATF Form 3310.4 For Multiple Purchases of Handguns Within 5 Consecutive Business Days."	Thank you for your interest in this information collection. Your comments have been noted.	5/18/2016
5/17/2016	Eric Moore FBI NICS	Eric.Moore@ic.fbi.gov	See attached (1 page)	Thank you for your interest in this information collection. ATF values input from our partners at FBI NICS. Your comments will be taken into consideration.	6/8/2016
5/18/2016	Elizabeth Rasberry State of Nevada, Dept. of Public Safety	erasberry@dps.state.nv,us	Here are Nevada's concerns if the 4473 is changed regarding what a fugitive from justice is. There is no way for the Point of Contact (POC) staff to determine if the person has knowingly fled to avoid prosecution to be able to deny them a firearm. If 922 g 2 changes we will not be able to deny on any warrants. We will have to either make them unresolved (open) or proceed them. This means people with active warrants will be able to get firearms. There are many different types of warrants. If they want to change it on misdemeanor traffic warrants there isn't a problem with that. Many times the people don't even know they have a warrant on traffic violations. They are misdemeanors and I know right now Las Vegas Metro is pulling these people over and telling them to just take care of it and letting them go. We would deny a lot less people and they would be able to get firearms but these aren't violent criminals. There are other warrants that are more serious. Such as battery DV, battery, dui and felony warrants. If the proposed change to 922 g 2 goes through these people may be able to get a firearm. They could be legally able to own and possess firearms until they are arrested and a final adjudication is issued. This is leaving law enforcement and the public in dangerous situations. With this proposed change, there is no way to differentiate between the various types of warrants and violent people may be able to get firearms.	Thank you for your interest in this information collection. This information collection does not propose to change the definition of "fugitive from justice". The instruction for Question 11.d. reflects the definition of "fugitive from justice" found in Federal regulation at 27 CFR 478.11. Comments regarding changes to this definition are outside the scope of this information collection.	5/25/2016
5/25/2016	GAO Supply LLC	gaosupplyllc@comcast.net	I have always thought a bold vertical line between questions 10a and 10b would make the separation clearer for the transferee. It is the most common omission on the form we have to have them correct.	Thank you for your interest in this information collection. Your comment will be taken into consideration.	5/31/2016

5/31/2016	Christopher Conte National Rifle Association of America, Institute for Legislative Action	Cconte@nrahq.org	See attached (8 pages)	See attached (5 pages)	8/9/2016
6/3/2016	Randal Nickerson Dunham' Sports	rnickerson@dunhamshq.com	Listed below are proposed / suggested revisions to the drafted copy of the new ATF Form 4473 (5300.9). Section A: After Line 2 Add a Line for Buyers Phone Number – Unlimited reasons / call after proceed obtained if originally delayed, manufacturers recall, additional evidence if sale to a prohibited person or a straw purchase. Section B: 19.g. Name of FFL Employee Competing NICS Check (Optional) – add or the appropriate State agency, make it Mandatory and have it two lines – printed name and signature. Section C: 24. – 28. Do not number these lines – one cannot always fit all information on these small lines and sometimes need two lines to complete – option make each line twice as deep. 31. For use by Licensee (line is now two small and of little use) needs to be a full line. 33. Combined line for Trade / Corporate Name and Address and FFL in now to narrow to use standard stamp – need to make it as wide as the prior version of the 4473. Thank you for taking the time to review these suggestions. Please feel free to contact me with any questions. Have a great day,	Thank you for your interest in this information collection. Your comments have been noted.	6/3/2016
6/1/2016	Adam Kraut Firearms Industry Consulting Group	akraut@princelaw.com	Would it be possible to have any comments that have been currently filed in relation to Agency Information Collection Activities; Proposed eCollection eComments Requested; Firearms Transaction Record (ATF Form 4473 (5300.9) emailed to me? I don't see them listed on Regulations.gov.	Thank you for your interest in this information collection. Comments received from this information collection will soon be available on the www.reginfo.gov website.	8/9/2016
6/6/2016	Kristin Roscoe National Shooting Sports Foundation	kroscoe@nssf.org	See attached (3 pages)	Thank you for your interest in this information collection. Your comments will be taken into consideration.	6/10/2016
6/6/2016	Joshua Prince on behalf of Thomas Beveridge, Esq., Cannabis Industry Law Group	joshua@princelaw.com	See Attached (249 Pages)	See attached (4 pages)	8/9/2016
6/6/2016	Adam Kraut Firearms Industry Consulting Group	akraut1@binhgamton.edu	See attached (17 pages)	See attached (5 pages)	8/9/2016
6/6/2016	Barry Laws American Firearms Retailers Association	barry@openrangesports.com	I would like to see a box for multiple handgun purchases that we as dealers could check, eliminating the need to fax a copy of a multiple handgun purchase to ATF. This faxing is a burden on the dealers and the fax machine doesn't answer on a regular basis causing the dealer to have to resend the fax multiple times. Also, the ATF can run a multiple handgun purchase from the information provided on 4473 to the NICS system. Again this is a redundant burden on the dealer and it only gives info of multiple handgun purchases if the buyer purchases from one store.	Thank you for your interest in this information collection. The Form 4473 cannot be utilized for reporting multiple handgun purchases as the form may contain information about other firearms that are not required to be reported. The firearms information recorded on the Form 4473 is not entered into the NICS system therefore ATF cannot obtain information reguarding multiple handgun purchases from that system.	6/10/2016
7/26/2016	Teresa Ficaretta Reeves and Dola	tficaretta@reevesdola.com	Pursuant to the proposed collection of information notice published in the Federal Register on July 26, 2016, I hereby request a copy of the proposed ATF Form 4473.	Thank you for your interest in this information collection. Attached is a copy of the proposed ATF Form 4473.	7/27/2016
7/27/2016	Greg D Griffin ATF	greg.griffin@atf.gov	Thanks again for the draft 4473. I do have 1 suggestion; The instructions for Section D questions 24-28 Firearms Description state that firearms manufactured prior to 1968 may not have a serial number, and if not to put "NONE", "N/A", or "NSN". We were taught at the academy, (11 years ago) to have them put "PRE-68". I've seen a lot of A&D logs and 4473's that had "NONE", "N/A", "NSN" because they didn't look under the grips or other accessories mounted on the gun. Can we have the instructions to say that if the gun does not have a serial number because it was manufactured prior to 1968 then put "PRE-68" so we out in the field don't have any question as to why there is no serial number? Just a suggestion. Thanks and have a great day!	Thank you for your interest in this information collection. Your comments have been noted.	8/9/2016

National Rifle Association of America

INSTITUTE FOR LEGISLATIVE ACTION
11250 WAPLES MILL ROAD
FAIRFAX, VIRGINIA 22030-7400
(703) 267-1160
Fax: (703) 267-1164

Office of Litigation Counsel — Christopher A. Conte

May 26, 2016

Ms. Carolyn King
Bureau of Alcohol, Tobacco, Firearms and Explosives
Firearms Industry Programs Branch
99 New York Avenue, NE
Washington, DC 20226

VIA E-mail: FederalRegisterNoticeATFF4473@atf.gov

Re: OMB Number 1140-0020, Proposed Collections of Information Relating to Revision of ATF Form 4473 (5300.9)

Dear Ms. King:

The purpose of this letter is to provide comments to the April 7, 2016, Federal Register notice published by the Bureau of Alcohol, Tobacco, Firearms and Explosives ("ATF") outlining ATF's proposed revisions to ATF Form 4473, Firearms Transaction Record. For the reasons outlined below, the National Rifle Association ("NRA") believes the portions of the form requiring completion only at the licensed premises amount to a legislative rule that may only be adopted pursuant to notice and comment rulemaking in accordance with the Administrative Procedure Act, 5 U.S.C. §§ 551-559 (2012).

I. Legal Background

A. Gun Control Act of 1968

The Gun Control Act of 1968 ("GCA"), 18 U.S.C. §§ 921-931 (2012), requires all persons engaged in the business of importing, manufacturing, or dealing in firearms to obtain a license issued by ATF. Id. § 922(a)(1)(A). Licensing provisions of the statute require ATF to issue a license to any person who meets all specified licensing criteria. Id. § 923(d)(1). One of the specified criteria is that the applicant has a premises from which he conducts business subject to license under the statute. Id. § 923(d)(1)(E). The GCA requires licensees to maintain records of

importation, production, shipment, receipt, sale, or other disposition of firearms at his place of business for such period, and in such form, as the Attorney General may prescribe. Id. § 923(g)(1)(A).

The GCA gives ATF authority to revoke any license issued under the statute if the holder has willfully violated any provision of the GCA or any rule or regulation issued thereunder. Id. § 923(e).

The GCA makes it unlawful to knowingly make any false statement or representation with respect to the information required to be kept in the records of a federal firearms licensee. Id. § 924(a)(1)(A).

The GCA gives ATF the authority to seize and forfeit any firearm or ammunition involved in knowing or willful violations of the GCA. Id. § 924(d)(1).

ATF regulations implementing the GCA make it clear that a federal firearms license covers the activity specified in the license only at the address specified therein. Licensees who wish to manufacture, import, or deal in firearms at more than one location must obtain a license for each location. 27 C.F.R. § 478.50. However, licensees are allowed to conduct business at in-state gun shows without obtaining a separate license for such location. 18 U.S.C. § 923(j); 27 C.F.R. §§ 478.50(c) and 478.100. The statute also authorizes ATF to prescribe all forms required by the regulations and that all the information called for in each form shall be furnished as indicated by the headings and instructions on the form. 27 C.F.R. § 478.21(a).

Regulations require licensees disposing of any firearm to a person other than another licensee record the transaction on ATF Form 4473. Id. § 478.124. This section specifies the information that must be recorded on the Form 4473, the procedure for transferring shotguns and rifles to nonresidents, and requires the licensee to verify the identity of the transferee by examining an identification document. Id. There is no requirement in the regulations that the Form 4473, or any part thereof, be executed at the licensed premises.

B. Administrative Procedure Act

The Administrative Procedure Act ("APA") specifies the procedures federal agencies must follow for "rule making," defined as the process of "formulating, amending, or repealing a rule." 5 U.S.C. § 551(5) (2012). The term "rule" is defined to include "statement[s] of general or particular applicability and future effect" that are designed to "implement, interpret, or prescribe law or policy." Id. § 551(4). The APA distinguishes between two types of rules: legislative rules and interpretive rules. The first may be issued only through notice and comment rule making. Id. § 553. This requires publication of a notice in the Federal Register, submission of comments from all interested parties, consideration of those comments, and issuance of the final rule. Legislative rules have the force and effect of law. By contrast, interpretive rules (also called interpretative rules) are not subject to the APA notice and comment rule making requirements. Id. § 553(b)(3)(A). Federal agencies, including ATF, often issue interpretive rules to provide

guidance to industry members through rulings, questions and answers, and other informal guidance documents. Interpretive rules do not have the force and effect of law.

C. APA Case Law: Legislative Rules Versus Interpretive Rules

A number of decisions of the D.C. Court of Appeals demonstrate the analysis used by the court in distinguishing legislative rules from interpretive rules. We summarize below three cases that are helpful to the analysis of the rules proposed by ATF in the new Form 4473.

1. Am. Mining Cong. v. Mine Safety & Health Admin.

In Am. Mining Cong. v. Mine Safety & Health Admin., 995 F.2d 1106 (D.C. Cir. 1993), the court addressed program policy letters issued by the Mine Safety & Health Administration ("MSHA") providing guidance on whether x-ray results amounted to a "diagnosis" of lung cancer that must be reported in accordance with the Mine Safety and Health Act and implementing regulations. The program policy letters stated that chest x-rays of miners with a history of exposure to lung cancer-causing dust that rated 1/0 or higher on a specified classification system would be considered a reportable "diagnosis" under the statute and regulations. The program policy letters were not published in the Federal Register, but they were distributed to all mine operators and trade unions. The court noted the "legal effect" test as marking the line between substantive and interpretive rules. Id. at 1109. Thus, if the disputed rule creates a duty on regulated persons that may be enforced against such persons, it has the legal effect of a legislative rule. In determining whether a purported interpretive rule has "legal effect," the court adopted a four-part analysis:

(1) Whether in the absence of the rule there would not be an adequate legislative basis for enforcement action to ensure the performance of duties;
(2) Whether the agency published the rule in the Code of Federal Regulations;
(3) Whether the agency has explicitly invoked its general legislative authority; or
(4) Whether the rule effectively amends a prior legislative rule.

Id. at 1112.

The court stated that if the answer to any of the above questions is in the affirmative, the rule is legislative. Id.

Based on the above analysis, the court held that MSHA's program policy letters were interpretive rules. The court held that the implementing regulations themselves required reporting of a "diagnosis," meaning there was no legislative gap that required the letters as a predicate to enforcement action. Nor did the letters amend the existing regulations, but merely provided more detailed guidance on the meaning of the regulations. Id.

2. ***Appalachian Power Co., et al. v. E.P.A***.

Appalachian Power Co., et al. v. E.P.A., 208 F.3d 1015 (2000), addressed a document titled "Periodic Monitoring Guidebook" issued by the Environmental Protection Agency ("EPA"). The guidance related to EPA's administration of the Clean Air Act, including requirements that stationary sources of air pollution must obtain operating permits from state or local authorities. EPA regulations specified the requirements for the state permit programs, including a requirement for periodic testing or monitoring. EPA issued guidance on the regulation stating that, for specified emission units, the periodic monitoring requirement would not be satisfied if there is a one-time testing requirement. The Periodic Monitoring Guidebook was not issued pursuant to notice and comment rulemaking, and electric power companies challenged it as a legislative rule.

Even though the EPA claimed the guidebook was not "binding," the court noted that the EPA conceded in its brief that the portion of the guidebook at issue was a settled position that would be used by the agency in reviewing state-issued permits. Id. at 1020. Because EPA would insist that state and local authorities comply with the requirements for period monitoring, as defined in the guidebook, the court found that legal consequences would flow from the rule. Id. at 1022. The court also noted it was clear that EPA would base enforcement actions on the policies set forth in the document and would likely lead to state permitting authorities declaring permits invalid unless they complied with the terms of the document. Id. at 1022. Accordingly, the court held that the guidebook was a legislative rule that was subject to the notice and comment requirements of the APA. Id. at 1028.

3. Catholic Health Initiatives v. Sebelius

In Catholic Health Initiatives v. Sebelius, 617 F.3d 490 (D.C. Cir. 2010), a nonprofit corporation and a group of its affiliated nonprofit hospitals filed suit against the Department of Health and Human Services ("HHS") claiming that a Medicare reimbursement manual that limited equity investments for certain offshore insurers was a legislative rule that violated the APA. The plaintiffs were seeking recovery of premiums the hospitals paid an offshore insurance company for malpractice, workers compensation, and other insurance. The Medicare Act allows such premiums to be considered part of a hospital's "reasonable costs" incurred in providing services to Medicare beneficiaries, which means such costs are reimbursable through Medicare. The Medicare Act provided that "reasonable cost" shall be determined in accordance with regulations. Implementing HHS regulations provided that reasonable costs include all necessary and proper costs incurred in furnishing Medicare and that are not "substantially out of line with" the costs of similar institutions. At issue in the litigation was a Provider Reimbursement Manual, which included guidelines and policies for determining the reasonable cost of provider services. The Manual provided rules for Medicare providers who established their own insurance companies – known as "captives." If the captive is offshore, the Manual prohibited reimbursement for insurance premiums if the captive's investments did not comply with specified low-risk investment rules. One of the low-risk rules was that the investments may include dividend paying equity securities listed on a U.S. stock exchange provided the investment does not exceed 10 percent of the company's admitted assets. The insurance

company established by the plaintiffs did not meet this requirement, and the hospitals disallowed premium payments to the insurance company.

The court stated that to be interpretive, a rule must derive a proposition from an existing document whose meaning compels or logically justifies the proposition. The substance of the derived proposition must flow fairly from the substance of the existing document. Id. at 494. Moreover, the court noted that if the rule cannot fairly be seen as interpreting a statute or a regulation and if it is enforced, the rule is not interpretive. Id. Despite the fact the manual stated it was interpreting the "reasonable cost" language in the statute and regulations, the court found the term was so vague that HHS could not credibly be interpreting it. Id. at 495. The court also noted that the specificity of the 10 percent rule cut against the Secretary's allegation the manual was an interpretive rule. The arbitrary nature of the 10 percent rule indicated it was a legislative rule because it represented a choice among various methods of implementation. Id. The court held that there was no way an interpretation of the "reasonable costs" language in the statute could produce the sort of detailed and rigid investment code set forth in the manual. The court noted that the connection between the manual and the "reasonable costs" language in the statute and regulations was too attenuated to be considered an interpretive rule. Id. at 496. Accordingly, the court held that the rule was a legislative rule that must be issued pursuant to the notice and comment provisions of the APA. Id. at 497.

II. ATF's Proposed Amendment of Form 4473

ATF proposes to revise ATF Form 4473, Firearms Transaction Record, in several significant respects. Our comments are limited to the following proposals:

- Revision of statement at top of first page, second paragraph stating "Prepare in original only at the licensed premises."
- Revision of licensee transferor statement on page 3 requiring that the individual employee of the licensee who transfers the firearm certify that the entire transaction has been completed at the licensed business premises.
- Revision of Notices, Instructions, and Definitions on page 3, second paragraph to state, "Generally, ATF Form 4473 must be completed at the licensed business premises when a firearm is transferred over-the-counter."

The NRA believes the proposed revisions above amount to a legislative rule that must be issued pursuant to notice and comment under the APA. There is no requirement of the GCA or implementing regulations requiring the Form 4473 to be executed at the licensed premises. To the extent ATF believes this requirement is an interpretation of the "premises" requirement of the GCA in 18 U.S.C.
§ 923(d)(1)(E), the NRA strongly disagrees. The only references in the law and regulations to activities that must be done at the licensed premises are (1) storage of records, Id. § 923(g)(1)(A)), and (2) storage of firearms and ammunition inventory, 27 C.F.R. § 478.50.

ATF has published a question and answer concerning activities at an out-of-state gun show indicating there are a number of activities ATF allows to be conducted off-site. The relevant

question and answer is available on ATF's website at https://www.atf.gov/firearms/qa/what-may-licensee-do-out%E2%80%93%E2%80%93state-gun-show (last visited 5/10/2016) and states as follows:

> **What may a licensee do at an out-of-state gun show?**
>
> A licensee may only display and take orders for firearms at an out-of-state gun show. In filling any orders for firearms, the licensee must return the firearms to his or her licensed premises and deliver them from that location. Any firearm ordered by a nonlicensee must be delivered or shipped from the licensee's premises to a licensee in the purchaser's state of residence, and the purchaser must obtain the firearm from the licensee located in the purchaser's state. A licensee is prohibited from transferring firearms to another licensee at an out-of-state gun show, except where the firearm being transferred is a curio or relic.
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> [18 U.S.C. 922(a)(1), (b)(3), 923(a) and (j); 27 CFR 478.100]

The above question and answer indicates ATF interprets the GCA as allowing licensees to display firearms and take orders for firearms away from its licensed premises. Apparently these are activities ATF would allow off premises without taking enforcement action against a licensee. However, this position, although helpful to licensees in determining which activities can take place away from the premises, is not included in the law, regulations, or on a form. Accordingly, it would be difficult for ATF to enforce the limitations expressed in the question and answer against a licensee who conducted activities at a gun show outside of those enumerated above. This is particularly the case in light of United States v. Caldwell, 49 F.3d 251 (6th Cir. 1995), in which the court held that a licensed firearms dealer who sold firearms away from his licensed premises cannot be convicted of a violation of 18 U.S.C. § 922(a)(1). Caldwell calls into question ATF's ability to charge a licensee with engaging in the business without a license for off-premises activities of any type.

We question ATF's decision to allow licensees to display firearms and take orders at off-premises locations while proposing a requirement that the Form 4473 be executed only at the licensed premises. The agency needs to explain its rationale for requiring some activities to be conducted at the licensed premises while others may be conducted elsewhere. A notice of proposed rulemaking articulating specific changes in the regulations and the reasons therefore is the appropriate course of action.

ATF's methods of adopting the two positions concerning what may be done at the licensed premises is also important in determining whether they are interpretive versus legislative rules. The key difference between the question and answer above and the proposed new language on the Form 4473 is that by adding this requirement to the form ATF and requiring a certification that the form has been executed at the licensed premises, ATF has created a method of enforcement. Thus, a licensed dealer who had a customer complete Part A of the form at the customer's home would provide a false certification in Section B, violating 18 U.S.C. § 924(a)(1)(A) and 27 C.F.R. § 478.21(a). If ATF obtained evidence that such a violation was

willful, ATF could revoke the license of the dealer. The dealer would also be subject to criminal prosecution under 18 U.S.C. § 924(a)(1)(A), and firearms involved in the violation would be subject to seizure and forfeiture. Id. § 924(d)(1).

Moreover, the proposed instructions and certification on the Form 4473 appear to be a binding "rule" that all ATF personnel, whether in the field or at ATF Headquarters, will follow. The case law issued by the D.C. Circuit cited above indicates the courts are likely to view this new requirement as a legislative rule that must be issued in accordance with the notice and comment provisions of the APA. As noted in the American Mining case, the legal effect of the proposal is to create a duty on the part of federal firearms licensees to complete Forms 4473 only at the licensed premises or risk enforcement action. See 995 F.2d at 1109. Absent the proposed language on the form, there is no adequate legislative basis for enforcing this requirement against federal firearms licensees. In addition, the new requirement effectively amends the regulations in 27 C.F.R. § 478.124 by adding a requirement that the Form 4473 be executed only at the licensed premises. Accordingly, two of the four factors identified by the court indicate that the proposal amounts to a legislative rule. See 995 F.2d at 1112.

The rationale the D.C. Circuit incorporated in the Appalachian Power case also indicates the proposal is a legislative rule. By incorporating the language in the certification and in the instructions for the Form 4473, ATF is adopting this requirement as a settled position with legal consequences flowing for licensees who do not execute the entire form at the licensed premises. See, 208 F.3d at 1022.

The Catholic Health Initiatives case also indicates the proposal would likely be viewed as a legislative rule by the D.C. Circuit. See 617 F.3d at 495. There is no provision of the GCA or implementing regulations that suggests an agency position that firearms transactions records must be completed only at the licensed premises. 18 U.S.C. § 923(d)(1)(E) specifies criteria for issuing licenses and has nothing to do with where firearms records are completed. If ATF believes the proposal is an interpretation of Section 922(a)(1)(A), this is a very attenuated interpretation that bears no resemblance to the statutory language. The proposed position does not flow fairly from any of the statutory provisions and fills in a significant gap that can only be addressed through regulations. Nor can the record keeping requirement of 18 U.S.C. § 923(g)(1)(A) be reasonably interpreted to include the proposed requirement.

Finally, the language on the form is arbitrary, as it indicates a choice on the part of the agency as to which dealing activities must occur at the licensed premises and which may occur elsewhere. As noted above, ATF allows licensed dealers to display firearms and take orders off premises. This type of line drawing indicates the agency is making choices about how to implement the statute. When these choices are made in a manner that results in settled positions that are enforceable against licensees, ATF must adopt them through notice and comment rulemaking.

III. Conclusion

ATF's proposal to require licensees to execute the Form 4473 only at the licensed premises by adding an instruction and certification to Form 4473 violates the APA. In addition to the

procedural defects outlined herein, the NRA has policy concerns about an agency position that prohibits licensees from conducting some portion of a firearms transaction at a location other than the licensed premises. We are advised that a number of dealers in rural areas occasionally conduct business by traveling to the homes of their customers to display firearms and take orders and may have a customer complete Section A of the Form 4473 during that initial encounter. As long as the dealer verifies the identity of the transferee through a valid identification document, returns to his licensed premises to conduct the NICS check and log the firearm out, and then delivers the firearm from the licensed premises, the transaction will comply with the law and regulations. There are no valid public safety considerations indicating ATF should limit licensees in completing the Form 4473 only at the licensed premises.

We also object to the proposed policy because it would prevent licensees from having purchasers complete Part A of the Form 4473 either in hard copy or on-line before traveling to the licensed premises. Allowing purchasers to provide their personal information in advance could save time at the dealer's place of business and presents no threat to the integrity of the transaction.

We urge ATF to publish a notice of proposed rulemaking on which activities, including completion of the Form 4473, must be completed at the licensed premises so that licensees will have an opportunity to provide you with information on their business processes. Firearms purchasers also have an interest in the requirements for purchasing firearms from licensed dealers and may wish to comment on ATF's proposals on this subject. This is the best way for the agency to make policy in an informed and considered manner. It is also the process required by law.

Thank you for the opportunity to comment on the proposed collection of information.

Sincerely,

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April 23, 2016

Ms. Carolyn King
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Dear Ms. King:

This letter responds to your Agency's request for public comments concerning the Proposed Information Collection Activity, ATF Form 4473 (5300.9), *Firearms Transaction Record*, published in the Federal Register on April 7, 2016.

1. Question 11.b. and its Instruction.

The instruction corresponding to question 11.b. ("Are you under information or indictment in any court for a felony, or any other crime for which the judge could imprison you for more than a year?") contains two areas requiring clarification.

a. Title 18, United States Code, Section 922(n) generally prohibits a "person who is under indictment for a crime punishable by imprisonment for a term exceeding one year" from receiving a firearm. The term "crime punishable by imprisonment for a term exceeding one year" is defined in Title 18, United States Code, Section 921(a)(20) to explicitly exclude two categories of offenses (State crimes punishable by up to two years imprisonment, but which are classified as misdemeanors; and certain white-collar crimes related to trade practices). Consequently, a person pending criminal proceedings for one of these excluded offenses is not subject to the 922(n) prohibition from receiving a firearm. I recommend that the instruction be amended to clarify this point.

b. The instruction is unclear on the applicability of the question to military Court-Martial proceedings.

i. The Uniform Code of Military Justice[1] (UCMJ) is a special Federal criminal code applicable to Service Members in the U.S. Armed Forces. Unlike civilian criminal codes, the UCMJ does not classify offenses as either felonies or misdemeanors. The maximum possible sentence for a conviction is set by a combination of an Executive Order prescribing punishments (the Manual for Courts-Martial) and the type of Court-Martial (Summary, Special, or General) hearing the case. Additionally, under the UCMJ, a sentence of imprisonment may be imposed either by a Military Judge alone or

[1] Title 10, United States Code, Chapter 47.

by a Panel, the equivalent of a jury. Criminal proceedings under the UCMJ are not initiated by either an indictment or information, by rather a charge sheet which is then referred to a Court-Martial by the Convening Authority, a military officer authorized to direct disposition. Finally, the sentence of a Court-Martial is subject to any agreed upon cap contained in a pretrial agreement between the Accused and the Convening Authority. In short, it is very different from any conventional civilian criminal justice system.

ii. Accordingly, a Service Member pending a charge under the UCMJ may not know if he is a prohibited person under this section. For example, if an enlisted Soldier is accused of violating Article 92, UCMJ, for failure to obey a general order or regulation, the maximum sentence in the Manual for Courts-Martial is two years imprisonment. A Convening Authority could elect to dispose of the offense by a General Court-Martial, where the Soldier would be subject to the maximum penalty upon conviction; by a Special Court-Martial, where the Soldier would be subject to a maximum of one year imprisonment; by a Summary Court-Martial, where the Soldier would be subject to a maximum of one month imprisonment; or by some lesser non-judicial or disciplinary means where there is no potential for imprisonment. Even if a referred charge sheet is deemed an equivalent of an information for these purposes, until the Convening Authority has made a determination as to disposition of the offense, there is no clear answer as to whether the Soldier is subject to more than one year imprisonment. Until the Convening Authority has taken dispositional action, the charge sheet is the equivalent of a criminal complaint, without any judicial or Court involvement at all.

iii. I recommend that the instructions provide a black letter rule applicable to UCMJ proceedings: A person answers "yes" to this question if, upon conviction, he is subject to a sentence of more than one year imprisonment per the Manual for Courts-Martial; and it has been referred to a General Court-Martial, the only level of Court-Martial authorized to impose more than one year imprisonment, for trial. This rule supports Congressional intent not to extend Gun Control Act prohibitions to convictions by Special or Summary Courts-Martial, as evidenced by the dishonorable discharge prohibited person category[2]; this type of punitive discharge can only be adjudicated by a General Court-Martial.[3]

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[2] See Title 18, United States Code, Section 922(g)(6).

[3] *N.B.* The several States and Territories also have codes within their own statutes governing the conduct of State military forces (the National Guard when not in Federal Service and State Defense Force (Militia) personnel). Many are closely patterned off the UCMJ and present the same challenges in determining what would constitute a "crime for which the judge could imprison you for more than a year" for the purposes of answering this question. Additionally, some states strictly limit the sentences that can be adjudicated by a state court-martial, regardless of type or offense charged. (See N.Mex. Statutes Annotated § 20-12-6(A) ("Except when the militia is in actual service in time of war or public danger, no punishment imposed by court martial shall exceed that prescribed for a misdemeanor.")) While examination of each state military code is beyond the scope of these comments, and the frequency of state courts-martial vary widely among jurisdictions, the Agency should be aware that these

2. Question 11.c. and its Instruction.

The instruction corresponding to question 11.c. ("Have you been convicted in any court for a felony, or any other crime for which the judge could have imprisoned you for more than one year, even if you received a shorter sentence including probation?") contains one substantial omission and one area requiring clarification.

a. While the proposed instruction for question 11.c. correctly excludes State misdemeanors with a maximum sentence of two years or less from its scope, it does not mention the white-collar trade practice offenses excluded from the definition in Title 18, United States Code, Section 921(a)(20) which are, consequently, also outside the definition of "crime punishable by imprisonment for a term exceeding one year."[4] I recommend amending the instruction to identify this additional excluded category of offenses.

b. As discussed above, the justice system established in the UCMJ does not align well with the traditional felony-misdemeanor distinction in civilian systems. For those same reasons, a Service Member or former Service Member may not be able to accurately determine if his conviction is the equivalent of a felony or one for which the Court-Martial could have sentenced him to more than a year imprisonment.

i. While a discharge under dishonorable conditions[5] is a separate prohibited person criterion, a General Court-Martial may, in its discretion, sentence an enlisted defendant to either a dishonorable or bad-conduct discharge, or an officer to a dismissal from the Service; a Special Court-Martial (in accordance with Service regulations) may only sentence an enlisted defendant to a bad-conduct discharge, not a dishonorable discharge, and has no jurisdiction to sentence an officer to a dismissal; a Summary Court-Martial has no jurisdiction to adjudicate a discharge or dismissal.

ii. Accordingly, as with question 11.b, I recommend that the instructions provide a black letter rule applicable to UCMJ proceedings: A person answers "yes" to this question if he was convicted or pled guilty at a General Court-Martial where the

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alternative state prosecution systems exist. I recommend Agency consultation with the State Judge Advocate, located at the National Guard Joint Forces Headquarters, in each of these jurisdictions to determine what impact, if any, their military codes would have in this area.

[4] "[a]ny Federal or State offenses pertaining to antitrust violations, unfair trade practices, restraints of trade, or other similar offenses relating to the regulation of business practices . . . ." 18 U.S.C. § 921(a)(20)(A).

[5] "Discharged under dishonorable conditions. Separation from the U.S. Armed Forces resulting from a dishonorable discharge or dismissal adjudged by a general court-martial. The term does not include any separation from the Armed Forces resulting from any other discharge, e.g., a bad conduct discharge." 27 C.F.R. § 478.11.

maximum sentence that could have been imposed, pursuant to the Manual for Courts-Martial, was greater than one year.[6]

3. Question 11.d. and its Instruction.

The instruction to question 11.d. ("Are you a fugitive from justice?") provides that "[t]he term also includes any person who knows that misdemeanor or felony charges are pending against such person and who leaves the state of prosecution." This expanded definition is inconsistent with the law. Consequently, I recommend that this language be removed from the form and that the Agency amend its regulation to conform to the law.

a. Title 18, United States Code, Section 921(a)(15) provides that "[t]he term "fugitive from justice" means any person who has fled from any State to avoid prosecution for a crime or to avoid giving testimony in any criminal proceeding." The proposed instruction abrogates the intent element, in that the mere act of crossing a state border creates fugitive status, even if the person intends to return and participate in all future Court proceedings.

b. Further, a defendant who is pending a criminal charge may not be prohibited under applicable law from leaving the state; travel restrictions are, most frequently, a discretionary condition of bond imposed by the Court.[7] Additionally, a Defendant subject to such a condition of bond may apply to the Court for a modification to permit out-of-state travel; this is frequently accompanied by a waiver of extradition or other means to ensure his return to the jurisdiction.

c. Finally, in jurisdictions such as New Mexico where minor traffic violations are classified as misdemeanors under State law, this instruction would have the effect of rendering an out-of-state motorist who receives a traffic ticket and returns home a "fugitive from justice" ineligible to receive a firearm. This example illustrates the absurd consequence of extending this term beyond its explicit statutory definition.

d. The language in this instruction is drawn from the Agency's regulatory definition of "fugitive from justice."[8] Commenter responses to the Agency's proposed rule pointed out key legal problems with the proposed definition:[9]

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[6] See footnote 3, above. The same concerns apply to state court-martial convictions and how they would count for the purposes of answering this question.

[7] *See*, e.g., N.Mex. Rules of Criminal Procedure for the District Courts, 5-401 (providing discretion for the Court to impose travel restrictions under an analysis of least restrictive bond conditions necessary to ensure appearance)

[8] "Fugitive from justice. Any person who has fled from any State to avoid prosecution for a felony or a misdemeanor; or any person who leaves the State to avoid giving testimony in any criminal proceeding. The term also includes any person who knows that misdemeanor or felony charges are pending against such person and who leaves the State of prosecution." 27 C.F.R. § 478.11.

[9] See T.D. ATF-391, 62 F.R. 124 at 34634-24640 (Jun. 27, 1997).

> One Federal agency stated that the term is defined in the statute (18 U.S.C. 921(a)(15)) and, as such, any expansion of the definition would require legislative action. ATF is not proposing to "expand" the definition of fugitive from justice. Rather, the proposed definition is intended to clarify the meaning of the term. As mentioned in the preamble of Notice No. 839, the legislative history of section 921(a)(15), defining "fugitive," indicates that the term includes both felonies and misdemeanors, but makes no specific reference to misdemeanors. In addition, the statute does not spell out that to be a fugitive from justice it is not necessary that the person left a State with the intent of fleeing the charges. Rather, a person is a fugitive from justice if the individual, knowing that charges are pending, purposefully leaves the State of prosecution and does not appear before the prosecuting tribunal. Accordingly, ATF's proposed regulatory definition merely clarifies the statutory definition by covering these points . . . .
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> ...
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> One State agency expressed concern regarding ATF's statement in the preamble of Notice No. 839 that a person is not a fugitive from justice merely because he or she has outstanding traffic citations. The commenter asked whether this includes criminal as well as civil traffic citations. The commenter also believed that the proposed definition should be amended to include individuals with outstanding traffic warrants. To be a fugitive from justice under the statute, a person must have left the State where criminal charges are pending against the person. A person who has an outstanding civil traffic citation or who has not left the State, does not meet the statutory definition. The statute and the final regulation make it clear that "fugitive from justice" does not include a person having only civil traffic citations.

The Agency's responses are unconvincing. As detailed above, under the Agency's regulatory expansion of the statute, a person who is not restricted from leaving the state, to include those defendants who have received special permission from the Court to leave the jurisdiction, are fugitives under the regulation. Likewise, the Agency makes assurances that a person who receives a "civil traffic citation" could not be a fugitive under this definition, but does not address those states where speeding and the like are low-grade misdemeanors. This regulation blatantly ignores very clear language in the statute and substitutes the Agency's judgment for that of Congress.

4. Question 11.g. and its Instruction.

As discussed above, Title 27, Code of Federal Regulations, Section 478.11 defines what constitutes a person "discharged from the Armed Forces under dishonorable conditions" to include only those dishonorably discharged (for enlisted members and warrant officers not commissioned) and dismissed from the Service (for cadets, midshipmen, commissioned officers, and commissioned warrant officers); it specifically

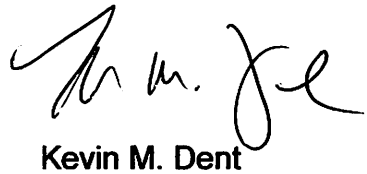
excludes bad-conduct discharges and characterizations of service in administrative separations.

a. A sentence to a punitive discharge is only final, and can be executed, under the UCMJ once the procedures in Rule for Courts-Martial 1113(c) have been completed. A sentence to a punitive discharge alone does not constitute a discharge. Accordingly, a Service Member could be sentenced to a dishonorable discharge or dismissal, but as result of a pretrial agreement, clemency by the Convening Authority, order of an appellate court, or action by the Service Secretary, it is not approved or executed. A former Service Member, under these circumstances, would not have been "discharged under dishonorable conditions" within the meaning of the regulation.

b. The instructions should be clarified to state that a "yes" is required in response to question 11.g. only as a result of a final, executed dishonorable discharge or dismissal from the Service. This will prevent confusion by persons who were discharged under some under non-qualifying characterization (such as an "other than honorable" administrative separation, or the formerly used "undesirable" discharge), as well as former officers who were dismissed and may not be aware that this is the legal equivalent of a dishonorable discharge.[10]

I appreciate the opportunity to comment upon this proposed information collection activity. In addition to the mailed copy, I will forward an electronic copy of this letter to the email address in the Federal Register notice.

Very truly yours,



Kevin M. Dent

cc:
FederalRegisterNoticeATFF4473@atf.gov

[10] Note that there is no equivalent of a "Bad Conduct Discharge" for an officer under the UCMJ. See Rule for Courts-Martial 1003(b)(8).

Bureau of Alcohol, Tobacco, Firearms, and Explosives

Agency Information Collection Activities Firearms Transaction Record (ATF Form 4473 (5300.9))	)))))

Firearms Industry Consulting Group's Comments as to ATF's Proposed Changes to the Firearms Transaction Record (ATF Form 4473 (5300.9))

On April 7, 2016, the Bureau of Alcohol, Tobacco, Firearms, and Explosives ("ATF" or the "Agency") published a notice in the Federal Register requesting comments on proposed changes to the Firearms Transaction Record (ATF Form 4473 (5300.9)) ("4473"), pursuant to the Paperwork Reduction Act, 44 U.S.C. §§ 3501-3520.

The Firearms Industry Consulting Group ("FICG"), a division of Prince Law Offices, P.C., represents numerous individuals, gun clubs, and Federal Firearms Licensees ("FFLs") in Pennsylvania with regard to State law issues. Furthermore, in relation to federal issues, FICG represents numerous FFLs across the United States in all matters relating to firearms. FICG actively works to defend, preserve, and protect constitutional and statutory rights of firearms owners, including through Article I, Section 21 of the Pennsylvania Constitution and the Second Amendment to the United States Constitution. In this comment, FICG represents the interests of its respective clients.

FICG's purpose is:

> To provide legal representation in the protection and defense of the Constitutions of Pennsylvania and the United States, especially with reference to the inalienable right of the individual citizen guaranteed by such Constitutions to acquire, possess, transport, carry, transfer ownership of, and enjoy the right to use arms, in order that the people may always be in a position to

> exercise their legitimate individual rights of self-preservation and defense of family, person, and property, as well as to serve effectively in the appropriate militia for the common defense of the Republic and the individual liberty of its citizens.

FICG's interest in this matter stems from its representation of numerous Pennsylvania citizens and FFLs nationwide, who would be required to use the proposed form if ATF were to modify it as proposed. In response to the request for comment, FICG offers this public comment for consideration.

FICG opposes some of the proposed changes to the 4473 and offers some additional suggestions for consideration for the reasons set forth below.

I. ATF Is Not the Appropriate Agency for Drafting, Modifying, or Amending the 4473 nor is it the Appropriate Agency for Defining or Clarifying What Constitutes an "Unlawful User of or Addicted to Any Controlled Substance" and "Fugitive from Justice"

ATF is not the appropriate agency for drafting, modifying or amending the 4473 nor is it the appropriate agency for defining or clarifying what constitutes an "unlawful user of or addicted to any controlled substance" or "fugitive from justice", because the Federal Bureau of Investigation ("FBI") is empowered with the interpretation of 18 U.S.C. § 922(g), and as such ATF cannot proceed in this matter. *See*, *United States v. Mead Corp.*, 533 U.S. 218 (2001).

a. FBI's Statutory and Regulatory Authority

FBI initially derives its authority to investigate crimes under 28 U.S.C. § 533. The Brady Handgun Violence Prevention Act (Brady Act), Public Law 103-159, 107 Stat. 1536 (1993), required the implementation of the National Instant Check System ("NICS"), pursuant to 18

U.S.C. § 922(t).[1] The Attorney General delegated the implementation and control of the NICS system, including providing for an appeal process for erroneous denials, to the FBI. See, 28 C.F.R. §§ 25.1, 25.3.[2] Pursuant to 28 C.F.R. § 25.5,

> (a) The FBI will be responsible for maintaining data integrity during all NICS operations that are managed and carried out by the FBI. This responsibility includes:
>
> (1) Ensuring the accurate adding, canceling, or modifying of NICS Index records supplied by Federal agencies;
>
> (2) Automatically rejecting any attempted entry of records into the NICS Index that contain detectable invalid data elements;
>
> (3) Automatic purging of records in the NICS Index after they are on file for a prescribed period of time; and
>
> (4) Quality control checks in the form of periodic internal audits by FBI personnel to verify that the information provided to the NICS Index remains valid and correct.
>
> (b) Each data source will be responsible for ensuring the accuracy and validity of the data it provides to the NICS Index and will immediately correct any record determined to be invalid or incorrect.

---

[1] Not all states are NICS states, such as Pennsylvania. In these non-NICS states, referred to as Point of Contact (POC) states, the state law enforcement agency tasked with performing background checks queries the NICS Index maintained by FBI. *See*, 28 C.F.R. § 25.2 defining POC as *"*a state or local law enforcement agency serving as an intermediary between an FFL and the federal databases checked by the NICS. A POC will receive NICS background check requests from FFLs, check state or local record systems, perform NICS inquiries, determine whether matching records provide information demonstrating that an individual is disqualified from possessing a firearm under Federal or state law, and respond to FFLs with the results of a NICS background check. A POC will be an agency with express or implied authority to perform POC duties pursuant to state statute, regulation, or executive order."

[2] *See*, 28 C.F.R. § 25.3 holding:

> (a) There is established at the FBI a National Instant Criminal Background Check System.
>
> (b) The system will be based at the Federal Bureau of Investigation, 1000 Custer Hollow Road, Clarksburg, West Virginia 26306-0147.
>
> (c) The system manager and address are: Director, Federal Bureau of Investigation, J. Edgar Hoover F.B.I. Building, 935 Pennsylvania Avenue, NW, Washington, D.C. 20535.

See also, 28 C.F.R. § 25.2 defining *NICS Index* as "the database, to be managed by the FBI, containing information provided by Federal and state agencies about persons prohibited under Federal law from receiving or possessing a firearm. The NICS Index is separate and apart from the NCIC and the Interstate Identification Index (III)."

More importantly, pursuant to 28 C.F.R. § 25.6, it is the FBI that is to determine whether or not an individual is prohibited when a NICS check is performed.[3]

> (c)(1) The FBI NICS Operations Center, upon receiving an FFL telephone or electronic dial-up request for a background check, will:
>
> (i) Verify the FFL Number and code word;
>
> (ii) Assign a NICS Transaction Number (NTN) to a valid inquiry and provide the NTN to the FFL;
>
> (iii) Search the relevant databases (i.e., NICS Index, NCIC, III) for any matching records; and
>
> (iv) Provide the following NICS responses based upon the consolidated NICS search results to the FFL that requested the background check:
>
> (A) "Proceed" response, if no disqualifying information was found in the NICS Index, NCIC, or III.
>
> (B) "Delayed" response, if the NICS search finds a record that requires more research to determine whether the prospective transferee is disqualified from possessing a firearm by Federal or state law. A "Delayed" response to the FFL indicates that the firearm transfer should not proceed pending receipt of a follow-up "Proceed" response from the NICS or the expiration of three business days (exclusive of the day on which the query is made), whichever occurs first. (Example: An FFL requests a NICS check on a prospective firearm transferee at 9:00 a.m. on Friday and shortly thereafter receives a "Delayed" response from the NICS. If state offices in the state in which the FFL is located are closed on Saturday and Sunday and open the following Monday, Tuesday, and Wednesday, and the NICS has not yet responded with a "Proceed" or "Denied" response, the FFL may transfer the firearm at 12:01 a.m. Thursday.)
>
> (C) "Denied" response, when at least one matching record is found in either the NICS Index, NCIC, or III that provides information demonstrating that receipt of a firearm by the prospective transferee would violate 18 U.S.C. 922 or state law. The "Denied" response will be provided to the requesting FFL by the NICS Operations Center during its regular business hours.

Moreover, where an individual believes he or she was erroneously denied, the FBI, not the ATF, is tasked with the responsibility of processing the appeal. Pursuant to 28 C.F.R. § 25.10

[3] *See also*, FBI's Fact Sheet regarding NICS on its website declaring that it is the NICS operator that makes the decision as to whether provide a response of proceed, delayed, or denied, *available at* http://www.fbi.gov/about-us/cjis/nics/general-information/fact-sheet.

> (c) If the individual wishes to challenge the accuracy of the record upon which the denial is based, or if the individual wishes to assert that his or her rights to possess a firearm have been restored, he or she may make application first to the denying agency, i.e., either the FBI or the POC.

And

> (d) … The FBI will consider the information it receives from the individual and the response it receives from the POC or the data source. If the record is corrected as a result of the challenge, the FBI shall so notify the individual, correct the erroneous information in the NICS, and give notice of the error to any Federal department or agency or any state that was the source of such erroneous records.

Maybe even more enlightening is Section 25.6(j)(2) that goes on to declare that FBI is to respond to an inquiry from ATF in relation to a civil or criminal enforcement matter relating to the Gun Control Act or National Firearms Act, because it is FBI, not ATF, that not only controls the database but also determines the prohibited status of an individual.

b. ATF's Statutory Authority

ATF's statutory authority is derived from 28 U.S.C. § 599A. In particular, the statute specifies that ATF is responsible for investigating:

> **(1)** criminal and regulatory violations of the Federal firearms, explosives, arson, alcohol, and tobacco smuggling laws;
>
> **(2)** the functions transferred by subsection (c) of section 1111 of the Homeland Security Act of 2002 (as enacted on the date of the enactment of such Act [enacted Nov. 25, 2002]); and
>
> **(3)** any other function related to the investigation of violent crime or domestic terrorism that is delegated to the Bureau by the Attorney General.

28 U.S.C. § 599A(b).

ATF is granted limited powers, which include being able to investigate criminal and regulatory violations of Federal firearms, explosives, arson, alcohol and tobacco smuggling laws,

as well as investigating violent crime or domestic terrorism that is delegated to the Bureau by the Attorney General.

None of the enumerated powers granted to ATF provide it the authority or ability to draft, modify or amend the 4473 nor the power to define an "unlawful user of or addicted to any controlled substance" or "fugitive from justice".

Further, even the Gun Control Act of 1968 ("GCA") does not give ATF the regulatory authority to draft, modify or amend the 4473 or promulgate a regulation relating to a "fugitive from justice". 18 U.S.C. § 926(a) provides:

> The Attorney General may prescribe only such rules and regulations as are necessary to carry out the provisions of this chapter [18 USCS §§ 921 et seq.], including—
>
> > **(1)** regulations providing that a person licensed under this chapter [18 USCS §§ 921 et seq.], when dealing with another person so licensed, shall provide such other licensed person a certified copy of this license;
> >
> > **(2)** regulations providing for the issuance, at a reasonable cost, to a person licensed under this chapter [18 USCS §§ 921 et seq.], of certified copies of his license for use as provided under regulations issued under paragraph (1) of this subsection; and
> >
> > **(3)** regulations providing for effective receipt and secure storage of firearms relinquished by or seized from persons described in subsection (d)(8) or (g)(8) of section 922 [18 USCS § 922].

Nowhere in the proscribing statute is there language that ATF has any such authority. Even if Section 926(a) were read to convey such power to regulate, that authority would rest with the FBI, not with ATF.

More importantly, ATF has already acknowledged in 27 C.F.R. § 478.11 that state-licensed physician prescribed marijuana for medicinal purposes is lawful and the Congress has already defined "fugitive from justice" in 18 U.S.C. § 921 as "…any person who has fled from any State to avoid prosecution for a crime or to avoid giving testimony in any criminal

proceeding." Therefore, both ATF and FBI lack the power to regulate contrary to the clear language enacted by the Congress.

* * *

Accordingly, pursuant to 28 C.F.R. §§ 25.6, 25.10, and 25.6, it is the FBI, not ATF, that is to determine whether an individual is prohibited under 18 U.S.C. § 922(g) and the Congress has already clearly defined a "fugitive from justice." Therefore, ATF is an inappropriate agency to regulate what constitutes a "fugitive from justice", because FBI has been empowered with the interpretation of 18 U.S.C. § 922(g), and FBI cannot proceed with defining a "fugitive from justice" because the Congress has already clearly defined it.[4]

II. Proposed Revision to Instructions for Question 11.d

ATF proposes to add the following language for instructions with regards to Question 11.d. Question 11.d reads "Are you a fugitive from justice?" The current version of the 4473 contains no instructions for this question. The proposed instructions read:

> Question 11.d. Fugitive from Justice: Any person who has fled from any State to avoid prosecution for a felony or a misdemeanor; or any person who leaves the State to avoid giving testimony in any criminal proceeding. The term also includes any person who knows that misdemeanor or felony charges are pending against such person and who leaves the State of prosecution. [5]

[4] As it is assumed that ATF will ignore this clear restriction on its power instead of requesting FBI to enter into rulemaking, the remaining issues are raised in the alternative, presupposing that ATF will find that it has authority to draft, modify or amend the 4473 and define or clarify "fugitive from justice."

[5] https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download at 4.

a. Fugitive from Justice as Defined by 18 U.S.C. § 921(a)(15)

Congress defined the term "fugitive from justice" when it passed the Gun Control Act of 1968 ("GCA"). The term "fugitive from justice" originally read "The term 'fugitive from justice' means any person who has fled from any State or possession to avoid prosecution for a crime punishable by imprisonment for a term exceeding one year or to avoid giving testimony in any criminal proceeding." [6] Congress modified the definition in October of 1968 to read, as it still does, "The term 'fugitive from justice' means any person who has fled from any State to avoid prosecution for a crime or to avoid giving testimony in any criminal proceeding." [7]

b. Fugitive from Justice as Defined by 27 C.F.R. § 478.11

ATF defined the term "fugitive from justice" when it modified the federal regulations in 1997. It defined the term "fugitive from justice" as

> Any person who has fled from any State to avoid prosecution for a felony or a misdemeanor; or any person who leaves the State to avoid giving testimony in any criminal proceeding. The term also includes any person who knows that misdemeanor or felony charges are pending against such person and who leaves the State of prosecution. [8]

ATF's definition mirrors that of the GCA with the addition of the last sentence adding a new class of individual to the term "fugitive from justice".

i. Comments ATF Received when Implementing its Regulatory Definition

ATF began to solicit comments with regard to proposed changes to its federal regulations on September 6, 1996 for a period of one (1) year. After the comment period closed, it received a

[6] Added June 19, 1968,P.L. 90-351, Title IV, § 902, 82 Stat. 226
[7] Added Oct. 22, 1968, P.L. 90-618, Title I, § 102, 82 Stat. 1214
[8] 27 C.F.R. § 478.11

total of eleven (11) comments, five (5) of which were relevant to the definition of "fugitive from justice".

In its response to the comment submitted by a federal agency, which stated the term was already defined in the GCA and as such any expansion would require an act of Congress, ATF responded that it was not seeking to expand the definition but rather clarify it. [9] ATF went on to state that

> …the statute does not spell out that to be a fugitive from justice it is not necessary that the person left a State with the intent of fleeing the charges. Rather, a person is a fugitive from justice if the individual, knowing that charges are pending, purposefully leaves the State of prosecution and does not appear before the prosecuting tribunal. Accordingly, ATF's proposed regulatory definition merely clarifies the statutory definition by covering these points. [10]

Yet, nowhere in the final definition of "fugitive from justice" does ATF include language that in order to be a fugitive from justice a person must purposefully leave the State of prosecution and fail to appear before the prosecuting tribunal. In fact, the person must only be aware of the pending charges and leave the State.

c. ATF Cannot Regulate the Definition of a "Fugitive from Justice" in these proceedings, as It Failed to Notify the Public of any such Intent and It Failed to Comply with 18 U.S.C. § 926(b)

As declared in *Connecticut Light & Power Co. v. NRC,* 673 F.2d 525, 528 (D.C. Cir. 1982), "[i]f the [NPR] fails to provide an accurate picture of the reasoning that has led the agency to the proposed rule, interested parties will not be able to comment meaningfully upon the agency's proposals." The court went on to find that an agency commits serious procedural

[9] 62 FR 34634 at 34636
[10] *Id*.

error when it fails to reveal the basis for a proposed rule in time to allow for meaningful commentary.

Moreover, 18 U.S.C. § 926(b) provides that ATF "shall give not less than ninety days public notice, and shall afford interested parties opportunity for hearing, before prescribing such rules and regulations."

As these proceedings failed to provide proper public notice and only afforded sixty days for comments, ATF lacks the authority to promulgate any definition in these proceedings.

d. In the Alternative, an Entirely New Class of Prohibited Persons Emerges Under ATF's Proposed Definition

Due to ATF's prior failure to clarify the definition of a "fugitive from justice" when it entered into rulemaking to promulgate the definition, it now seeks to create an entirely new class of prohibited persons.

ATF's proposed definition does not reflect the understanding that an individual is *required* to know that felony or *misdemeanor* charges are pending, leaves the state purposefully and does not appear before the prosecuting tribunal. In fact, ATF's proposed definition of "fugitive from justice" seemingly takes individuals who would not otherwise be prohibited and turns them into a "fugitive from justice".

In point of fact, if an individual resides in Pennsylvania, who knows he/she is charged with a Misdemeanor of the second degree[11] or a Misdemeanor of the third degree[12] (neither of which are federally prohibiting offenses, as they are not punishable by more than two years of

[11] *See* 18 Pa.C.S. § 106(b)(7) ("…if a person convicted thereof may be sentenced to a term of imprisonment, the maximum of which is not more than two years.")
[12] *See* 18 Pa.C.S. § 106(b)(8) ("…if a person convicted thereof may be sentenced to a term of imprisonment, the maximum of which is not more than one year.")

imprisonment), travels to a surrounding state on a vacation, shopping trip, etc., and attempts to purchase a gun, he/she would be unable to answer question 11d by checking "no" truthfully, even though the Congress never sought to prohibit an individual during charging, where even if convicted of the offenses, the individual would not be prohibited. The Congress only sought to prohibit an individual under charging from purchasing new firearms, where the individual would be prohibited if convicted of the charges, since one is presumed innocent until proven guilty. *Coffin v. United States*, 156 U.S. 432, 453 (1895)

With the proposed definition of "fugitive from justice," individuals who are not under charging for an offense that would result in a prohibition and regardless of their intent to return to the state to answer for the charges, would be proscribed from completing the 4473.

III. Proposed Revision to Question 11.e

For brevity, FICG joins in and supports all of Cannabis Industry Law Group's ("CILG") Comment, which, *inter alia*, proposes that ATF specifically find that users of state-licensed physician prescribed marijuana for medicinal purposes are not "unlawful user of or addicted to any controlled substance", pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11, or, in the alternative, that ATF stay these proceedings pending the outcome of the Drug Enforcement Administration's review and consideration of the removal or re-scheduling of marijuana.

IV. Proposed Revision to the Instructions for Box 20

Box 20 on the proposed 4473 reads "No NICS check was required because a background check was completed during the NFA approval process on the individual who will receive the NFA firearm(s), as reflected on the approved NFA application." [13]

The proposed instructions read:

> **Questions 20 and 21. NICS EXCEPTIONS**: A NICS check is not required if the transfer qualifies for any of the exceptions in 27 CFR 478.102(d). Generally these include: (a) transfers of National Firearms Act firearms to an individual who has undergone a background check during the NFA approval process; (b) transfers where the transferee/buyer has presented the licensee with a permit or license that allows the transferee/buyer to possess, acquire, or carry a firearm, and the permit has been recognized by ATF as a valid alternative to the NICS check requirement; or (c) transfers certified by ATF as exempt because compliance with the NICS check requirements is impracticable. If the transfer qualifies for one of these exceptions, the licensee must obtain the documentation required by 27 CFR 478.131. A firearm must **not** be transferred to any transferee/buyer who fails to provide such documentation.
>
> *A NICS check must be conducted if an NFA firearm has been approved for transfer to a trust, or to a legal entity such as a corporation, and no background check was conducted as part of the NFA approval process on the individual who will receive the firearm. Individuals who have undergone a background check during the NFA application process are listed on the approved NFA transfer form.* [14]

(Emphasis added).

While ATF 41F was designed to purportedly solve the issue of individuals using legal entities to acquire NFA firearms without a background check, ATF instructs licensees to conduct background checks on the individual receiving the firearm if they were not listed on the NFA application. [15]

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[13] https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download
[14] *Id*.
[15] ATF violated numerous administrative law requirements during the rulemaking process of ATF 41P/F, failed to account for a single instance where prohibited persons utilized a legal entity to acquire an NFA firearm to avoid a background check (purportedly the entire premise of the rulemaking process) and seemingly colluded with the National Firearms Act Trade and

a. Pennsylvania's Instant Check System and the Inability to Utilize it to Perform Background Checks on Individuals Receiving Certain NFA Firearms

Pennsylvania law defines the term "firearm" as

> Any pistol or revolver with a barrel length less than 15 inches, any shotgun with a barrel length less than 18 inches or any rifle with a barrel length less than 16 inches, or any pistol, revolver, rifle or shotgun with an overall length of less than 26 inches. The barrel length of a firearm shall be determined by measuring from the muzzle of the barrel to the face of the closed action, bolt or cylinder, whichever is applicable.

18 Pa.C.S. § 6102.

While Pennsylvania's definition of a firearm would include that of a short barrel rifle and short barrel shotgun, the term is noticeably devoid of any reference to a silencer or firearm muffler.

As Pennsylvania is a "point of contact state" for utilizing the National Instant Check System, all background checks must go through the Pennsylvania State Police. The uses for the Pennsylvania Instant Check System (PICS) are defined in 18 Pa.C.S. § 6111(b). The statute, in the pertinent part, reads:

> No … licensed dealer shall sell or deliver any **firearm** to another person … until the conditions of subsection (a) have been satisfied and until he has:
> (1) For purposes of a firearm as defined in section 6102 (relating to definitions), obtained a completed application/record of sale from the potential buyer or transferee…
> (2) Inspected photo identification of the potential purchaser or transferee…
> (3) Requested by means of a telephone call that the Pennsylvania State Police conduct a criminal history, juvenile delinquency history and a mental health record check.
> (4) Received a unique approval number for that inquiry from the Pennsylvania State Police and recorded the date and the number on the application/record of sale form.
> (5) Issued a receipt containing the information from paragraph (4), including the unique approval number of the purchaser….

18 Pa.C.S. § 6111(b). (Emphasis added).

Collectors Association (NFATCA) in order to institute a cumbersome, unneeded and questionable regulatory scheme with regard to legal entities and NFA firearms.

Pennsylvania law even expands the definition of firearm, solely for the purpose of this section to read "… 'firearm' shall mean any weapon which is designed to or may readily be converted to expel any projectile by the action of an explosive or the frame or receiver of any such weapon." 18 Pa.C.S. § 6111(f). Yet, even with the expanded definition, there is nothing that would include a silencer in the term firearm.

To make matters worse, ATF would now be instructing dealers to violate state law and commit a *felony* of the third degree. 18 Pa.C.S. § 6111(g)(3) is instructive, stating

> Any … licensed dealer … who knowingly and intentionally requests a criminal history, juvenile delinquency or mental health record check or other confidential information from the Pennsylvania State Police under this chapter for **any purpose other than compliance with this chapter … commits a felony of the third degree**.

(Emphasis added). Regardless of ATF's instructions, a Pennsylvania dealer *cannot* utilize PICS to run a background check on an individual who is picking up a silencer from a licensee. Surely there are other point of contact states which present the same or similar problem.

V. The Proposed 4473 Fails to Include a Field for Firearms Being Received on Behalf of a Legal Entity

One of the issues that licensees face when disposing of a firearm to an individual on behalf of a legal entity is that ATF offers no sample forms, wording, etc., beyond the instructions for Section A. This has not been changed in the current proposed iteration of the 4473.

FICG urges ATF to promulgate a field that would allow a licensee to mark that the firearm is being disposed of to a legal entity and include an area for the licensee or transferee/buyer to list the name and address of the legal entity, as is provided for on the ATF Form 1 and Form 4 forms.

This would eliminate the need of licensees to have to promulgate their own form, store them with the corresponding 4473, and have any violations levied against them for not having the statement with all the required information or in the format preferred by the Industry Operations Inspector.

ATF could revise the language in the certification statement to include language to the effect that if the firearm being transferred is done to an officer authorized to act on behalf of the entity, the firearm is being acquired for the use and will be the property of the entity.

This simple solution would reduce the paperwork burden on licensees and allow ATF to collect all of the required information on one form, as is done with the ATF Form 1 and Form 4.

VI. The Certification Statement for Transferors

While ATF revised the certification statement for Transferors to reflect that "[u]nless this transaction has been denied or cancelled, I further certify on the basis of.." to properly allow an individual to complete boxes 34-36, the statement still presents issues.

Specifically, the individual is certifying that based on the "information in the current ATF Publication '*State Laws and Published Ordinances*' – it is my belief that it is not unlawful for me to sell, deliver, transport, or otherwise disposes of the firearm(s) listed on this form to the person identified in Section A." The current publication of ATF's *State Laws and Published Ordinances*, as of the writing of this comment, is the 31st Edition, which was published in 2011 and contains laws and ordinances effective through January 2011. This results in *at least* a 5-year lapse of current information.

While not all inclusive, since January of 2011, New York implemented its blatantly unconstitutional Secure Ammunition and Firearms Enforcement (SAFE) Act [16], Washington began universal background checks on all firearms transfers [17], Colorado banned the manufacture or ability to purchase "high capacity" (read "standard capacity") magazines [18], Connecticut deprived its citizens of the ability to transfer and/or possess "assault weapons" (read "America's Rifle, Modern Sporting Rifles and Arms") [19], Maryland criminalized the ability for an individual to manufacture, sell, offer for sale, purchase, receive, or transfer a detachable magazine that has a capacity of more than 10 rounds of ammunition for a firearm [20], California is in the process of passing even more laws to criminalize a fundamental constitutional right [21] and three (3) states have legalized silencer ownership [22].

Thus a licensee/employee is left to guess whether they transferred the firearm in accordance with the actual state law or ordinance (if the transferee/buyer is a non resident purchasing a long gun). This puts licensees in a precarious position as many states have recently changed their laws, including the ban on modern sporting rifles such as the AR-15 or "America's Rifle".

Further, ATF's *own regulations* require that "[t]he Director *shall* annually revise and furnish Federal firearms licensees with a compilation of State laws and published ordinances which are relevant to the enforcement of this part." [23] In an interesting twist of fate, the ATF has *failed to comply with its own regulations* that it promulgated in 1988 and amended in 2004,

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[16] *See* http://legislation.nysenate.gov/pdf/bills/2013/S2230
[17] *See* Rev. Code Wash. (ARCW) § 9.41.113
[18] *See* Colo. Rev. Stat. §§ 18-12-301 through 18-12-303
[19] *See* Conn. Gen. Stat. § 53-202b - § 53-202o
[20] *See* Md. Criminal Law Code Ann. § 4-305
[21] *See* http://www.reuters.com/article/us-california-politics-guncontrol-idUSKCN0YO05Y
[22] *See* http://americansuppressorassociation.com/education/
[23] *See* 27 C.F.R. § 478.24

which will come with no repercussions, yet if a licensee were to fail compliance with the regulations, ATF would likely take the position the licensee "willfully violated the Gun Control Act and its regulations".

CONCLUSION

For the reasons set-forth above, ATF lacks the authority to define or clarify what constitutes an "unlawful user of or addicted to any controlled substance" or "fugitive from justice".

ATF should thoroughly consider the suggestions and comments in opposition to proposed changes contained in this comment as well as the implications of the proposed changes. Additionally, as the statutory and regulatory requirements of licensees to correctly complete and retain the 4473 are quite arduous, ATF must promulgate a form that is easy for licensees to complete.

Respectfully submitted,

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Counsel
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Chief Counsel

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888-313-0416

Date: June 6, 2015

Block 1—IO and NMN check boxes to be added-This will eliminate the abbreviations being added to the search and messing up the algorithm. (Saves the initial R from turning into RIO.)

Question 32—Add instructions for the FFL to denote it is a private sale when they conduct the check thru NICS? Is there a way to alert the FFL closer to block 16 of the private sale issue?

Instructions 9, last sentence—Recommend rewording "The licensee should provide the UPIN when conducting a background check through the NICS or the State POC."

Instructions 11 e—Regarding the Warning—If we are now able to provide a clarification of the prohibitor. Let's give them some that will reduce appeals at the same time. Add – A conviction for use or possession of a controlled substance with in the past year and multiple arrests for use or possession of a controlled substance within the past five years remains unlawful under Federal law. Is it possible to add to the instructions for this prohibitor also?

Instructions 19—The licensee must also check the "Overturned" box and attach the overturn certificate issued by NICS or the State POC to the ATF Form 4473. (This is not required to be issued on all overturns. This would hinder or eliminate all NPPs from ATF Field Offices if left in place and also any incorrect denial decision that was found during quality review.)

Instructions 20—A new background check doesn't have to be ran if there was a background check completed during the NFA approval process. Is there a time constraint of any kind (i.e., a background check must be ran if the NFA check is over 30-days old)? (Helen—This is in relation to the NICS with III. The record is only good for 30 days and then must be run again.)

Bureau of Alcohol, Tobacco, Firearms, and Explosives

Agency Information Collection Activities Firearms Transaction Record (ATF Form 4473 (5300.9))	)

Cannabis Industry Law Group's Comments as to ATF's Proposed Changes to the Firearms Transaction Record (ATF Form 4473 (5300.9))

On April 7, 2016, the Bureau of Alcohol, Tobacco, Firearms, and Explosives ("ATF" or the "Agency") published a notice in the Federal Register requesting comments on proposed changes to the Firearms Transaction Record (ATF Form 4473 (5300.9)) ("4473"), pursuant to the Paperwork Reduction Act, 44 U.S.C. §§ 3501-3520.

Cannabis Industry Law Group ("CILG"), a division of Civil Rights Defense Firm, P.C., provides legal representation and consultation services to businesses, professionals and individuals with regards to interpretation of marijuana laws in the Commonwealth of Pennsylvania and at the federal level. CILG guides businesses, non-profit organizations and professionals in the creation and operation of lawful medical marijuana businesses, including adoption of appropriate practices and obtaining requisite licenses. Additionally, CILG represents patients and caregivers through the intricacies of securing access to cannabis medication and protecting and defending their individual and inalienable rights as impacted by such use.

The purpose of CILG is to protect, defend and assert the legal rights of businesses, professionals and individuals to operate lawful cannabis-related businesses and professions and to use cannabis medication without discrimination.

CILG's interest in this matter stems from its representation of and consultation with numerous lawful cannabis-related businesses, professionals and individuals in Pennsylvania and nationwide, who would be required to use the proposed form if ATF were to modify it as proposed. In response to the request for comment, CILG offers this public comment for consideration.

CILG opposes ATF's inclusion on the draft 4473 the new statement that medically prescribed marijuana and its use by a patient results in the patient being prohibited under 18 U.S.C. § 922(g)(3). CILG offers some additional suggestions for consideration for the reasons set forth below and in the Exhibits to this Comment incorporated herein by reference. In the alternative, CILG requests that ATF delay implementing the proposed language until the Drug Enforcement Agency ("DEA") completes its review of whether to reclassify or remove marijuana in its entirety from Schedule I under the Controlled Substances Act ("CSA"), 21 U.S.C. §§ 801, *et seq*.

I. ATF Is Not the Appropriate Agency for Drafting, Modifying, or Amending the 4473 nor is it the Appropriate Agency for Defining or Clarifying What Constitutes an "Unlawful User of or Addicted to Any Controlled Substance"

For brevity, CILG joins in and supports all of Firearms Industry Consulting Group's ("FICG") Comment, which, *inter alia*, correctly argues that ATF is neither the appropriate agency for drafting, modifying or amending the 4473 nor is it the appropriate agency for defining or clarifying what constitutes an "unlawful user of or addicted to any controlled substance." *See*, *United States v. Mead Corp.*, 533 U.S. 218 (2001).

CILG additionally challenges whether FBI is the appropriate agency to define an "unlawful user of or addicted to any controlled substance," when DEA is responsible for interpreting the CSA.

a. DEA's Statutory and Regulatory Authority

Pursuant to 21 U.S.C. § 811, the Attorney General is empowered to administer, regulate and enforce the CSA. The Attorney General has delegated this authority to the DEA, pursuant to 28 C.F.R. § 0.100(b)[1] – not to ATF.

Pursuant to 28 C.F.R. § 0.100(b),

> The following-described matters are assigned to, and shall be conducted, handled, or supervised by, the Administrator of the Drug Enforcement Administration
> …
> (b) Except where the Attorney General has delegated authority to another Department of Justice official to exercise such functions, and except where functions under 21 U.S.C. 878(a)(5) do not relate to, arise from, or supplement investigations of matters concerning drugs, functions vested in the Attorney General by the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. This will include functions which may be vested in the Attorney General in subsequent amendments to the Comprehensive Drug Abuse Prevention and Control Act of 1970, and not otherwise specifically assigned or reserved by him.

More importantly and as discussed more in-depth *infra*, pursuant to 21 U.S.C. §§ 811-812, the placement of drugs or other substances into schedules under the CSA is based upon the substance's medical use, potential for abuse, and safety or dependence liability. Section 811 also provides a mechanism for substances to be added to a schedule, decontrolled, or removed from the scheduling framework altogether, and rescheduled or transferred from one schedule to

[1] *See also*, Congressional Research Service, *The Controlled Substances Act: Regulatory Requirements*, by Brian T. Yeh, Dec. 13, 2012, at 1, *available at* https://fas.org/sgp/crs/misc/RL34635.pdf, declaring that DEA "administers and enforces the CSA." A copy is also attached as Exhibit 1.

another.

In compliance with Section 811, DEA, in conjunction with the U.S. Department of Health and Human Services ("HHS"), is actively in the process of reviewing whether marijuana should be rescheduled or completely removed from all schedules given its medical benefits, low potential for abuse and general lack of tendency to create user-dependence.[2] In relation to the question of whether "DEA has received the HHS evaluations and scheduling recommendations," DEA responds that it "has received the HHS scientific and medical evaluations, as well as a scheduling recommendation, and is currently reviewing these documents and all other relevant data to make a scheduling determination in accordance with the CSA." *See*, Exhibit 2 at 6. DEA also responded in relation to when a determination might be made that it hopes to "release its determination in the first half of 2016." *Id*.

Accordingly, it is blatantly clear that it is DEA, not ATF, that is the appropriate agency for determining whether an individual is an unlawful user or addicted to a controlled substance under the CSA and 18 U.S.C. § 922(g)(3).[3]

---

[2] April 4, 2016 Letter of Chuck Rosenberg, Acting Administrator of Drug Enforcement Administration, Sylvia M. Burwell, Secretary of U.S. Department of Health and Human Services, and Michael Botticelli, Director of the Office of National Drug Control Policy. A copy is attached as Exhibit 2.

See also, http://fortune.com/2016/04/06/dea-decision-marijuana-reschedule/; http://www.huffingtonpost.com/entry/dea-marijuana-reschedule_us_5704567de4b0537661881644; https://www.washingtonpost.com/news/wonk/wp/2016/04/06/the-dea-will-decide-whether-to-change-course-on-marijuana-by-july/; http://abcnews.go.com/Health/federal-reclassification-marijuana-major-impact-medical/story?id=38308268/.

[3] As it is assumed that ATF will ignore this clear restriction on its power instead of requesting DEA to enter into rulemaking or finalize its rescheduling of marijuana, the remaining issues are raised in the alternative, presupposing that ATF will find that it has authority to draft, modify or amend the 4473 and define or clarify "unlawful user of or addicted to any controlled substance."

II. Proposed Revision to Instructions for Question 11.e

ATF proposes to modify the language on the 4473 and the instructions with regards to Question 11.e.

Question 11.e currently inquires, "Are you an unlawful user of, or addicted to, marijuana or any depressant, stimulant, narcotic drug, or any other controlled substance?" The current instructions for this question, Section A, Question 11.b – 11.l, merely recite the language found in Question 11.e.

The newly proposed language for Question 11.e reads:

> Question 11.e. Are you an unlawful user of, or addicted to, marijuana or any depressant, stimulant, narcotic drug, or any other controlled substance? **Warning: The use of possession of marijuana remains unlawful under Federal law regardless of whether it has been legalized or decriminalized for medicinal or recreational purposes in the state where you reside**. [4]

The instructions for 11.e, found in Section A, Question 11.b – 12, have not been modified on the newly proposed 4473.

a. The Statutory and Regulatory Definitions of an "Unlawful User of or Addicted to any Controlled Substance"

The statutory and regulatory enactments contradict ATF's proposed language for Question 11.e.

i. Unlawful User or Addicted to Any Controlled Substance as Defined by 18 U.S.C. § 921(g)(3)

Congress defined the term "unlawful user of or addicted to any controlled substance" by adding the explanation of (as defined in section 102 of the Controlled Substances Act (21 U.S.C. 802))." 18 U.S.C. § 922(g)(3).

[4] https://www.atf.gov/resource-center/docs/form-example-firearms-transaction-record/download at 4.

ii. Unlawful User of or Addicted to Any Controlled Substance as Defined by 27 C.F.R. § 478.11

ATF defined the term "unlawful user of or addicted to any controlled substance," as

> *Unlawful user of or addicted to any controlled substance*. A person who uses a controlled substance and has lost the power of self-control with reference to the use of controlled substance; and any person who is a current user of a controlled substance in a manner other than as prescribed by a licensed physician. Such use is not limited to the use of drugs on a particular day, or within a matter of days or weeks before, but rather that the unlawful use has occurred recently enough to indicate that the individual is actively engaged in such conduct. A person may be an unlawful current user of a controlled substance even though the substance is not being used at the precise time the person seeks to acquire a firearm or receives or possesses a firearm. An inference of current use may be drawn from evidence of a recent use or possession of a controlled substance or a pattern of use or possession that reasonably covers the present time, e.g., a conviction for use or possession of a controlled substance within the past year; multiple arrests for such offenses within the past 5 years if the most recent arrest occurred within the past year; or persons found through a drug test to use a controlled substance unlawfully, provided that the test was administered within the past year. For a current or former member of the Armed Forces, an inference of current use may be drawn from recent disciplinary or other administrative action based on confirmed drug use, e.g., court-martial conviction, nonjudicial punishment, or an administrative discharge based on drug use or drug rehabilitation failure. [5] (Emphasis added)

b. The Medicinal Use of Marijuana is Lawful

As discussed *infra*, the medicinal use of marijuana, prescribed by a licensed physician, is already acknowledged as lawful and does not result in a prohibition, pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11.

i. The Regulations Already Acknowledge that Licensed Physician Prescribed Marijuana is Lawful and Does Not Trigger a Prohibition, pursuant to 18 U.S.C. § 922(g)(3)

As set-forth in the regulatory definition enacted by ATF in Section 478.11, an individual

[5] 27 C.F.R. § 478.11

is only prohibited pursuant to 18 U.S.C. § 922(g)(3), where the individual is a "current user of a controlled substance in a manner other than as prescribed by a licensed physician." (emphasis added). Although there exists federal standards governing medical training and testing, "each state has its own licensing board, and doctors must procure a license for every state in which they practice medicine." [6]

Accordingly, the law already acknowledges that a patient's use of state-licensed physician prescribed marijuana for medicinal purposes does not result in the patient becoming prohibited under Section 922(g)(3).[7] Therefore, ATF's proposed language of "**Warning: The use or possession of marijuana remains unlawful under Federal law regardless of whether it has been legalized or decriminalized for medicinal or recreational purposes in the state where you reside**" is in direct contravention to Section 478.11.

ii. The Oregon Supreme Court has Declared that State-Licensed Physician Prescribed Marijuana for Medicinal Purposes is Lawful

In *Willis v. Winters*, 350 Ore. 299, 253 P.3d 1058 (2011), the Supreme Court of Oregon reviewed whether an individual was prohibited from obtaining a firearm license, as a result of the petitioner's use of medically prescribed marijuana, pursuant to the Oregon Medical Marijuana

[6] *See*, http://healthaffairs.org/blog/2014/02/18/doctors-without-state-borders-practicing-across-state-lines/. *See also*, http://www.ama-assn.org/ama/pub/education-careers/becoming-physician/medical-licensure.page.

[7] ATF does not purport in this proceeding to revise or amend its regulatory definition of "unlawful user of or addicted to any controlled substance" in 27 C.F.R. § 478.11 and the revision of instructions in a form would seem to present an inappropriate means to circumvent the APA process for revising the applicable regulation. Moreover, ATF failed to provide notice to the public of any such intent and it would violate 18 U.S.C. § 926(b), since it requires that ATF "shall give not less than ninety days public notice, and shall afford interest parties opportunity for hearing, before prescribing such rules and regulations."

Act, ORS 475.300, *et seq*. The Supreme Court found that an individual utilizing medicinal marijuana could not be denied from obtaining the license by the Sheriff. *Id*. at 317.

In light of the general trend in favor of permitting use of marijuana for medicinal purposes, as reflected by Oregon's determination that its firearm laws needed to exempt medicinal use authorized under its laws, an ATF statement to the contrary would sow confusion and work at cross-purposes with both other federal agencies as well as the determinations of various States.

iii. ATF Should Acknowledge that a Patient's Use of State-Licensed Physician Prescribed Marijuana for Medicinal Purposes is Lawful

For the reasons set-forth *supra*, ATF should change the proposed language in 11.e to "**The use or possession of marijuana in relation to a physician's prescription is lawful solely for medicinal purposes, if lawful in your state. All other uses or possession of marijuana remains unlawful, regardless of whether decriminalized in your state.**"

* * *

Accordingly, as state-licensed physician prescribed marijuana for medicinal purposes is lawful, pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11, ATF should modify the proposed text to specifically acknowledge such.

c. In the Alternative, ATF Should Delay These Proceedings, Until DEA Issues a Determination

Alternatively, as DEA is already in the process of determining whether marijuana should

be removed from or rescheduled under the CSA, ATF should delay these proceedings until DEA issues a determination, which is expected in the next several months.

i. DEA's Scheduling of Drugs and Other Substances

As discussed *supra*, the placement of drugs or other substances into schedules under the CSA is based upon the substance's medical use, potential for abuse, and safety or dependence liability. Section 811 of the CSA also provides a mechanism for substances to be added to a schedule, decontrolled, or removed from the scheduling framework altogether, and rescheduled or transferred from one schedule to another.

The proceedings to add, delete, or change the schedule of a drug or substance may be initiated by the DEA, the HHS, or by petition by any interested person. 21 U.S.C. § 811(a). When a petition is received by the DEA, the agency initiates its own investigation of the drug or substance. The DEA may also initiate an investigation at any time in response to information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

> After the DEA's initial investigation, the DEA Administrator (Administrator) requests from the Assistant Secretary of Health of HHS (Assistant Secretary of Health) a scientific and medical evaluation and recommendation as to whether the drug or substance should be controlled or removed from control. The Assistant Secretary of Health in turn solicits information from the Commissioner of the Food and Drug Administration, and obtains evaluations and recommendations from the National Institute on Drug Abuse. The Assistant Secretary of Health then consolidates the requested information and transmits back to the DEA a medical and scientific evaluation regarding the drug or substance, along with a recommendation as to whether the drug or substance should be controlled and into which schedule it should be placed.
>
> The Administrator then evaluates all of the relevant data and makes a final determination as to whether the drug or substance should be controlled or removed entirely from control. In making a determination regarding the control of a drug or substance, the Administrator must consider factors such as the drug's actual or relative potential for

> abuse; scientific evidence of its pharmacological effect; the current state of scientific knowledge regarding the drug or substance; the risk to the public health; and whether the substance is an immediate precursor of a substance already controlled under the act. After the Administrator makes such a determination, he must make specific findings concerning the drug or substance that dictate the schedule in which the substance will be placed.
> *See*, Exhibit 1, at 1-2.

As reflected in Exhibit 2, Acting Administrator Chuck Rosenberg of the DEA acknowledges that DEA is currently in the process of reviewing whether marijuana should be removed from or rescheduled under the CSA.

ii. Marijuana's Medical Benefits, Low Potential for Abuse and General Lack of Dependence Liability all Support it being Removed, or at a Minimum, Re-Scheduled

As reflected in Exhibits 3 and 4, there exists substantial medical research and literature indicating the beneficial medicinal qualities of marijuana use, as well as, the low potential for abuse and general lack of dependence liability. The beneficial medicinal uses include:

> Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, post-traumatic stress disorder, or the treatment of these conditions, and
>
> A chronic or debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia or wasting syndrome; severe, debilitating pain; severe nausea; seizures; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis

Exhibit 1, at 1.

Furthermore, the Institute of Medicine published a monumental publication on *Marijuana and Medicine, Assessing the Science Base*. A copy is attached as Exhibit 4. While extensive, some of the findings include that "[t]he accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and

vomiting, and appetite stimulation," "[t]he evidence is relatively strong for the treatment of pain and, intriguing although less well established, for movement disorders," "[fo]r patients such as those with AIDS or who are undergoing chemotherapy and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication," and "[t]he most encouraging clinical data on the effects of cannabinoids on chronic pain are from three studies of cancer pain." *Id*., at 3, 70, 177, and 142.

Additionally, medical marijuana is not likely to be abused and does not lead to other more dangerous drugs – "[t]here is no evidence that marijuana serves as a stepping stone on the basis of its particular physiological effect" and "[i]nstead, the legal status of marijuana makes it a gateway drug." *Id*., at 99.

* * *

As the requisite criteria has been established under Section 811 for removal or re-scheduling of marijuana, in the event ATF contends that state-licensed physician prescribed marijuana for medicinal purposes is unlawful, these proceedings should be stayed until DEA can make a determination on whether to remove or re-schedule marijuana, as otherwise, the proposed printed forms will have to be thrown out, resulting in a loss of taxpayer money, and new forms proposed and printed with additional costs incurred at the expense of the taxpayers.

CONCLUSION

For the reasons set-forth above, as state-licensed physician prescribed marijuana for medicinal purposes is lawful, pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11, ATF should modify the proposed text to specifically acknowledge such.

In the alternative, ATF should stay these proceedings until DEA can make a determination on whether to remove or re-schedule marijuana.

Respectfully submitted,

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Date: June 6, 2015

Exhibit 1

The Controlled Substances Act: Regulatory Requirements

Brian T. Yeh
Legislative Attorney

December 13, 2012

Congressional Research Service
7-5700
www.crs.gov
RL34635

CRS Report for Congress
Prepared for Members and Committees of Congress

Summary

This report highlights certain non-criminal regulatory requirements of the Controlled Substances Act (CSA). The CSA and its implementing regulations establish a framework through which the federal government regulates the use of controlled substances for legitimate medical, scientific, research, and industrial purposes, and prevents these substances from being diverted for illegal purposes. The CSA assigns various plants, drugs, and chemicals (such as narcotics, stimulants, depressants, hallucinogens, and anabolic steroids) to one of five schedules based on the substance's medical use, potential for abuse, and safety or dependence liability. Schedule I contains substances that have no currently accepted medical use and cannot safely be made available to the public under a prescription, while Schedules II, III, IV, and V include substances that have recognized medical uses and may be manufactured, distributed, and used in accordance with the CSA. The order of the schedules reflects substances that are progressively less dangerous and addictive. To restrict access to chemicals used in the illicit manufacture of certain controlled substances, the CSA also regulates 40 "listed chemicals." Furthermore, the CSA regulates controlled substance "analogues," which are substances that are not controlled but are structurally or pharmacologically similar to substances found in Schedule I or II and have no accepted medical use.

Unless specifically exempted by the CSA, any person who handles controlled substances or listed chemicals (such as drug manufacturers, wholesale distributors, doctors, hospitals, pharmacies, and scientific researchers) must register with the Drug Enforcement Administration (DEA) in the U.S. Department of Justice, which administers and enforces the CSA. Registrants must keep accurate and complete records of all transactions involving controlled substances, maintain detailed inventories of the substances in their possession, and periodically file reports with the DEA, as well as ensure that controlled substances are securely stored and safeguarded in accordance with DEA regulations.

Between 10%-11% of all drug prescriptions written in the United States are for pharmaceutical controlled substances. Only licensed medical practitioners (who are registered with the DEA) are authorized to prescribe controlled substances listed in Schedules II-V to patients; such prescriptions may only be issued by a practitioner who is "acting in the usual course of his professional practice," and for a "legitimate medical purpose." The CSA authorizes the DEA Administrator to suspend or revoke a physician's prescription privileges upon a finding that he has "committed such acts as would render his registration ... inconsistent with the public interest."

While the CSA provides criminal sanctions for *illicit* possession, manufacture, or distribution of controlled substances, the statute also contains a few noteworthy penalty provisions that are specifically applicable to persons who are authorized by the DEA to handle controlled substances lawfully. The CSA sets forth certain offenses involving listed chemicals and DEA registration and other prohibited acts relating to registrants who manufacture, distribute, and dispense controlled substances.

Contents

Appendixes

Contacts

The Controlled Substances Act (CSA or the act)[1] is the statutory framework through which the federal government regulates the lawful production, possession, and distribution of controlled substances. The CSA places various plants, drugs, and chemicals (such as narcotics, stimulants, depressants, hallucinogens, and anabolic steroids) into one of five schedules based on the substance's medical use, potential for abuse, and safety or dependence liability. Further, the act requires persons who handle controlled substances or listed chemicals (such as drug manufacturers, wholesale distributors, doctors, hospitals, pharmacies, and scientific researchers) to register with the Drug Enforcement Administration (DEA) in the U.S. Department of Justice, which administers and enforces the CSA. Registrants must maintain detailed records of their respective controlled substance inventories as well as establish adequate security controls to minimize theft and diversion.[2] Although the CSA sets forth criminal provisions[3] for the unlawful manufacture, possession, and distribution of controlled substances, this report will instead focus on the act's non-criminal regulatory requirements[4] for those who legitimately produce, distribute, and dispense controlled substances.

Formal Scheduling

The placement of drugs or other substances into schedules under the CSA is based upon the substance's medical use, potential for abuse, and safety or dependence liability.[5] The act further provides a mechanism for substances to be controlled,[6] or added to a schedule; decontrolled, or removed from the scheduling framework altogether; and rescheduled or transferred from one schedule to another.[7]

The proceedings to add, delete, or change the schedule of a drug or substance may be initiated by the DEA, the U.S. Department of Health and Human Services (HHS), or by petition by any interested person.[8] When a petition is received by the DEA, the agency initiates its own investigation of the drug or substance. The DEA may also initiate an investigation at any time in response to information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

After the DEA's initial investigation, the DEA Administrator (Administrator)[9] requests from the Assistant Secretary of Health of HHS (Assistant Secretary of Health) a scientific and medical

[1] 21 U.S.C. §§ 801 et seq.

[2] *See* 21 C.F.R. § 1304.11(a) ("Each inventory shall contain a complete and accurate record of all controlled substances on hand ..."); *see also* 21 C.F.R. § 1301.74(a) ("All applicants and registrants shall provide effective controls to guard against theft and diversion of controlled substances ...").

[3] For a detailed summary of the CSA's criminal provisions, *see* CRS Report RL30722, *Drug Offenses: Maximum Fines and Terms of Imprisonment for Violation of the Federal Controlled Substances Act and Related Laws*, by Brian T. Yeh.

[4] This report does not cover all the requirements under the CSA, nor does it address state controlled substances regulations. Although federal and state governments both regulate controlled substances, federal law preempts state law when state law conflicts with the CSA. 21 U.S.C. § 903.

[5] 21 U.S.C. §§ 811-812.

[6] For the purposes of the CSA, the term "control" as defined by 21 U.S.C. § 802(5) means "to add a drug or other substance, or immediate precursor, to a schedule under [§ 812 of the act], whether by transfer from another schedule or otherwise."

[7] The procedures for these actions are found at 21 U.S.C § 811.

[8] 21 U.S.C. § 811(a).

[9] Although the CSA grants to the Attorney General the authority to enforce its provisions, 21 U.S.C. §§ 801 et seq., the Attorney General has delegated this authority to the DEA Administrator at 28 C.F.R. § 0.100(b). Accordingly, the term (continued...)

evaluation and recommendation as to whether the drug or substance should be controlled or removed from control.[10] The Assistant Secretary of Health in turn solicits information from the Commissioner of the Food and Drug Administration, and obtains evaluations and recommendations from the National Institute on Drug Abuse. The Assistant Secretary of Health then consolidates the requested information and transmits back to the DEA a medical and scientific evaluation regarding the drug or substance, along with a recommendation as to whether the drug or substance should be controlled and into which schedule it should be placed.[11]

The Administrator then evaluates all of the relevant data and makes a final determination as to whether the drug or substance should be controlled or removed entirely from control.[12] In making a determination regarding the control of a drug or substance, the Administrator must consider factors such as the drug's actual or relative potential for abuse; scientific evidence of its pharmacological effect; the current state of scientific knowledge regarding the drug or substance; the risk to the public health; and whether the substance is an immediate precursor of a substance already controlled under the act.[13] After the Administrator makes such a determination, he must make specific findings concerning the drug or substance that dictate the schedule in which the drug or substance will be placed.[14]

Congress may also add a substance to a schedule through legislation.

Emergency or Temporary Scheduling

The CSA was amended by the Comprehensive Crime Control Act of 1984[15] to include a provision allowing the Administrator to place a drug or substance, on a temporary basis, into Schedule I when necessary to avoid an "imminent hazard to public safety."[16] The Administrator, however, may not issue a temporary scheduling order until thirty days after he notifies both the public and the HHS Secretary of his intent to issue the temporary scheduling order and of his justification for issuing the order.[17] Further, the Administrator must consider any of the HHS Secretary's comments regarding the temporary order.[18]

When issuing a temporary scheduling order, the Administrator must consider, with respect to the finding of an imminent hazard to public safety (i) the history of the drug or substance and its

(...continued)

"Administrator" will be used instead of the term "Attorney General" for the remainder of this report.

[10] 21 U.S.C. § 811(b).

[11] The medical and scientific evaluations are binding on the DEA with respect to such matters and form a part of the scheduling decision. The recommendation on the initial scheduling of a substance is binding only to the extent that if HHS recommends that the drug or substance not be controlled, the DEA may not add it to its schedules. *Id*.

[12] *Id*.

[13] *See* 21 U.S.C. § 811(c)(1)-(8) (complete listing of factors Administrator must consider when determining control or removal of substances from schedules).

[14] *See* 21 U.S.C. § 812(b) ("[A] drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance"). For a summary of the findings necessary for Schedules I-V, *see* **Appendix**.

[15] P.L. 98-473.

[16] 21 U.S.C. § 811(h)(1).

[17] *Id*.

[18] 21 U.S.C. § 811(4).

current pattern of abuse; (ii) the scope, duration, and significance of the drug or substance's abuse; (iii) the risk to public health; (iv) diversion of the drug or substance from legitimate channels; and (v) the drug or substance's "clandestine importation, manufacture, or distribution."[19] A drug or substance may be temporarily scheduled for two years and possibly longer—up to an additional year—if formal scheduling procedures have been initiated.[20] This emergency scheduling applies only to substances with no accepted medical use in the United States.

Listed Chemicals

In an effort to restrict access to chemicals used in the illicit manufacture of certain controlled substances in violation of the CSA, Congress passed the Chemical Diversion and Trafficking Act (CDTA) in 1988.[21] The CDTA and its subsequent amendments[22] allow the DEA to control 40 chemicals[23] and restrict their diversion. These 40 chemicals are referred to by the CSA as "listed chemicals."[24] Listed chemicals are divided into two categories: List I[25] and List II.[26] While both categories of chemicals can be used to illicitly manufacture controlled substances, List I chemicals are more strenuously regulated than List II chemicals because List I chemicals are "important to the manufacture of a controlled substance."[27]

Controlled Substances Analogues

Controlled substance analogues are substances that are not controlled but are structurally or pharmacologically similar to substances found in Schedule I or II and have no accepted medical use.[28] A substance that meets the definition of the term "controlled substance analogue" and is intended for human consumption is treated as if it were a controlled substance in Schedule I.[29] Controlled substance analogues are different from listed chemicals because such analogues are typically intended for human consumption as a substitute for a controlled substance, whereas listed chemicals are not intended for human consumption but are instead used as "ingredients" in the manufacture of certain controlled substances.

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[19] 21 U.S.C. § 811(h)(3).

[20] 21 U.S.C. § 811(h)(2), as amended by the Synthetic Drug Abuse Prevention Act of 2012, P.L. 112-144.

[21] P.L. 100-690.

[22] Domestic Chemical Diversion Control Act of 1993, P.L. 103-200; Comprehensive Methamphetamine Control Act of 1996, P.L. 104-237; Methamphetamine Anti-Proliferation Act of 2000, P.L. 106-310; Combat Methamphetamine Epidemic Act of 2005, P.L. 109-177.

[23] The 40 listed chemicals are set forth at 21 C.F.R. § 1310.02(a) and (b).

[24] *See* 21 U.S.C. §§ 802(33)—(35) and 21 C.F.R. §§ 1300.02(b)(17)—(19) (defining listed chemicals).

[25] 21 C.F.R. § 1300.02(b)(18) defines the term "List I chemical" as "a chemical specifically designated by the Administrator in [21 C.F.R.] § 1310.02(a) ... that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the [CSA] and is important to the manufacture of a controlled substance."

[26] 21 C.F.R. § 1300.02(b)(19) defines the term "List II chemical" as "a chemical, other than a List I chemical, specifically designated by the Administrator in [21 C.F.R.] § 1310.02(b) ... that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the [CSA]."

[27] 21 C.F.R. § 1300.02(b)(18).

[28] 21 U.S.C. §§ 802(32)(A) and (B).

[29] *See* 21 U.S.C. § 813 ("A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I").

Synthetic Drugs

Synthetic drugs are chemically produced in a laboratory; their chemical structure can be either identical to or different from naturally occurring drugs, and their effects are designed to mimic or even enhance those of natural drugs.[30] Many synthetic cathinones (central nervous system stimulants) are marketed under household names such as "bath salts" or "plant food" and are stamped with the warning "not intended for human consumption." This action is intended to circumvent the CSA's statutory definition of a controlled substance analogue. In October 2011, the DEA used its temporary scheduling authority to place three synthetic cathinones on Schedule I of the CSA.[31] In June 2012, Congress passed the Synthetic Drug Abuse Prevention Act of 2012—Subtitle D of Title XI of the Food and Drug Administration Safety and Innovation Act (P.L. 112-144)—which permanently added two of these synthetic cathinones to Schedule I of the CSA, along with cannabimimetic substances (commonly referred to as synthetic marijuana).[32]

International Treaty Obligations

The United States is a party to the Single Convention on Narcotic Drugs of 1961, which was designed to establish effective control over international and domestic traffic in narcotics, coca leaf, cocaine, and marijuana. The United States is also party to the Convention on Psychotropic Substances of 1971, which was designed to establish similar control over stimulants, depressants, and hallucinogens. Treaty obligations may require the Attorney General to control or reschedule a substance if existing controls are less stringent than those required by a treaty.[33]

Regulation

The CSA creates a "closed system" of distribution[34] in which distribution may lawfully occur among registered handlers of controlled substances, referred to as "registrants."[35] Central to this closed system of distribution is the registration of all persons or entities authorized by the DEA to handle controlled substances. The DEA has described the movement of a controlled substance from manufacture to the patient as follows:

> [A] controlled substance, after being manufactured by a DEA-registered manufacturer, may be transferred to a DEA-registered distributor for subsequent distribution to a DEA-registered retail pharmacy. After a DEA-registered practitioner, such as a physician or a dentist, issues a prescription for a controlled substance to a patient (i.e., the ultimate user), that patient can fill that prescription at a retail pharmacy to obtain that controlled substance. In this system, the manufacturer, the distributor, the practitioner, and the retail pharmacy are

[30] United Nations Office on Drugs and Crime, *Synthetic Drugs*, *at* http://www.apaic.org/index.php?option=com_content&view=article&id=91&Itemid=63.

[31] Drug Enforcement Administration, *Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cathinones Into Schedule I*, 76 Fed. Reg. 65371 (Oct. 21, 2011).

[32] For more information on this law and this topic generally, *see* CRS Report R42066, *Synthetic Drugs: Overview and Issues for Congress*, by Kristin M. Finklea and Lisa N. Sacco.

[33] The procedures for these scheduling actions are found at 21 U.S.C. § 811(d).

[34] Drug Enforcement Administration, *Electronic Prescriptions for Controlled Substances,* 75 Fed. Reg. 16235, 16237 (Mar. 31, 2010).

[35] According to 21 C.F.R. § 1300.02(b)(24), the term "registrant" means "any person who is registered [with the DEA] pursuant to [21 U.S.C. §§ 823 or 957]."

> all required to be DEA registrants, or to be exempted from the requirement of registration, to participate in the process.[36]

All registrants are required by the CSA to maintain complete and accurate inventories and records of all regulated transactions involving controlled substances and listed chemicals, as well as provide adequate security controls to prevent their diversion. Therefore, a particular controlled substance is always under the control of a DEA-registered person until it reaches the patient or is destroyed, and the CSA's regulatory requirements "ensure that all controlled substances are accounted for from their creation until their dispensing or destruction."[37]

Registration

The CSA defines who must register with the DEA in order to handle controlled substances.[38] Every person who manufactures, distributes, dispenses, imports, or exports any controlled substance, or who proposes to engage in the manufacture, distribution, dispensing, importation, or exportation of any controlled substance, must register with the DEA, unless they are exempt.[39] Generally, all manufacturers, distributors, and practitioners who deal with controlled substances must register. The CSA refers to an individual patient as an "ultimate user," which it defines as "a person who has lawfully obtained, and who possesses, a controlled substance for his own use or for the use of a member of his household or for an animal owned by him or by a member of his household."[40] Ultimate users are not required to register with the DEA[41] because the controlled substances in their possession "are no longer part of the closed system of distribution and are no longer subject to DEA's system of corresponding accountability."[42]

Manufacturers and distributors of controlled substances must register with the DEA annually, and those who dispense controlled substances must obtain registrations that may not be issued for less than one year or more than three years.[43] Any person who is required to register in order to manufacture, distribute, or dispense controlled substances, but has not yet registered, may apply for registration at any time.[44] Those who already are registered can apply for re-registration not more than 60 days before the expiration date of their current registration.[45] Registrations specify the extent to which registrants are authorized to manufacture, possess, distribute, or dispense controlled substances. The Administrator is authorized to charge reasonable fees relating to the registration and control of the manufacturing, distribution, and dispensing of controlled

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[36] DEA, *Disposal of Controlled Substances by Persons Not Registered With the Drug Enforcement Administration,* 74 Fed. Reg. 3480, 3481 (January 21, 2009).

[37] DEA, *Definition and Registration of Reverse Distributors*, 70 Fed. Reg. 22591 (May 2, 2005).

[38] 21 U.S.C. § 822; 21 C.F.R. Part 1301.

[39] 21 C.F.R. §§ 1301.22-1301.24 (exempting agents of registrants, certain military personnel, and law enforcement officials from DEA registration requirements).

[40] 21 U.S.C. § 802(27).

[41] 21 U.S.C. § 822(c)(3).

[42] DEA, *Definition and Registration of Reverse Distributors*, 68 Fed. Reg. 41222, 41226 (proposed July 11, 2003).

[43] 21 C.F.R. § 822(a).

[44] 21 C.F.R. § 1301.13.

[45] *Id*.

substances under the act.[46] In addition, the Administrator can inspect the establishments of registrants or applicants for registration.[47]

Registration is granted to applicants only if it would be consistent with the "public interest" to do so.[48] The Administrator uses several criteria to assess whether registering an applicant is consistent with the "public interest." The criteria differ depending on the substance involved and whether the applicant is a manufacturer, distributor, or practitioner, but generally include factors such as those relating to public health and safety and compliance with state and local laws.[49]

The Administrator also has the authority to deny, revoke, or suspend registrations under certain circumstances but must provide adequate grounds for doing so.[50] Before the DEA can deny an application, the agency must provide the applicant with an opportunity to demonstrate why the registration should not be denied.[51] However, the Administrator can suspend without notice any registration in order to avoid imminent danger to public health and safety.[52] A revocation or suspension of a registration may be applicable to a particular controlled substance or class of controlled substances. For example, a manufacturer who has been found to have violated the registration provisions regarding a Schedule II substance will still be able to manufacture controlled substances in Schedules III-V because the revocation or suspension relates only to one class of controlled substances.[53]

The registration of an individual terminates when the person dies, ceases legal existence, or discontinues business or professional practice.[54] A registrant who ceases legal existence or discontinues business or professional practice must notify the DEA promptly of this occurrence. A

[46] 21 U.S.C. § 821; *see also* 21 C.F.R. § 1301.13(e)(1) (chart detailing specific types of registrations and respective fees).

[47] 21 U.S.C. § 822(f); 21 C.F.R. § 1301.31.

[48] 21 U.S.C. § 823.

[49] 21 U.S.C. §§ 823(a)-(f).

[50] 21 U.S.C. § 824(a) states in pertinent part: "A registration pursuant to section 823 of this title to manufacture, distribute, or dispense a controlled substance or a list I chemical may be suspended or revoked by the [Administrator] upon a finding that the registrant—

(1) has materially falsified any application filed pursuant to or required by this subchapter or subchapter II of this chapter;

(2) has been convicted of a felony under this subchapter or subchapter II of this chapter or any other law of the United States, or of any State, relating to any substance defined in this subchapter as a controlled substance or a list I chemical;
(3) has had his State license or registration suspended, revoked, or denied by competent State authority and is no longer authorized by State law to engage in the manufacturing, distribution, or dispensing of controlled substances or list I chemicals or has had the suspension, revocation, or denial recommended by competent State authority;

(4) has committed such acts as would render his registration under section 823 of this title inconsistent with the public interest as determined under such section; or

(5) has been excluded (or directed to be excluded) from participation in a program pursuant to section 1320a—7(a) of [the Social Security Act, which excludes certain individuals and entities from participation in Medicare and State healthcare programs] . . ."

[51] 21 U.S.C. § 824(c).

[52] 21 U.S.C. § 824(d); 21 C.F.R. § 1301.36(e).

[53] THOMAS C. FOX, CAROL COLBORN LOEPERE & JOSEPH W. METRO, HEALTH CARE FINANCIAL TRANSACTIONS MANUAL § 20:62 (2005).

[54] 21 C.F.R. § 1301.52.

registration cannot be transferred to someone else unless the Administrator provides his express, written consent for such a transfer to occur.[55]

In some instances, applicants must apply for several separate registrations in order to comply with the CSA. Separate registrations are required for each principal place of business or professional practice where controlled substances are manufactured, distributed, imported, exported, or dispensed.[56] For example, a physician who is regularly engaged in dispensing controlled substances at one location must register to dispense controlled substances at other locations if he chooses to dispense controlled substances at these other locations.[57] However, with the enactment of the Ryan Haight Online Pharmacy Consumer Protection Act of 2008, the DEA Administrator must modify existing registrations of pharmacies to authorize them to dispense controlled substances by means of the Internet, unless the Administrator determines that such modification would be inconsistent with the public interest.[58]

Recordkeeping Requirements

In addition to registration requirements, the CSA contains several recordkeeping provisions.[59] A registrant authorized to handle controlled substances must keep accurate records and maintain detailed inventories in compliance with applicable federal and state law. For example, a registrant must maintain a complete and accurate record of each substance manufactured, received, sold, delivered, or otherwise disposed of by the registrant.[60] Furthermore, inventories must be available for inspection for at least two years.[61] These records are generally open for inspection by federal authorities and state officers tasked with enforcing state narcotics laws.[62] The CSA declares that is unlawful for any person to "refuse or negligently fail to make, keep, or furnish any record, report, notification, declaration, order or order form, statement, invoice, or information required" by the CSA;[63] it is also unlawful for any person knowingly or intentionally "to furnish false or fraudulent material information in, or omit any material information from, any application, report, record, or other document required to be made, kept, or filed" under the CSA.[64]

Certain DEA regulations implementing the CSA also apply to listed chemicals.[65] For example, all registrants authorized to handle listed chemicals (List I and List II) must maintain records of regulated transactions and submit various reports to the DEA.[66] However, the Administrator has the authority to exempt specified concentrations of listed chemical mixtures from the

[55] 21 C.F.R. § 1301.52(b).

[56] 21 C.F.R. § 1301.12.

[57] *See* United States v. Clinical Leasing Service, Inc., 925 F.2d 120 (5th Cir. 1991).

[58] Section 3(b) of P.L. 110-425, amending 21 U.S.C. § 823(f).

[59] 21 U.S.C. § 827; 21 C.F.R. Part 1304.

[60] 21 U.S.C. § 827(a)(3); 21 C.F.R. § 1304.21(a).

[61] 21 U.S.C. § 827(b)(3); 21 C.F.R. § 1304.04(a).

[62] *Id*.

[63] 21 U.S.C. § 842(a)(5).

[64] 21 U.S.C. § 843(a)(4).

[65] *See generally* 21 C.F.R. Part 1310 (records and reports of listed chemicals).

[66] 21 U.S.C. § 830(a) and (b); 21 C.F.R. §§ 1310.03-06.

recordkeeping requirements set forth in section 830 of the act that require registrants to maintain detailed records of every regulated transaction.[67]

Distribution

As a means to ensure that only authorized registrants obtain Schedule I and II drugs from manufacturers and distributors, the CSA requires registrants who legitimately distribute[68] controlled substances or listed chemicals to keep records of shipments to purchasers.[69] Manufacturers and distributors must receive a special order form from a purchaser prior to shipping Schedule I and II drugs.[70] The form is preprinted by the DEA with the name and address of the purchaser and the drugs must be shipped by the supplier filling the order to the purchaser's registered location.[71] All manufacturers must forward copies of completed order forms to the DEA by the close of the month in which the shipment is made.[72] The CSA also provides for electronic orders of Schedule I and II drugs.[73] Manufacturers must also forward copies of filled electronic orders to the DEA within 2 business days.[74]

The DEA further monitors the distribution of controlled substances by requiring manufacturers and distributors of Schedule I and II drugs to file reports[75] through the Automated Reports and Consolidated Orders System (ARCOS).[76] Certain narcotics listed in Schedules III and IV are also covered by the ARCOS reporting requirements.[77]

Registered pharmacies that are authorized to dispense controlled substances by means of the Internet must report to the DEA Administrator the total quantity of each controlled substance that the pharmacy has dispensed each month.[78] In addition, online pharmacies[79] must clearly display on their website homepage a statement that they comply with federal and state law concerning the delivery or sale of controlled substances, as well as post certain disclosure information such as

[67] *See* chart at 21 C.F.R. § 1310.12(c).

[68] For the purposes of the CSA, the term "distribute," as defined by 21 U.S.C. § 802(11), means "to deliver (other than by administering or dispensing [to an ultimate user or research subject]) a controlled substance or listed chemical."

[69] 21 C.F.R. Part 1305.

[70] DEA Form 222 is only issued to customers who are properly registered with the DEA.

[71] 21 C.F.R. § 1305.13(c).

[72] 21 C.F.R. § 1305.13(d).

[73] 21 C.F.R. § 1305 Subpart C.

[74] 21 C.F.R. § 1305.29.

[75] 21 C.F.R. §§ 1304.31 and 1304.32.

[76] 21 C.F.R. § 1304.33.

[77] 21 C.F.R. § 1304.33(d).

[78] Section 3(c) of the Ryan Haight Online Pharmacy Consumer Protection Act of 2008, P.L. 110-425, adding new 21 U.S.C. § 827(d)(2). However, pharmacies are exempt from such reporting requirement if they do not exceed in a given month either of two thresholds: (1) 100 or more prescriptions dispensed, or (2) 5,000 or more dosage units of all controlled substances combined. *Id.*

[79] An "online pharmacy" means a person, entity, or Internet site, whether in the United States or abroad, that knowingly or intentionally delivers, distributes, or dispenses, or offers or attempts to deliver, distribute, or dispense, a controlled substance by means of the Internet, but does *not* include, among other things, (1) manufacturers and distributors who do not dispense controlled substances to an unregistered individual or entity, (2) advertisements that do not attempt to facilitate an actual transaction involving a controlled substance, or (3) a registered pharmacy whose dispensing of controlled substances via the Internet consists solely of refilling or filling new prescriptions for controlled substances in schedule III, IV, or V. 21 U.S.C. § 802(52), as added by section 3(a) of P.L. 110-425.

- the name and address of the pharmacy as it appears on the pharmacy's DEA registration certificate,
- the pharmacy's telephone number and email address,
- a list of states in which the pharmacy is licensed to dispense controlled substance,
- the identification and contact information of the pharmacist-in-charge, and
- the following statement: "This online pharmacy will only dispense a controlled substance to a person who has a valid prescription issued for a legitimate medical purpose based upon a medical relationship with a prescribing practitioner. This includes at least one prior in-person medical evaluation or medical evaluation via telemedicine in accordance with applicable requirements of section 309."[80]

An online pharmacy must notify the DEA Administrator, and the state boards of pharmacy in any states in which the online pharmacies operate, thirty days before offering a controlled substance for sale, delivery, distribution, or dispensing; such notification must include pharmacy's Internet site address, the information that is required to be posted on the pharmacy's website, and the DEA registration numbers of the pharmacy and practitioners who work for it.[81] Online pharmacies that were already operational as of April 13, 2009, had to submit this notification to the DEA Administrator and any applicable state boards of pharmacy no later than May 12, 2009.

Dispensing to Patients

The CSA further provides special control mechanisms for licensed practitioners and pharmacists who dispense[82] controlled substances in Schedules II-V to patients for legitimate medical purposes. Because controlled substances classified as Schedule I drugs are deemed to have no accepted medical purpose in the United States, they may only be used for research, and practitioners may not prescribe them to patients. Under the CSA, only licensed medical practitioners[83] are authorized to prescribe controlled substances listed in Schedules II-V to patients.[84] A prescription for a controlled substance must be "issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice."[85] Accordingly, practitioners have a responsibility to ensure that the controlled substance is properly prescribed and dispensed.[86]

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[80] Section 3(d) of P.L. 110-425, adding new § 311 to the Controlled Substances Act.

[81] *Id.*

[82] According to 21 U.S.C. § 802(10), the term "dispense" means "to deliver a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling or compounding necessary to prepare the substance for such delivery."

[83] According to 21 U.S.C. § 802(21), the term "practitioner" means "a physician, dentist, veterinarian, scientific investigator, pharmacy, hospital, or other person licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he practices or does research, to distribute, dispense, conduct research with respect to, administer, or use in teaching or chemical analysis, a controlled substance in the course of professional practice or research."

[84] *See* 21 C.F.R. § 1306.03 (persons entitled to issue prescriptions).

[85] 21 C.F.R. § 1306.04; United States v. Moore, 4223 U.S. 122 (1975).

[86] Pharmacists share with practitioners the responsibility to ensure that controlled substances are properly prescribed and dispensed. Both practitioners and pharmacists are subject to the criminal and civil provisions of the CSA for knowingly prescribing and dispensing a controlled substance in a manner inconsistent with the act. 21 C.F.R. § (continued...)

No controlled substance in Schedules II may be dispensed to a patient by a pharmacist without a written prescription[87] from a practitioner, except in certain cases where the practitioner administers the controlled substance directly to the patient.[88] However, in the case of an emergency situation, a practitioner may orally authorize a pharmacist to fill a prescription for a Schedule II controlled substance. DEA regulations define "emergency situation" as those in which the prescribing practitioner determines:[89]

1. that immediate administration of the controlled substance is necessary, for proper treatment of the intended ultimate user; and
2. that no appropriate alternative treatment is available, including administration of a drug which is not a controlled substance under schedule II of the act; and
3. that it is not reasonably possible for the prescribing practitioner to provide a written prescription to be presented to the person dispensing the substance, prior to the dispensing.

Such an emergency oral authorization for a Schedule II substance may be filled by a pharmacist if the following conditions are met:[90]

1. the quantity of the drug prescribed and dispensed is limited to an amount adequate to treat the patient during the emergency period;
2. the prescription is immediately reduced to writing by the pharmacist and contains all the information that federal regulations require of prescriptions,[91] except for the signature of the prescribing individual practitioner;
3. if the prescribing individual practitioner is not known to the pharmacist, he must make a reasonable effort to determine that the oral authorization came from a registered individual practitioner, which may include a callback to the prescribing individual practitioner using his phone number as listed in the telephone directory and/or other good faith efforts to insure his identity; and
4. within seven days after authorizing an emergency oral prescription, the prescribing individual practitioner must deliver a written prescription to the dispensing pharmacist. The practitioner must write on the face of the prescription "Authorization for Emergency Dispensing" and also write the date of the oral order. Upon receipt, the dispensing pharmacist must attach this paper prescription to the oral emergency prescription that had earlier been reduced to writing. The pharmacist must notify the nearest DEA office if the prescribing individual practitioner fails to deliver a written prescription to him; failure of the pharmacist

(...continued)

1306.04(a).

[87] 21 U.S.C. § 829(a); *see also* 21 C.F.R. § 1306.05 (manner of issuance of prescriptions for Schedule II controlled substances).

[88] 21 U.S.C. § 829(a); *see also* 21 C.F.R. § 1306.11(b) (authorizing individual practitioners to administer or dispense controlled substances directly to patients without prescription).

[89] 21 C.F.R. § 290.10.

[90] 21 C.F.R. § 1306.11(d).

[91] 21 C.F.R. § 1306.05.

> to do so shall void the authority to dispense without a written prescription of a prescribing individual practitioner.

Controlled substances in Schedules III-V may be dispensed by a pharmacy pursuant to either a written or oral prescription, including a facsimile of a written prescription;[92] these substances may also be administered or dispensed directly by the practitioner in the course of his professional practice without a prescription.[93]

Practitioners are permitted to sign and transmit electronic prescriptions for controlled substances, assuming that the electronic prescription complies with detailed requirements set forth in the applicable federal regulations.[94]

Pharmacists may partially fill a prescription for Schedule II substances under certain circumstances.[95] Pharmacists are prohibited from refilling prescriptions for Schedule II substances.[96] Prescriptions for controlled substances in Schedules III and IV, however, may be filled or refilled by pharmacists up to five times within six months after the date on which the prescription was issued, unless the prescribing practitioner authorizes a renewal of the prescription.[97] A pharmacy may process electronic prescriptions for controlled substances if it has satisfied several conditions described in the applicable federal regulations.[98]

A controlled substance that is a prescription drug may not be delivered, distributed, or dispensed by means of the Internet without a "valid prescription."[99] Only with respect to this provision of the Controlled Substances Act, a "valid prescription" means a prescription that is issued for a legitimate medical purpose in the usual course of professional practice by a practitioner who has conducted at least one medical evaluation of the patient in the physical presence of the practitioner.[100]

Quotas

The DEA limits the quantity of Schedule I and II controlled substances which may be produced in a given calendar year. The CSA authorizes the Administrator to

- establish aggregate production quotas for all manufacturers;

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[92] 21 U.S.C. § 829(b). If the prescription is made orally, the pharmacist must promptly reduce to writing all of the information required to be in a prescription under 21 C.F.R. § 1306.05, except for the signature of the practitioner. 21 C.F.R. § 1306.21(a).

[93] 21 U.S.C. § 829(b); 21 C.F.R. § 1306.21(b).

[94] Drug Enforcement Administration, *Electronic Prescriptions for Controlled Substances,* 75 Fed. Reg. 16235, 16307 (Mar. 31, 2010).

[95] *See* 21 C.F.R. § 1306.13(a) ("The partial filling of a prescription for a substance listed in Schedule II is permissible if the pharmacist is unable to supply the full quantity called for in a written or emergency oral prescription.... The remaining portion of the prescription may be filled within 72 hours of the first partial filling").

[96] 21 U.S.C. § 829(a)("No prescription for a controlled substance in schedule II may be refilled.").

[97] 21 U.S.C. 829(b); 21 C.F.R. § 1306.22(a).

[98] Drug Enforcement Administration, *Electronic Prescriptions for Controlled Substances,* 75 Fed. Reg. 16235, 16316 (Mar. 31, 2010).

[99] Section 2 of the Ryan Haight Online Pharmacy Consumer Protection Act of 2008, P.L. 110-425, adding new 21 U.S.C. § 829(e).

[100] *Id.*

- establish individual production quotas for specific registered manufactures;
- establish individual production quotas for registrants who have not manufactured controlled substances during one or more proceeding years; and
- implement quota increases for individual manufacturers where necessary.[101]

By regulation, the Administrator must consider the following factors in making his quota determinations: (i) the total disposal of the controlled substance during the current and two preceding years; (ii) trends in the national rate of new disposal of the controlled substance; (iii) total inventories (actual or estimated) of "the class and all substances manufactured from the class [of controlled substances listed in Schedule I or II];" (iv) projected demand for a particular controlled substance; and (v) other relevant factors affecting the use of controlled substances including, changes in the currently accepted medical use of a controlled substance, the economic and physical availability of the raw materials necessary to produce a controlled substance, and recent unforeseen emergencies (i.e., natural disasters).[102]

Security

For the purposes of ensuring the secure storage and distribution of controlled substances and listed chemicals, all applicants and registrants must generally "provide effective controls and procedures to guard against theft and diversion of controlled substances."[103] DEA regulations further require all applicants and registrants to substantially comply with specific security standards for storage of controlled substances and List I chemicals.[104] Applicants and registrants must also be prepared to make adjustments to their security systems in the event that a controlled substance is transferred to another schedule or removed from control under the CSA.[105]

DEA regulations also detail specific security requirements for the different types of applicants and registrants. For example, non-practitioners (i.e., manufacturers, distributors, and narcotic treatment programs) are required to store Schedule I and II substances in electronically monitored safes, steel cabinets or vaults that meet or exceed certain specifications.[106] Licensed practitioners must store controlled substances in a "securely locked, substantially constructed cabinet"[107] and must notify the DEA of the theft or significant loss of any controlled substances within one business day of discovering such loss or theft.[108] Furthermore, all practitioners are prohibited from hiring employees who have been convicted of a drug-related felony or who have had a DEA

[101] *See* 21 U.S.C. §§ 826(a)-(e) (general provisions regarding the establishment of production quotas for Schedule I and II controlled substances).

[102] 21 C.F.R. §§ 1303.11(b)(1)-(5).

[103] *See* 21 C.F.R. § 1301.71 (general security requirements and standards for measuring compliance).

[104] 21 C.F.R. § 1301.71(b) states: "Substantial compliance with the standards set forth in §§ 1301.72-1301.76 may be deemed sufficient by the Administrator after evaluation of the overall security system and needs of the applicant or registrant." Section 1301.71(b) also sets forth a list of fifteen discretionary factors for Administrator to consider when evaluating the overall security system of an applicant or registrant; *see also* 21 C.F.R. § 1309.71(a)-(c) (general security requirements for List I chemicals).

[105] 21 C.F.R. § 1301.71(c).

[106] *See* 21 C.F.R. §§ 1301.72(a)(1)(i)-(iii) (specifications required for safes and steel cabinets storing Schedule I and II drugs or substances); *see also* 21 C.F.R. §§ 1301.72(a)(2) and 1301.72(a)(3)(i)-(vi) (specifications required for vaults storing Schedule I and II drugs or substances).

[107] *See* 21 C.F.R. § 1301.75 (physical security controls for practitioners).

[108] 21 C.F.R. § 1301.76(b).

registration denied or revoked.[109] DEA regulations recommend that non-practitioners carefully screen individuals before hiring them as employees, to ensure that job applicants do not have convictions for crimes or have engaged in unauthorized use of controlled substances.[110]

Disposal of Controlled Substances[111]

DEA registrants may need to dispose of controlled substances in their possession when they are expired, damaged, contaminated, or otherwise unwanted. Under the CSA and DEA regulations, there are three different options for registrants to dispose of controlled substances:[112]

1. The distributor or dispenser may return the controlled substance to the pharmaceutical manufacturer who accepts returns of outdated or damaged controlled substances.
2. The distributor, dispenser, or manufacturer may itself dispose of the controlled substances under procedures specified by federal regulation.[113]
3. The distributor, dispenser, or manufacturer may transfer the controlled substances to a "reverse distributor" to take custody of the controlled substances for the purpose of returning them to the manufacturer or arranging for their disposal.[114]

Penalties

While the criminal provisions of the CSA focus mainly on the *illicit* possession, manufacture, and distribution of controlled substances,[115] there are a few noteworthy penalty provisions applicable to persons registered with the DEA. The CSA sets forth certain offenses involving listed chemicals,[116] DEA registration,[117] and other prohibited acts related to registrants who manufacture, distribute and dispense controlled substances.[118]

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[109] 21 C.F.R. § 1301.76(a).

[110] 21 C.F.R. § 1301.90.

[111] For information about disposal by patients who possess already dispensed controlled substances (as opposed to DEA registrants that want to dispose of them), *see* CRS Report R40548, *Legal Issues Relating to the Disposal of Dispensed Controlled Substances*, by Brian T. Yeh. This report discusses the Secure and Responsible Drug Disposal Act of 2010, P.L. 111-273, which, among other things, amended the Controlled Substances Act to allow a patient to deliver controlled substances to an entity that is authorized by federal law to dispose of them, providing that such disposal occurs in accordance with regulations issued by the Attorney General to prevent diversion of controlled substances.

[112] DEA, *Definition and Registration of Reverse Distributors*, 70 Fed. Reg. 22591, 22592 (May 2, 2005).

[113] Under 21 C.F.R. § 1307.21, any person may request permission from DEA to dispose of controlled substances without the need for a DEA or state government witness. If a registrant has a regular need to dispose of controlled substances, the DEA may grant blanket authorization for such disposal; however, "DEA normally requires that the registrant provide two designated responsible individuals to accompany the drugs to the disposal site and witness the destruction." DEA, *Definition and Registration of Reverse Distributors*, 70 Fed. Reg. 22591 (May 2, 2005).

[114] A "reverse distributor" is a DEA-registered entity "who receives controlled substances acquired from another DEA registrant for the purpose of—(1) returning unwanted, unusable, or outdated controlled substances to the manufacturer or the manufacturer's agent; or (2) where necessary, processing such substances or arranging for processing such substances for disposal." 21 C.F.R. § 1300.01(b)(41).

[115] For a description of the criminal penalty provisions of the CSA, *see* CRS Report RL30722, *Drug Offenses: Maximum Fines and Terms of Imprisonment for Violation of the Federal Controlled Substances Act and Related Laws*, by Brian T. Yeh.

[116] 21 U.S.C. §§ 841(c); (e)-(f).

With respect to DEA registration generally, registrants authorized to distribute or dispense any controlled substance are prohibited from distributing, dispensing, or manufacturing controlled substances that are not authorized by a registrant's registration.[119] Registrants must maintain accurate records and furnish them when required to do so by law enforcement officials.[120] Registrants must also maintain a degree of transparency by allowing law enforcement officials access to their premises for inspections authorized by the CSA.[121] Failure to adhere to the registration requirements of the CSA may subject a registrant to civil fines, imprisonment, or both.[122]

The CSA also proscribes certain acts related to the manufacture and distribution of controlled substances and listed chemicals. Registrants who knowingly or intentionally (i) distribute Schedule I and II substances without a valid order form;[123] (ii) use an invalid registration number during the course of handling or acquiring controlled substances;[124] (iii) furnish false or fraudulent material information in a record or report required by the act;[125] or (iv) present false or fraudulent identification when receiving a listed chemical,[126] are subject to criminal fines, imprisonment, or both.[127] Additionally, registrants who violate the aforementioned provisions may be subject to injunctive or declarative actions filed by the Attorney General in federal district court.[128]

Finally, the CSA specifies several offenses regarding listed chemicals. For example, criminal fines and/or imprisonment are available for any person who knowingly or intentionally (i) possesses a listed chemical with the intent to manufacture a controlled substance without proper registration; (ii) possesses or distributes a listed chemical with knowledge or a reasonable belief that the listed chemical will be used to manufacture a controlled substance; or (iii) evades the CSA's recordkeeping and reporting requirements by receiving or distributing listed chemicals in small units.[129] Also, any person who knowingly possesses or distributes listed chemicals in violation of the CSA, or knowingly violates the CSA's recordkeeping requirements, is subject to criminal fines, imprisonment, or both.[130] Furthermore, in addition to the other applicable penalties, violators of the aforementioned provisions may also be enjoined for up to ten years from handling listed chemicals.[131]

(...continued)

[117] 21 U.S.C. § 842.

[118] 21 U.S.C. § 843.

[119] 21 U.S.C. § 842(a)(2).

[120] 21 U.S.C. § 842(a)(5).

[121] 21 U.S.C. § 842(a)(6).

[122] *See generally* 21 U.S.C. § 842(c) (penalties for committing prohibited acts set forth in § 842(a)).

[123] 21 U.S.C. § 843(a)(1).

[124] 21 U.S.C. § 843(a)(2).

[125] 21 U.S.C. § 843(a)(4)(A).

[126] 21 U.S.C. § 843(a)(4)(B).

[127] *See generally* 21 U.S.C. § 843(d) (penalties for committing prohibited acts set forth in § 843(a)).

[128] 21 U.S.C. § 843(f).

[129] 21 U.S.C. §§ 841(c)(1)-(3).

[130] *See* 21 U.S.C. § 841(f)(1) and (2) (penalties for offenses involving listed chemicals).

[131] 21 U.S.C. § 841(e).

Exceptions to the Regulatory Requirements Under the CSA

It is important to note that the CSA allows for exceptions and also exempts certain individuals from some or all of its regulatory requirements. For example, individuals exempted from registration requirements include, among others, officers or employees of the DEA, officers of the U.S. Customs Service, offers or employees of the U.S. Food and Drug Administration, and any other federal officers who are authorized to possess, import, or export controlled substances in the course of their official duties.[132] Officers or employees of any state, or political subdivision of a state, who are engaged in enforcement of state or local laws relating to controlled substances, are also exempt from registering with the DEA.[133] A person who has lawfully obtained, and who possesses, a controlled substance for his own use is also not required to register.[134]

In addition, only those actually engaged in activities relating to manufacturing, distributing, and dispensing controlled substances are required to obtain registration, but related or affiliated persons who are not engaged in such activities are not required to register. For example, a stockholder or parent corporation of a corporation that manufactures controlled substances is not required to obtain registration, nor are employees of a registered manufacturer, distributor, or dispenser.[135]

The DEA Administrator may, by regulation, waive the registration requirement for certain manufacturers, distributors, or dispensers, if he finds it consistent with the public health and safety.[136]

In certain circumstances, the CSA recordkeeping provisions do not apply. The CSA recordkeeping provisions do not apply to the prescribing or administering of a controlled substance in Schedules II-V by practitioners acting in the lawful course of their professional practice *unless* such substance is prescribed or administered in the course of maintenance or detoxification treatment of an individual.[137] For example, the prescribing or administering of methadone for the treatment of narcotic addiction must be in conformity with the CSA's recordkeeping provisions. The CSA also does not apply to research conducted in conformity with the exemption granted under certain provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA) or to preclinical research or teaching.[138]

[132] 21 C.F.R. § 1301.24(a)(1).

[133] 21 C.F.R. § 1301.24(a)(2). For additional registration exceptions, see 21 C.F.R. §§ 1301.22-1301.23.

[134] 21 U.S.C. § 822(c).

[135] 21 C.F.R. § 1301.11(a); 21 U.S.C. § 822(c).

[136] 21 U.S.C. § 822(d).

[137] 21 U.S.C. §§ 827(c)(1)(A), 827(c)(1)(B).

[138] 21 U.S.C. § 827(c)(2).

Appendix. Classification of Controlled Substances

Schedule	CSA Statutory Provision	Examples of Scheduled Substances
Schedule I	Pursuant to 21 U.S.C. § 812(b)(1), a substance will be placed in Schedule I based on specific findings made by the Administrator that "(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision."	Heroin, lysergic acid diethylamide (LSD), marijuana, MDMA (Ecstacy), methaqualone (Quaalude), synthetic marijuana.[a]
Schedule II	Pursuant to 21 U.S.C. § 812(b)(2), a substance will be placed in Schedule II based on specific findings made by the Administrator that "(A) The drug or substance has a high potential for abuse. (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. (C) Abuse of the drug or other substance may lead to severe psychological or physical dependence."	Methadone, methamphetamine, methylphenidate (Ritalin®), morphine, oxycodone (OxyContin®), phencylidine (PCP).[b]
Schedule III	Pursuant to 21 U.S.C. § 812(b)(3), a substance will be placed in Schedule III based on specific findings made by the Administrator that "(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug may lead to moderate or low physical dependence or high psychological dependence."	Anabolic steroids, synthetic delta—9 tetrahydrocannabinol (THC), codeine, hydrocodone with aspirin or Tylenol®.[c]
Schedule IV	Pursuant to 21 U.S.C. § 812(b)(4), a substance will be placed in Schedule IV based on specific findings made by the Administrator that "(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III."	Xanax®, Valium®, Equanil®, Talwin®, Darvon®.[d]
Schedule V	Pursuant to 21 U.S.C. § 812(b)(5), a substance will be placed in Schedule V based on specific findings made by the Administrator that "(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV."	Certain cough medicines with codeine, and certain opium preparations.[e]

a. *See* 21 C.F.R. § 1308.11(b)-(f) (complete listing of Schedule I drugs and substances); *see also* 21 C.F.R. § 1308.11(g) (temporary listing of substances subject to emergency scheduling in Schedule I).

b. *See* 21 C.F.R. § 1308.12(b)-(g) (complete listing of Schedule II drugs and substances).

c. *See* 21 C.F.R. § 1308.13(b)-(g) (complete listing of Schedule III drugs and substances).

d. *See* 21 C.F.R. § 1308.14(b)-(f) (complete listing of Schedule IV drugs and substances).

e. *See* 21 C.F.R. § 1308.15(b)-(e) (complete listing of Schedule V drugs and substances).

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Exhibit 2

APR 1 2016

Thank you for your December 21, 2015, letter. We hope that you will find the enclosed attachment, which provides detailed written responses to the questions raised in your letter, informative. In addition to information regarding the supply, scheduling, and surveillance of marijuana, the response includes a detailed listing of the strains available through NIDA's contract with the University of Mississippi, and a thorough, step-by-step explanation of the process for researchers seeking to conduct marijuana research.

As you know, senior officials and subject matter experts from the Department of Health and Human Services (HHS), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP) provided an in-person briefing for your staff on November 13, 2015, during which they shared a comprehensive overview of ongoing work to facilitate scientific research on the potential health benefits of marijuana, its components, and derivatives.

During this briefing, staff explained the specific roles of each agency as they relate to enforcement, regulatory, and research activity; identified the collaboration taking place at the federal level; discussed the requirements and limitations of the Single Convention on Narcotic Drugs, 1961 (Single Convention or "the treaty"); explained the specific requirements of the Controlled Substances Act (CSA) as they relate to scheduling and rescheduling; outlined the current federal portfolio regarding marijuana research; and walked through the process in which researchers ultimately can apply for and receive marijuana for research purposes.

Our agencies are committed to working together, along with federal, state, and local entities, to facilitate research and development efforts in accordance with the law. We support research on marijuana and its components that complies with applicable laws and regulations to advance our understanding about the health risks and potential therapeutic benefits of medications using marijuana or its components or derivatives. We will also provide this response to the co-signers of your letter.

Sincerely,

Sylvia M. Burwell, Secretary
U.S. Department of Health and Human Services

Michael Botticelli, Director
Office of National Drug Control Policy

Chuck Rosenberg, Acting Administrator
Drug Enforcement Administration

Attachment: Responses to Questions concerning Medical Marijuana Research

1. *The supply of marijuana for research purposes. DEA is charged with issuing permits for the bulk manufacture of marijuana for research purposes. The National Institute on Drug Abuse (NIDA) has an exclusive contract with the University of Mississippi (which holds the only bulk manufacture permit granted by DEA) to grow its entire research supply of marijuana. In our July 2015 letter, we raised concerns that this NIDA-held monopoly on supply of marijuana for research purposes limits access to adequate supply and appropriate varieties of marijuana and presents significant barriers to research.*

   At the November briefing, ONDCP and DEA indicated that they did not view supply limits as a barrier, citing a recent overproduction of one variety of marijuana for research and noting that DEA has only received one request for an additional bulk manufacture permit to date. But DEA assertions only applied to one strain of marijuana and do not reflect feedback we have heard from researchers in our states. Because the format of the briefing did not allow for discussion of this issue in appropriate detail, we therefore seek the following additional information:

a. Please provide detailed information on the current supply of marijuana at the University of Mississippi, including a breakdown of all strains, amounts available in each strain, amount of each strain that has been requested, and the amount of each strain that is in surplus.

As an entity registered under the CSA to manufacture marijuana, the University of Mississippi is responsible for maintaining records, including inventories of all stocks of controlled substances on hand.

Also under the CSA, DEA is responsible for issuing yearly aggregate production quotas (APQ) for each schedule I and II controlled substance. As part of this responsibility, DEA sets the individual manufacturing quota for marijuana produced by the University of Mississippi at the level sufficient to meet the estimated research needs of the United States. In establishing this production quota, DEA works closely with NIDA. Where NIDA indicates to DEA that there is a research need in the United States for a particular strain of marijuana, or for certain extracts thereof, DEA adjusts the APQ accordingly to ensure an adequate supply. In addition, consistent with the CSA and DEA regulations, registered manufacturers routinely provide DEA with information describing the desired manufacturing quota. These manufacturers may also contact DEA at any time throughout the year to request revisions to their quota. Regarding the surplus, DEA regulations provide that the quotas shall be sufficient to allow bulk manufacturers to maintain an inventory equal to 50 percent of its average estimated net disposal for the current calendar year.

The University of Mississippi currently has approximately 185 batches of marijuana with varying concentrations of tetrahydrocannabinol (THC) and cannabidiol (CBD) (**see Appendix A**). Many of these batches/strains have similar concentrations of THC and CBD and may be blended to achieve specific cannabinoid concentrations of interest to researchers. Bulk marijuana is generally available in the following 12 categories:

- Placebo marijuana (produced by solvent extraction)
  - THC (0%) / CBD (0%)
- Low THC varieties
  - Low THC (<1%) / Medium CBD (1-5%)
  - Low THC (<1%) / High CBD (5-10%)
  - Low THC (<1%) / Very High CBD (>10%)
- Medium THC varieties
  - Medium THC (1-5%) / Low CBD (<1%)
  - Medium THC (1-5%) / Medium CBD (1-5%)
  - Medium THC (1-5%) / High CBD (5-10%)
  - Medium THC (1-5%) / Very High CBD (>10%)
- High THC varieties
  - High THC (5-10%) / Low CBD (<1%)
  - High THC (5-10%) / High CBD (5-10%)
  - High THC (5-10%) / Very High CBD (>10%)
- Very high THC varieties
  - Very High THC (>10%) / Low CBD (<1%)

In addition, marijuana cigarettes are available with the following characteristics:

Batch #	**Marijuana Cigarettes**	**THC%**	**CBD%**	**cigarettes available**
11554-1005-62	Hand Rolled Placebo Marijuana Cigarettes, 70mm; 0.000%	0.00	No Data	14
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	36000
12792-1208-77-Open	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	119
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	300
10074-0301-97-OP	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	25
6567-0194-47	Marijuana Cigarettes, 3.2% THC, 0.12% CBD	3.20	0.12	300
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	20400
12792-0109-120-Open	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	114
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	17400
12792-0109-146-Open	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	428
10604-0203-95	Marijuana Cigarettes, High Potency, 7.4% THC, 0.22% CBD	7.40	0.22	56400
10604-0203-95-	Marijuana Cigarettes, High Potency;	7.40	0.22	305

OP	7.4% THC, 0.22% CBD			
12944-0509-105-Open	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	No Data	122
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	No Data	31200

In 2015, NIDA fulfilled 23 requests for marijuana from researchers (detailed in **Appendix B**). There are four additional requests currently pending as of February 5, 2016.

b. Please describe how agencies, including HHS, DEA, Department of Justice (DOJ), National Institutes of Health (NIH), NIDA, and the ONDCP, plan to increase the number of permits for the bulk manufacture of marijuana for research purposes. If there is no plan, please describe why not.

In determining how many persons may become registered as bulk manufacturers of marijuana for research purposes, DEA must adhere to the CSA and Single Convention. Under the CSA, DEA must limit the number of bulk manufacturers of marijuana "to a number of establishments which can produce an adequate and uninterrupted supply of [marijuana] substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes," 21 U.S.C. §823(a)(1). Under the Single Convention, DEA must ensure that registered manufacturers adhere to the system of controls required by the treaty, under which the United States Government must, among other things, maintain a monopoly on the distribution of cannabis material for research. The United States has historically met this treaty obligation through an arrangement whereby NIDA oversees the domestic production and distribution of marijuana by its contractor, the University of Mississippi.

As discussed during the briefing for your staff on November 13, 2015, the United States may, consistent with the CSA and Single Convention, expand the number of registered bulk manufacturers of marijuana, provided the statutory and treaty requirements are met. Among these requirements would be a determination by DEA (in consultation with NIDA) that the current NIDA contractor (the University of Mississippi) is unable to meet the demands of lawful researchers in the United States. While we cannot forecast the future interests of researchers, if such researchers required additional strains of marijuana that the University of Mississippi is unable to supply, this could provide a basis for DEA to register additional growers. Under such circumstances, for the United States to continue to meet its treaty requirements, any additional growers would likewise have to be acting under the direct control of the United States Government with respect to the production and distribution of the cannabis material.

c. Please indicate how many applications have been received for permits for bulk manufacture of marijuana for research purposes to date, what their status is, and the length of time between initial application and denial.

Since the enactment of the CSA in 1970, the only application by a person seeking to become registered as a bulk manufacturer of marijuana to supply researchers (in addition to the University of Mississippi) is that submitted by Lyle Craker, a researcher at the University of Massachusetts. An extensive analysis of that application and DEA's grounds for denial were

published in two documents in the Federal Register: 76 FR 51403 (2011) and 74 FR 2101 (2009). The decision by the DEA to deny the application was upheld by the United States Court of Appeals for the First Circuit in *Craker v. DEA*, 714 F.3d 17 (1st Cir. 2013).

d. Your response to our July letter indicates that DEA has approved 265 researchers to conduct medical marijuana research. For each of these approvals, please provide information on the requested strain, and how long it has taken to fulfill the researchers request for marijuana after the study has been approved.

Please note that the 265 researchers that DEA mentioned in the July letter were the number of persons registered with DEA to conduct research (clinical, preclinical, or analytical) with marijuana (including its constituents). A researcher who submits an application for such registration is not required to identify the strain of marijuana to be used in the research and DEA does not tabulate such data with respect to researchers.

Information on the marijuana NIDA sent to researchers in 2015 is included in Appendix B. On average, in 2015 shipments were sent about 25 days after the order was received. Shipments included:

- In 2010: 19 shipments to 9 researchers
- In 2011: 21 shipments to 8 researchers
- In 2012: 16 shipments to 9 researchers
- In 2013: 15 shipments to 8 researchers
- In 2014: 23 shipments to 12 researchers
- In 2015: 20 shipments to 8 researchers

To expedite fulfillment requests, all researchers are encouraged to contact NIDA during the registration process to ensure that their strains of interest are available or can be produced in sufficient quantities.

e. How are your agencies planning to work within the bounds of the Single Convention on Narcotics Drugs to allow researchers to utilize the already existing supply of marijuana in states that have enacted laws to make the drug available for medical or recreational use?

Please see the answer to question 1(b) and note that, under the Single Convention, the United States may not permit the production, distribution, or use of marijuana produced outside the system of controls described under the treaty.

f. The United Kingdom, Canada, Israel, the Netherlands, Czech Republic, Portugal, and Uruguay have acted to increase the diversity of sources for the production of marijuana for research while still complying with the Single Convention on Narcotic Drugs. Why has the United States not taken similar actions?

The International Narcotics Control Board is the component of the United Nations responsible for monitoring compliance with the treaties. Please see the answer to question 1(b) for an explanation of how the registration of additional marijuana growers to supply

researchers in the United States might be carried out in conformity with the CSA and the Single Convention. We do not have sufficient information regarding the cultivation of cannabis in these other nations on which to base an opinion as to whether such activity is in compliance with international treaty obligations.

2. Assessment of marijuana rescheduling. In our July letter, we asked about the timeline for the Food and Drug Administration (FDA) to complete its analysis on the rescheduling of marijuana and to make a recommendation to DEA. We also asked what the DEA timeline was for assessment upon receipt of FDA recommendation. These questions were not answered in the written response from your agencies, and at the staff briefing you repeatedly informed our staff that you could not provide the requested information. However, after the briefing we learned that in fact FDA has already made the recommendation. In a September 30, 2015, letter to Congressman Earl Blumenauer, DOJ wrote that "DEA recently received the HHS scientific and medical evaluations as well as a scheduling recommendation," which indicates FDA has completed its evaluation, and that "DEA is currently reviewing these documents ... to make a scheduling determination in accordance with the Controlled Substances Act." Failure to provide us with this information at the briefing leaves us with continued questions about the process and timeline for a re-scheduling determination. We therefore ask that you provide us with the following information:

a. Please confirm whether or not DEA has received the HHS evaluations and scheduling recommendations.

DEA has received the HHS scientific and medical evaluations, as well as a scheduling recommendation, and is currently reviewing these documents and all other relevant data to make a scheduling determination in accordance with the CSA.

b. What is the DEA timeline for assessment upon receipt of the FDA recommendation?

DEA will carry out its assessment of the FDA recommendation in accordance with the CSA requirements set forth in 21 U.S.C. §§ 811 and 812. Once a final determination has been made, DEA will notify the petitioners. DEA understands the widespread interest in the prompt resolution of these petitions and hopes to release its determination in the first half of 2016. Our staff would be happy to share the final assessment with your offices when available.

c. Has DEA requested that FDA complete a scientific analysis for the rescheduling of cannabadiol (CBD)? If so, please describe how FDA will conduct the review.

DEA, FDA, and NIDA have been working together to address the issues relating to CBD, including scheduling considerations. The scheduling determinations must undergo a scientific and deliberate interagency process (see **Appendix C**). NIDA and FDA have been working to complete an extensive literature review of human and animal studies that have evaluated CBD in terms of its abuse potential, pharmacology chemistry, adverse effects and dependence. However, FDA has indicated that a human abuse liability study may be necessary to make a final determination on abuse potential. FDA and NIDA have been exploring options for completing this study to generate this data. In carrying out scheduling activities related to CBD, DEA and

FDA will follow the procedures set forth in 21 U.S.C. § 811 and § 812.

3. Interagency coordination and research applications. At the briefing, you explained to us that ONDCP is coordinating regular meetings with relevant federal agencies about encouraging research, and you explained that these discussions ultimately led to the elimination of the HHS Public Health Service Review Board. This was a positive step, because this board significantly delayed research approval and existed for no other Schedule I substance. However, we continue to hear from the research community that the research application approval process is long, cumbersome, and difficult to navigate. We therefore ask that you:

a. Please clarify how you plan to work together to encourage qualified research applications.

We recognize that the current process for initiating research on marijuana or its constituent compounds is time consuming and some researchers have indicated to NIDA that this can be a disincentive to conducting research in this area. HHS and DEA have been working together to explore ways to streamline the process by which marijuana-related research may be conducted while also meeting our international and legislative obligations under the Single Convention and the CSA to control the production and distribution of marijuana for research purposes to prevent diversion.

In addition to eliminating the Public Health Service (PHS) committee review for non-federally funded marijuana research (discussed in our last letter), DEA recently streamlined the administrative process for CBD research. In the past, researchers who expanded the scope of their approved studies and needed more CBD than initially anticipated had to request, in writing, a modification to their DEA research registrations—potentially delaying that research while the modification underwent an approval process that included both DEA and FDA. The new policy removes this step for previously registered CBD clinical researchers who are granted a waiver. [1]

Steps like these represent our commitment to work together to identify ways of streamlining research on marijuana and its constituents.

DEA and NIDA continue to meet to explore other potential steps that can be taken to facilitate research with marijuana and its constituents.

b. Please describe the application process for qualified researchers who wish to conduct research using marijuana, including all steps at DEA, FDA, and local Institutional Review Boards, from initial application to receipt of marijuana from NIDA, including data on how long the entire process has taken for previously approved applications.

The application process for persons seeking to become registered to conduct research with marijuana (or any other schedule I controlled substance) is set forth in 21 U.S.C. § 823(f) and 21 CFR 1301.18 and 1301.32. We note that in addition to the process outlined below, applicants

[1] http://www.dea.gov/divisions/hq/2015/hq122315.shtml

must adhere to particular state, local, and/or institutional requirements.

The process for conducting research using marijuana or components of marijuana includes:

1. A review of scientific validity and ethical soundness.

    a. For NIH-funded research, this occurs through the NIH grant review process and consists of three steps that take approximately nine months (which is the same amount of time taken to review grants for non-marijuana related research):
        i. The NIH peer review system, which assesses the scientific and technical merit of all grant applications;
        ii. Review by the National Advisory Council of the funding Institute, comprising eminent scientists as well as public members; and
        iii. Review by the Director of the funding Institute, who makes the final decision on the merit of an application for funding, based on peer review, public health significance, and Institute priorities.

    [Note: review by the institutional review board (IRB) of the researchers organization occurs before NIH review]

    b. For non-NIH funded basic research, not involving human subjects, the research protocol is reviewed for scientific merit by a minimum of two non-government scientists, identified by the NIDA Drug Supply Program, with expertise in the research topic. This step typically takes 4-6 weeks but can take longer if the reviewers have additional questions or concerns that need to be addressed by the researcher. As with all requests for controlled substances from NIDA's Drug Supply Program, investigators must submit a detailed research protocol including:
        i. The specific aims and goals of proposed study;
        ii. The experimental design, including the number of experiments and experimental subjects and the dosages or concentration of drugs;
        iii. Justification of quantities of drug(s) requested; and
        iv. A document demonstrating that the research is approved by the Animal Care & Use Committee and that adequate care in conducting animal research will be exercised (if applicable).
        v. Documentation of local IRB approval.

2. For research involving human subjects (whether NIH-supported or not), the researcher must also have an active-status Investigational New Drug (IND) application on file with FDA, which has been evaluated by FDA and found safe to proceed. FDA reviews scientific validity and ethical soundness. The review assures the safety and rights of subjects and the scientific quality of the clinical investigations, and assesses the likelihood that investigations will yield data capable of meeting the statutory standards for drug marketing approval. FDA has a 30-day regulatory timeframe for completion of this review. The researcher may start the study(ies) after 30 days, unless notified by FDA that the study(ies) are on hold (may not proceed until certain deficiencies are resolved) or on notification by FDA that the study(ies) may start sooner.

3. For all research (involving animal or human subjects), the researcher must obtain a DEA registration for marijuana, a Schedule I controlled substance. However, it should be noted that some states have separate registration requirements that often need to be completed sequentially. [2], [3] Obtaining a DEA registration includes:
    a. Completing and submitting a DEA application for each Schedule I drug used:
        i. The applicable fee is currently $244 for a one-year registration period.
        ii. The application includes the research protocol and the amount of drug needed for the study.

    b. A DEA investigator conducts a site visit to ensure that diversion controls are in place.

    c. DEA sends the research protocol to FDA for review. Once received, FDA has 30 days to review and respond to DEA about protocols involving human subjects and 21 days to respond for protocols involving non-human research. However, if more information is needed from the researcher, the DEA investigator will contact the researcher which can extend the time.

    d. Once all of the DEA requirements have been satisfied, the researcher will receive a DEA registration number. This typically occurs within an average of 62 days after receiving input from FDA.
        i. Registration needs to be renewed every year.

    e. A local IRB approval must accompany the application for registration (DEA Form 225).

4. When the above steps have been completed, investigators contact the NIDA Drug Supply Program to place an order for marijuana with specific characteristics regarding concentrations of THC, CBD, and other cannabinoids. The program official verifies that the application is complete (with all the above-mentioned steps fulfilled), and forwards the order to the contractor responsible for shipping the marijuana. This process typically takes about two to four weeks.
    a. Researchers are encouraged to contact NIDA before all of the above steps have been completed to ensure that their strains of interest are already available or can be produced in sufficient quantities.

    Please note that the majority of the applications that DEA receives do not conform to the application requirements. In these instances, DEA works with the applicant to obtain the information missing before initiating the interagency review process described above.

4. Surveillance and epidemiological studies. Federal agencies should work to facilitate surveillance and epidemiological studies to assess how medical marijuana is being used. This should also include investigations in diverse populations and with multiple modes of

[2] https://www.txdps.state.tx.us/internetforms/Forms/NAR-77-78.pdf
[3] http://www.ct.gov/DCP/cwp/view.asp?a=1622&Q=500858&PM=1

administration. We inquired about this work in our initial letter and our briefing, and we are concerned that there was no mention of efforts to collect these data. We therefore ask that you address the following:

a. Is the Centers for Disease Control and Prevention (CDC), in collaboration with NIDA and any other federal agencies, collecting data about the total number of medical marijuana patients in the United States, the nature of their ailments, modes of use, and patient reported outcomes?

We note that the Substance Abuse and Mental Health Services Administration (SAMHSA), CDC, and NIH will continue to conduct routine monitoring of marijuana use through the National Survey on Drug Use and Health, the Youth Risk Behavior Surveillance System, and the Monitoring the Future survey, respectively. Currently, these surveys do not collect information that distinguishes medical use from recreational use.

Additionally, CDC is in the process of modifying questions asked on the annual Behavioral Risk Factor Surveillance Survey (BRFSS) to better understand patterns of use of marijuana broadly. These questions may be added either as an optional module which states decide whether or not to administer, or as part of the core survey set. These added questions will increase our understanding of patterns of marijuana use -- in terms of frequency, mode of use, and self-report regarding whether use was for medical, recreational, or both purposes.

At the population level, drawing a line between medical and recreational use is challenging for multiple reasons. For example, a previous study conducted by CDC utilizing an online survey called Healthstyles examined self-reported reasons for using marijuana, and among current users found that 53 percent reported using for recreational reasons only, 10 percent medical only, and 36 percent reported using for both recreational and medical reasons. Of all those reporting use for medical purposes, more than three quarters also used marijuana recreationally.[4]

There is also broad variation from state-to-state around reporting requirements, including some states that have no reporting or state-level registry and thus cannot address the questions raised such as total number of medical marijuana users, nature of ailments addressed, modes of use, and patient outcomes. To our knowledge, even in states with patient-level registries, mode of use and patient reported outcomes are not collected.

We anticipate future work with federal agencies and states to attempt to increase the collection of usable data, both from enhanced federal and state surveys of the general population, as well as from medical marijuana registries where these exist and from chronic disease registries.

b. How are your agencies working with state public health departments in order to coordinate research on medical marijuana use so that data can be compared between states?

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[4] Schauer G et al, Toking, Vaping and Eating for Health or Fun: Marijuana Use Patterns in Adults, U.S., 2014. American Journal of Preventive Medicine 2015

CDC helped facilitate communication between the four states that have legalized recreational use, including coordination of public health surveillance and research efforts. However, as noted above, these states have not drawn strict demarcation lines between data collection on public health issues associated with medical and recreational use.

In addition, CDC and SAMSHA are currently working with states through an effort coordinated by the Council of State and Territorial Epidemiologists to develop uniform surveillance questions, including a question to address medical use, that can be integrated into state and national surveillance systems and facilitate state-to-state comparisons. A similar process was used to develop a marijuana surveillance module for the 2016 BRFSS (mentioned above) and is expected to guide the development of modules for other CDC public health surveillance systems that collect state-specific, population-based data, like the Pregnancy Risk Assessment Monitoring System (PRAMS).

c. *How are your agencies ensuring that studies on the benefits of medical marijuana include diverse populations?*

Applications for NIH funding are required to detail plans for the inclusion of women, minorities, and children. Specifically, when the proposed project involves human subjects, the review committee evaluates the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. Additional information on this review is included in the Guidelines for the Review of Inclusion in Clinical Research (**see Appendix D**).

d. Please describe in detail what measures are being taken to encourage research that investigates the variable risks, benefits, and efficacy of different modes of administration, including smoking, inhalation of vaporized product, oral administration of cannabis, and types of products, including purified products or specific compounds?

NIH supports and conducts a broad portfolio of research regarding the potential therapeutic benefits and harms of marijuana and its constituent components. NIH supports a diverse portfolio of research on cannabinoid compounds that in fiscal year (FY) 2015 spanned more than half of the NIH Institutes and Centers and totaled more than $110 million. Examples of funded studies include:

- The basic biology of the endocannabinoid system
  1. Pharmacological activity of cannabinoids and cannabinoid receptors
  2. Endocannabinoid signaling during pregnancy
  3. Genetic and environmental impact on risk for marijuana use
- Therapeutic effects of cannabinoids
  1. The efficacy of CBD and THC for treatment of pain
  2. Cannabinoids including CBD and nabilone as treatments for substance use disorders (opioids, alcohol, cannabis, and methamphetamine)
  3. The use of cannabinoids to treat cannabis use disorder
  4. The impact of the endogenous cannabinoid system on pain, traumatic brain injury,

and substance use disorders

- Risks associated with marijuana use
  1. Effects of smoked cannabis on driving
  2. Immunosuppression associated with CBD
  3. Epigenetic, neurological, psychiatric, and cognitive effects of heavy cannabis use
- Routes of administration
  1. Transdermal delivery of CBD to treat alcoholism
  2. Acute and chronic effects of vapor inhalation of synthetic cannabinoids
  3. Development of a standard vaporizer system for use in research
  4. Development of a rodent self-administration system for vapor inhalation of THC for pre-clinical studies
- The impact of changing state policies on use of marijuana and related health and other outcomes

In addition, to support additional research in this area NIH has issued funding opportunity announcements that focus on:

1. Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment[5]
2. Effects of Cannabis Use and Cannabinoids on the Developing Brain[6]
3. Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain (including cannabinoids)[7]

In March 2016, NIH will hold a neuroscience research summit on Marijuana and Cannabinoids[8] to discuss the state of science on marijuana's harms as well as its potential therapeutic uses, focusing on neurologic and psychiatric disorders. The meeting is being sponsored by several NIH Institutes and Centers: NIDA; the National Institute on Alcohol Abuse and Alcoholism; the National Center for Complementary and Integrative Health, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.

e. Canada and the state of California have established medical marijuana patient registries. A patient registry could significantly support the work of researchers and physicians, while also improving our understanding of the population of medical marijuana patients in the United States. We understand that NIDA is analyzing these programs to determine the feasibility of a national patient registry. Please describe any ongoing work to establish a national patient registry, including any necessary funding that would be necessary to launch this effort, and the timeline for implementation.

We are aware of the registry being developed in Canada to collect health outcome and safety information on medical marijuana patients; however, to our knowledge the State of California has not yet set up a similar registry. Marijuana use registries could provide a resource to help target research, and NIDA has been exploring the possibility of funding researchers to analyze

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[5] PA-15-188
[6] PA-14-163
[7] PAR-14-225
[8] http://apps1.seiservices.com/nih/mj/2016/Default.aspx

data from existing registries. Given the disparities between federal and state laws on use or marijuana for medical conditions, we are not considering a national registry.

5. Coordination with states and inter-agency cooperation. Cooperation is vital to ensure that medical marijuana is being used effectively and appropriately by those who need it. We asked a number of questions about such cooperation in our letter and our briefing and the responses were not complete. For example, you informed us that federal agencies have been in communication and are coordinating on this issue, but failed to describe in detail the nature and type of these communications. We therefore ask that you address the following:

a. Please describe in detail any regular and organized communication between HHS and state public health departments to coordinate research efforts regarding medical marijuana.

FDA encourages and supports medical research into the safety and efficacy of marijuana products through adequate and well-controlled clinical trials conducted under an IND and consistent with DEA requirements for research on Schedule I substances. FDA has talked with representatives from several states as they consider support for medical research of marijuana and its derivatives to provide scientific advice and to help ensure that their research is rigorous and appropriate.

FDA has also been in communication with individual states to exchange information on the number and types of reported adverse events related to the use of products containing marijuana and marijuana-derivatives which are currently being marketed, and has provided technical support to states that have made marijuana available under state law and are interested in supporting the conduct of medical research to be carried out in conformity with federal law.

b. Please describe in detail any efforts by federal agencies to provide guidance to states for testing standards to ensure patient safety and access needs are met.

Please see the answer to 5(a) above.

c. Please describe in detail any regular and organized communication taking place between agencies that are charged with marijuana research, policy, or data collection (including but not limited to CDC, FDA, NIH, ONDCP, and SAMHSA), to coordinate efforts and long term plan development.

The HHS Secretary's Behavioral Health Coordinating Council (BHCC) is a coordinating body within the Department, established in 2010, to share information and identify and facilitate collaborative, action-oriented approaches to address the HHS behavioral health agenda without duplicating efforts. A BHCC Marijuana Subcommittee was established a few years ago and focuses on four key areas of HHS engagement—research and surveillance; regulatory oversight; education; and treatment. This group is in regular communication and meets as needed to address concerns.

Further, ONDCP has been convening regular meetings and calls for relevant federal agencies, such as HHS, NIDA, FDA, CDC, SAMHSA, DEA, and DOJ, to exchange

information on marijuana-related activities and to discuss opportunities for collaboration on issues related research, policy, or data collection.

ONDCP has also convened more targeted meetings of specific federal agencies to discuss how to stimulate research on marijuana, including the potential therapeutic benefits of marijuana and its constituent components.

Appendix A: NIDA Stocks of Marijuana as of January 6, 2016**

Batch No.	Description	THC (%)	CBD (%)	2015 Inventory Weight (kilograms)
	High THC /Low CBD			
1304-1	HIGH POTENCY (Reprocessed)	13.17	0.05	0.37
1290A	HIGH CBD/HIGH THC (Reprocessed)	9.85	0.02	0.32
1426	MX	9.54	0.00	8.83
1357	High THC Clones (MX)	8.74	0.11	2.74
1431	MX	8.48	0.14	1.42
1291C	HIGH CBG/HIGH THC (Reprocessed)	8.45	0.04	0.37
1292A	HIGH CBG/HIGH THC	8.44	0.03	0.15
1292	HIGH THC	8.38	0.00	0.26
1313	HIGH POTENCY	8.29	0.00	8.12
1324	High THC Clones (MX)	7.96	0.02	14.75
1424	MX	7.26	0.32	3.18
1309	HIGH POTENCY	7.07	0.00	16.78
1428	MX	7.06	0.00	7.51
1427	MX	6.97	0.00	3.82
1291	HIGH THC	6.95	0.06	0.56
1296	HIGH POTENCY	6.94	0.00	14.43
1308	HIGH POTENCY	6.68	0.00	4.57
1430	MX	6.67	0.00	8.30
1306	HIGH POTENCY	6.27	0.00	5.40
1289A	HIGH CBG/HIGH THC	6.11	0.04	0.25
1300	HIGH POTENCY	6.01	0.00	15.80
1297	HIGH POTENCY	5.83	0.00	13.88
1299	HIGH POTENCY	5.78	0.00	13.70
1272	HIGH POTENCY	5.64	0.00	4.57
1314	HIGH POTENCY	5.62	0.00	7.85
1291D	HIGH THC/CBD~CBN	5.58	0.31	0.08
1315	HIGH POTENCY	5.34	0.00	10.38
1425	MX	5.30	0.16	1.50
1273	HIGH POTENCY	4.96	0.00	6.71
1432	MX	4.96	0.00	0.32
1429	MX	4.93	0.00	1.12
1298	HIGH POTENCY	4.89	0.00	16.08
1379	High THC/Low CBD MX Clones (Mixed	4.83	0.17	1.71

	Fines)			
1289	HIGH THC	4.75	0.00	0.54
1290C	MED CBD/LOW THC	4.39	1.09	0.09
1290	HIGH THC	4.24	0.66	0.74
1302	HIGH POTENCY	2.78	0.03	11.06
1305	HIGH POTENCY	2.66	0.00	7.01
1303	HIGH POTENCY	2.44	0.00	10.72
1307	HIGH POTENCY	2.22	0.00	12.38
1200	CMEF-00	1.65	0.00	2.84
1200		1.29	0.00	0.93
1158	CMEF-01	1.43	0.00	9.86
1317	HIGH THC CLONES-NonGMP	8.78	0.01	4.78
	Low THC / High CBD			
1375B	Fines (Mixed Fines) [Reprocessed}	1.26	23.91	0.03
1371A	Fines (V1-20) {Reprocessed}	0.96	21.46	0.06
1375A	High CBD/Low THC Clones (Mixed Fines) {Reprocessed}	0.52	13.96	0.04
1371	Low THC/High CBD Clones (V1-20) {Reprocessed}	0.42	11.13	3.77
1368	Low THC/High CBD Clones (V1-30)	0.43	9.62	1.83
1345	Low THC/High CBD Clones (V1-20)	0.21	6.49	12.22
1348	Low THC/High CBD Clones (V1-20)	0.22	6.47	12.85
1341	Low THC/High CBD Clones (V1-20)	0.23	6.47	12.06
1333	Low THC/High CBD Clones (V1-30)	0.24	6.45	10.79
1381	V1-16	0.39	6.12	1.69
1328	Low THC/High CBD Clones (V1-20)	0.27	6.10	7.22
1334	Low THC/High CBD Clones (V1-30)	0.22	6.08	9.97
1340	Low THC/High CBD Clones (V1-20)	0.21	5.99	12.61
1329	Low THC/High CBD Clones (V1-20)	0.25	5.99	10.66
1346	Low THC/High CBD Clones (V1-20)	0.19	5.96	12.35
1339	Low THC/High CBD Clones (V1-20)	0.21	5.92	13.04
1332	Low THC/High CBD Clones (V1-30)	0.24	5.86	11.46
1350	Low THC/High CBD Clones (V1-20)	0.22	5.72	11.07
1383	V1-20	0.22	5.68	3.55
1349	Low THC/High CBD Clones (V1-20)	0.19	5.67	11.88
1353	Low THC/High CBD Clones (V1-30)	0.22	5.66	13.49
1342	Low THC/High CBD Clones (V1-20)	0.20	5.66	13.12
1351	Low THC/High CBD Clones (V1-30)	0.18	5.65	11.83
1331	Low THC/High CBD Clones (V1-30)	0.23	5.63	4.55
1347	Low THC/High CBD Clones (V1-20)	0.18	5.61	11.83

1386	V1-20	0.18	5.56	4.20
1337	Low THC/High CBD Clones (V1-30)	0.19	5.55	11.10
1343	Low THC/High CBD Clones (V1-20)	0.18	5.55	12.26
1389	V1-20	0.20	5.55	3.11
1344	Low THC/High CBD Clones (V1-20)	0.20	5.51	14.32
1336	Low THC/High CBD Clones (V1-16)	0.29	5.39	10.90
1338	Low THC/High CBD Clones (V1-20)	0.18	5.38	0.00
1387	V1-20	0.18	5.34	3.63
1335	Low THC/High CBD Clones (V1-19)	0.23	5.28	0.00
1356	Low THC/High CBD Clones (V1-30)	0.21	5.26	6.90
1403	B4	0.32	4.97	2.99
1352	Low THC/High CBD Clones (V1-30)	0.16	4.95	6.43
1384	V1-20	0.18	4.94	2.14
1398	V1-30	0.17	4.90	6.87
1385	V1-20	0.16	4.82	4.19
1370	Low THC/High CBD Clones (V1-20)	0.19	4.73	11.32
1390	V1-20	0.15	4.68	5.06
1388	V1-20	0.14	4.61	4.80
1392	V1-20	0.14	4.52	4.51
1369	Low THC/High CBD Clones (V1-30)	0.18	4.50	0.00
1391	V1-20	0.18	4.42	4.45
1393	V1-19	0.21	4.36	1.65
1399	V1-30	0.13	4.16	5.39
1395	V1-30	0.15	4.15	0.23
1330	Low THC/High CBD Clones (V1-20)	0.15	3.88	10.34
1417	V6-8	0.16	3.36	0.75
1380	V 1 Leaves	0.13	3.80	3.80
1396	V1-14	0.15	3.75	1.30
1394	V1-30	0.12	3.55	0.69
1416	V6-8	0.16	3.30	0.07
1397	V1-14	0.25	3.23	9.23
1382	V1-16	0.14	3.12	1.63
1418	B5	1.03	2.89	1.42
	Mixed Varieties			
1423	MX-Leaves	7.47	3.31	12.68
1322	Medium THC/CBD Clones (A-17)	3.32	4.02	4.90
1323	Medium THC/CBD Clones (A-17)	3.49	4.17	4.52
1325	Medium THC/CBD Clones (B4)	3.88	5.38	12.74
1326	Medium THC/CBD Clones (B4)	4.25	6.03	13.20

1327	Medium THC/CBD Clones (B4)	5.16	6.80	8.41
1354	Medium THC/CBD Clones (B-5)	2.97	4.89	6.46
1355	Medium THC/CBD Clones (B-4)	3.91	5.99	12.25
1358	Medium THC/CBD Clones (B-4)	4.29	6.20	11.79
1359	Medium THC/CBD Clones (B-4)	4.78	6.85	10.95
1360	Medium THC/CBD Clones (B-4)	4.40	6.50	10.70
1361	Medium THC/CBD Clones (B-4)	3.97	5.82	11.88
1362	Medium THC/CBD Clones (B-4)	4.33	6.27	10.32
1363	Medium THC/CBD Clones (B-4)	4.71	6.70	16.81
1364	Medium THC/CBD Clones (B-4)	4.31	6.06	11.99
1365	Medium THC/CBD Clones (V3-22)	1.36	3.14	10.20
1366	Medium THC/CBD Clones (V3-22)	1.58	3.46	10.63
1367	Medium THC/CBD Clones (V6-8)	2.85	4.93	13.35
1372	Medium THC/CBD Clones (B-4)	3.54	5.41	5.11
1373	Medium THC/CBD Clones (V3-15)	2.29	4.05	11.50
1374	Medium THC/CBD Clones (V3-15)	3.17	5.03	11.71
1377	CBD/THC Clones (Mixed Fines)	1.81	3.38	8.78
1291A	THC~CBD	4.43	4.92	0.00
1376A	High CBD/Medium THC Clones (Mixed Fines) {Reprocessed}	3.05	13.66	1.70
1376B	Fines (Mixed Fines) [Reprocessed}	7.04	20.72	0.28
1378A	High CBD/High THC Clones (Mixed Fines) {Reprocessed}	9.13	15.49	0.11
1378B	Fines (Mixed Fines) {Reprocessed}	8.44	16.74	0.08
1406	B4	2.72	4.65	2.02
1415	V1-15	2.17	3.80	5.14
1400	B5-Leaves	2.66	4.39	6.82
1413	A18	3.28	4.38	0.86
1419	B6-8	3.98	5.27	1.60
1405	B4	2.82	4.38	2.76
1404	B4	3.51	4.79	4.70
1402	B4	2.85	4.91	6.39
1412	A18	3.98	5.27	1.05
1407	B4	3.91	5.82	6.76
1414	B5-Leaves	3.79	6.39	1.19
1408	B4	3.14	4.80	4.10
1409	B4	4.08	6.07	3.92
1410	B4	3.38	5.11	4.42
1401	B4	2.79	4.50	2.74
1420	B3-15			1.54

1421	B4	2.72	4.65	5.60
1411	A17	2.62	3.54	0.83
1422	V3-15	1.64	3.17	11.53
	Bulk Material			
	HIGH POTENCY MARIJUANA PLANT MATERIAL BULK	6.70		0.93
1200	MARIJUANA PLANT MATERIAL BULK	1.29		0.04
1231	MARIJUANA PLANT MATERIAL BULK	3.53		0.04
1232	MARIJUANA PLANT MATERIAL BULK	8.16		4.00
090709A	MARIJUANA PLANT MATERIAL BULK	6.44		0.25
1352	MARIJUANA PLANT MATERIAL BULK	0.10	4.10	4.99
1371	MARIJUANA PLANT MATERIAL BULK	0.42	11.13	1.99
1375A	MARIJUANA PLANT MATERIAL BULK	0.47	11.41	1.99
1024	MARIJUANA PLANT MATERIAL BULK	1.20	0.00	2.98
1200	MARIJUANA PLANT MATERIAL BULK	1.20	0.01	1.99
1304-1	MARIJUANA PLANT MATERIAL BULK	10.10	0.04	1.99
1304-1	MARIJUANA PLANT MATERIAL BULK	12.60	0.04	4.95
13494-22	MARIJUANA PLANT MATERIAL BULK	14.10	0.03	0.93
1009	MARIJUANA PLANT MATERIAL BULK	2.00	0.16	1.51
13322-21-1	MARIJUANA PLANT MATERIAL BULK	3.10	0.01	1.08
1327	MARIJUANA PLANT MATERIAL BULK	4.00	6.70	4.99
1291-A	MARIJUANA PLANT MATERIAL BULK	4.50		0.35
1291-A	MARIJUANA PLANT MATERIAL BULK	4.50	5.31	0.19
13322-21-2	MARIJUANA PLANT MATERIAL BULK	4.70	0.01	1.82
12792-143-7	MARIJUANA PLANT MATERIAL BULK	6.10	0.01	13.54
1292	MARIJUANA PLANT MATERIAL BULK	6.70	0.03	0.19
1378A	MARIJUANA PLANT MATERIAL BULK	7.50	13.80	2.93
13851-0715-139	MARIJUANA PLANT MATERIAL BULK	7.70	7.90	2.93
13494-8	MARIJUANA PLANT MATERIAL BULK	7.90	0.05	0.92
1266	MARIJUANA PLANT MATERIAL BULK	8.40	0.04	3.06
3857-105-10	MARIJUANA PLANT MATERIAL BULK	6.50	0.01	3.99
12792-1208-77A	MARIJUANA PLANT MATERIAL BULK	1.10	0.00	0.70
12792-0109-145-1	MARIJUANA PLANT MATERIAL BULK	5.50	0.02	12.99
	MARIJUANA PLANT MATERIAL BULK	2.22		10.00
	MARIJUANA PLANT MATERIAL BULK	2.41		0.13
	MARIJUANA PLANT MATERIAL BULK	4.06		0.13
	MARIJUANA PLANT MATERIAL BULK	8.04		0.13

12944-0509-105-1	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.01	nd	2.70
13322-21-3	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.02	nd	1.77
4022-0598-111-1	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.01	nd	2.22
	PLACEBO MARIJUANA PLANT MATERIAL BULK			0.30
	MARIJUANA PLANT MATERIAL BULK			5.00
	Marijuana Cigarettes			**cigarettes**
11554-1005-62	Hand Rolled Placebo Marijuana Cigarettes, 70mm; 0.000%	0.00		14
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	36000
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	119
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	300
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	25
6567-0194-47	Marijuana Cigarettes, 3.2% THC, 0.12% CBD	3.20	0.12	300
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	20400
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	114
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	17400
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	428
10604-0203-95	Marijuana Cigarettes, High Potency, 7.4% THC, 0.22% CBD	7.40	0.22	56400
10604-0203-95	Marijuana Cigarettes, High Potency; 7.4% THC, 0.22% CBD	7.40	0.22	305
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	nd	122
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	nd	31200

***nd- not detected**

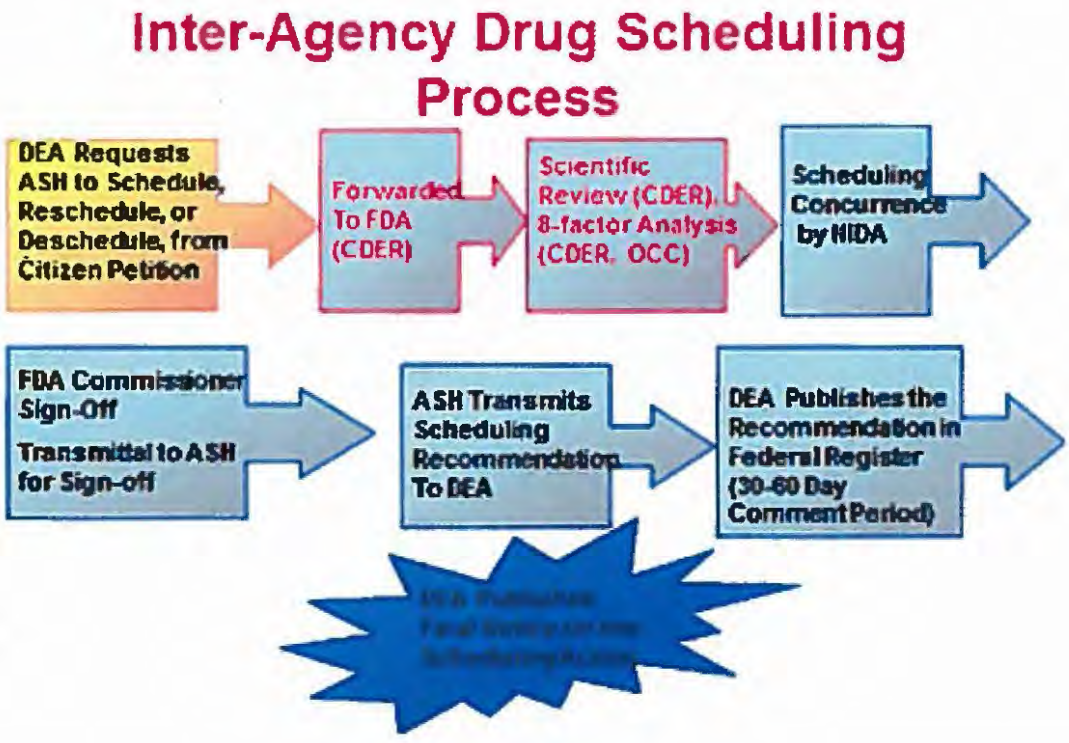
****please note descriptions in Appendix A are for internal cataloging purposes only.**

Appendix B: Shipments/ Pending Requests of Marijuana Cigarettes and Bulk Material – 2015 (Report as of January 6, 2015)

Ship Date	Compound	Shipped	Unit of Measure
3/30/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
3/30/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	300	cig
4/20/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
4/20/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	300	cig
5/20/2015	Marijuana Plant Material Bulk 14.1% THC, 0.03% CBD	0.001	grams
5/20/2015	Marijuana Plant Material Bulk 2.0% THC, 0.16% CBD (UMISS Batch # 1009)	0.99938	grams
5/20/2015	Marijuana Plant Material Bulk 4.7% THC, 0.01% CBD	0.99982	grams
5/20/2015	Marijuana Plant Material Bulk 7.9% THC, 0.05% CBD	1	gram
6/8/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	1800	cig
6/9/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	1800	cig
6/25/2015	Marijuana Plant Material Bulk 4.%THC, 6.7%CBD (Batch/Barrel#1327)	600	grams
6/30/2015	Marijuana Plant Material Bulk 1.2% THC, 0.00% CBD (UMISS Batch # 1024)	24.998	grams
7/23/2015	Marijuana Plant Material Bulk 1.2%THC, 0.01%CBD (Batch/Barrel#1200)	100	grams
7/23/2015	Marijuana Plant Material Bulk 4.5%THC, 5.31%CBD (Batch/Barrel#1291A)	100	grams
7/23/2015	Marijuana Plant Material Bulk 6.7%THC, 0.03%CBD (Batch/Barrel#1292)	99.999	grams
7/23/2015	Placebo Marijuana Plant Material Bulk 0.026% THC, CBD not detected	99.999	grams
11/9/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	1800	cig
11/17/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	36	cig
11/17/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	20	cig
12/2/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
2/25/2-15	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3	cig
2/25/2-15	Marijuana Cigarettes, High Potency; 7.4% THC, 0.22% CBD	3	cig
2/25/2-15	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	3	cig
	Pending Requests		
	Marijuana Plant Material Bulk 0.01% THC, 4.10% CBD	30	grams
	Marijuana Plant Material Bulk 0.47 % THC, 11.41 % CBD	30	grams
	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	150	cig
	Placebo Marijuana Cigarettes	50	cig

Appendix C: Summary of scheduling/re-scheduling process

The process by which determinations are made with regard to scheduling or re-scheduling must go through a scientifically credible and deliberate interagency process, outlined through the graphic and text below.



Section 201(c) of the CSA requires HHS to consider eight factors as part of its scientific review:

Actual or relative potential for abuse
Scientific evidence of its pharmacological effect
State of current scientific knowledge regarding the substance
History and current pattern of abuse
Scope, duration, and significance of abuse
Risk to the public health
Psychic or physiological dependence liability
Immediate precursor of a substance already controlled

Appendix D: Guidelines for Review of Inclusion on Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

Office of Extramural Research
August 2014

Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

Requirements and Responsibilities

As required by federal law (42 USC 289a-2) and NIH policy, applications that propose to involve human subjects must address:

1. the inclusion of women, minorities, and children in the proposed research
2. for an NIH-defined Phase III clinical trial, plans for the valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study.

Background Information

- Federal law requires that women and minorities be included in all clinical research studies, as appropriate for the scientific goals of the work proposed.
- Additionally, for NIH-defined Phase III clinical trials, applicants must also consider whether the study can be expected to identify potential differences by sex/gender, race, and/or ethnicity and, unless there is clear evidence that such differences are unlikely to be seen, they must include plans describing how potential group differences will be evaluated. Further information about valid analysis is available here.
- NIH policy also states that children (currently defined as persons under the age of 21) be included in human subjects research supported by NIH unless an acceptable justification for their exclusion is provided.
- Therefore, when the research involves human subjects (excluding research that qualifies for IRB exemption 4), reviewers must evaluate the proposed plans for inclusion of women, minorities, and children as one of the review criteria that factor into the evaluation of scientific and technical merit.
- **It is not expected that every study will include both sexes/genders, all racial and ethnic groups and subgroups, and children. Inclusion on the basis of sex/gender, race, and ethnicity, as well as the inclusion of children should be guided by the scientific aims of the study. Applicants should describe and justify fully the distribution of individuals that will be included in the research.**
- Policy links:
  - http://grants.nih.gov/grants/funding/women_min/women_min.htm
  - http://grants.nih.gov/grants/funding/children/children.htm

Applicant Responsibilities

Applicants must designate if human subjects are involved, and if so, whether the proposed activities meet the criteria for an IRB exemption. Applications that involve human subjects with the exception of those meeting the requirements for IRB Exemption 4 must address 1) inclusion of individuals on the basis of their sex/gender, race, and ethnicity and 2) inclusion of children (defined as persons under the age of 21). Applicants must also provide a planned enrollment table(s) with the proposed sample distributed on the basis of sex/gender, race, and ethnicity (or a cumulative inclusion enrollment report if working with an existing dataset). When conducting an NIH-defined Phase III clinical trial, applicants must also provide a description of the plans for valid analysis and evaluation of potential group differences on the basis of sex/gender, race, and ethnicity.

Scientific Review Group (SRG) Responsibilities

The NIH Peer Review regulations (42 C.F.R. 52h) specify that reviewers will take into account, in determining overall impact that the project in the application could have on the research field

involved, the adequacy of plans to include both sexes/genders, minorities, children, and special populations as appropriate for the scientific goals of the research. Therefore, the SRGs must factor their evaluation of the proposed plans for the inclusion of individuals on the basis of their sex/gender, race, ethnicity, and age into their overall evaluation of an application's scientific and technical merit.

Reviewer Responsibilities

I. Evaluate the applicant's plans for inclusion on the basis of sex/gender, race, and ethnicity

i. Does the applicant provide a description of their plans for including individuals on the basis of their sex/gender, race, and ethnicity considering the points in Section I of the Inclusion worksheet (provided below)?

If NO, rate the inclusion plans as UNACCEPTABLE.

If YES, is there an adequate justification for the proposed sample considering the required four points (see the worksheet for additional details)?

If YES, rate the inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY.

ii. In addition to (i), for NIH-defined Phase III clinical trials, does the applicant address plans for a valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity considering the points in Section II of the Inclusion worksheet?

If NO, rate the inclusion plans as UNACCEPTABLE [even if acceptable for (i)].

If YES, does the description of expected sex/gender, racial, and ethnic differences in intervention effect include selection and discussion of one of the required analysis plans? (see Section II of the Inclusion worksheet for details)

If the discussion is inadequate, rate the plans as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY.

II. Evaluate the applicant's plans for the inclusion of children (currently defined as individuals under the age of 21)

Does the applicant provide a description of their plans for including children (currently defined as individuals under the age of 21)?

If NO, rate the inclusion plans as UNACCEPTABLE.

If YES, is there an adequate justification for the inclusion or exclusion of children considering the points in Section III of the Inclusion worksheet?

If Yes, rate the inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for the inclusion of children and EXPLAIN WHY.

III. Prepare written comments, including specific comments describing all inclusion concerns when rated as Unacceptable.

Office of Extramural Research
August 2014

Worksheet to Assist in Reviewing the Required Points of Section on the Inclusion of Women, Minorities, and Children in Clinical Research and Clinical Trials

I. Evaluating inclusion on the basis of sex/gender, race, and ethnicity:

Point 4.2.1 Planned Distribution of Subjects

Does the applicant describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study considering the following?

___ Is there a description of the planned distribution using the Planned Enrollment Report format? If there is no report, does the applicant provide sufficient information to understand the planned distribution of subjects by sex/gender, race, and ethnicity?

___ For studies planning to use an existing dataset(s):
- ___ Is there a description of the planned distribution using the Planned Enrollment Report format?, or
- ___ Is there an explanation if sex/gender, racial, and/or ethnic composition of existing dataset is unknown?, if so
- ___ Is there a description of the sex/gender, racial, and ethnic composition for the population base of the existing dataset(s), if known?

Point 4.2.2 Description and Rationale of Subject Selection

Does the applicant adequately describe the subject selection criteria and rationale for selection considering the population at risk for the disease/condition under study and the scientific objectives and proposed study design?

Point 4.2.3 Rationale for Exclusion

If the proposed sample is not representative of those at risk for the disease/condition under study, does the applicant provide an adequate justification of this considering the following:
- ___ the literature on the existence of (or lack of) differences on the basis of sex/gender, race, and ethnicity
- ___ the proposed sample size
- ___ the need to fill a particular research gap
- ___ the feasibility of establishing collaborative arrangements (cost is not an acceptable justification)
- ___ the purpose of the research constrains applicant selection (e.g., unique stored specimens, rare surgical specimens etc.)

Point 4.2.4 Description of Outreach Programs for Recruitment

Does the applicant adequately describe recruitment and outreach plans or other methods for enrolling the individuals proposed as part of the sample?

II. Additional requirements when evaluating NIH-defined Phase III Clinical Trials:

Does the applicant adequately consider whether clinically important sex/gender, racial, and/or ethnic differences are expected?

Does the applicant describe one of the following?

___ Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender, racial, and/or ethnic subgroups when prior studies strongly support these significant differences among subgroups, or

___ Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged), or

___ Plans to conduct valid analyses of intervention effect in sex/gender, racial and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

III. Evaluation inclusion of children (individuals under the age of 21):

Does the applicant adequately describe plans for the inclusion/exclusion of children (individuals under the age of 21) including:

___ Description and rationale of the age ranges of individuals expected to be recruited
___ Description and justification of the exclusion of children altogether or of a subset of children (Refer here for a complete description of justifications for excluding children)

If children are included, does the applicant adequately describe the:
___ Expertise of the investigative team for working with the children at the ages included
___ Facilities available to accommodate children
___ Inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study

Exhibit 3

Medical Marijuana Research

MPP's model medical marijuana bill allows patients to obtain a medical marijuana card if they have a qualifying medical condition and their licensed health care practitioner believes they are likely to receive therapeutic or palliative benefit from the use of medical marijuana. The qualifying medical conditions listed in the bill are as follows (the state department of health can add others):

1. Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, post-traumatic stress disorder, or the treatment of these conditions, and

2. A chronic or debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia or wasting syndrome; severe, debilitating pain; severe nausea; seizures; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.

Key medical references addressing marijuana's ability to alleviate these conditions are below, with related symptoms or conditions grouped together.

Nausea, Vomiting, Appetite Loss, Cachexia, Cancer, and HIV/AIDS

In its 1999 report "Marijuana and Medicine: Assessing the Science Base," the Institute of Medicine concluded, "Nausea, appetite loss, pain and anxiety are all afflictions of wasting, and all can be mitigated by marijuana." Marijuana and its active components (cannabinoids) can both stimulate appetite and reduce the nausea, vomiting, and weight loss experienced by patients in many circumstances, including the side effects of drug therapies given for cancer, HIV infection, and hepatitis C. Observational studies suggest this may improve treatment adherence among patients experiencing gastrointestinal toxicity from drug therapy.

Cancer References

(1) Vincent Vinciguerra, et al., "Inhalation Marijuana as an Antiemetic for Cancer Chemotherapy," *New York State Journal of Medicine* (October 1988).

In this clinical trial sponsored by the state of New York, "Fifty-six patients who had no improvement with standard antiemetic agents were treated and 78% demonstrated a positive response to marijuana ... inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."

(2) Richard Musty and Rita Rossi, "Effects of Smoked Cannabis and Oral Δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials," *Journal of Cannabis Therapeutics* 1, no. 1 (2001): 43-56.

Musty and Rossi reviewed data from a series of state-sponsored clinical trials of marijuana for relief of nausea and vomiting caused by cancer chemotherapy conducted in the 1970s and 1980s, concluding, "Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief."

(3) Manuel Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews* 3 (2003): 745-766.

In this review article, Dr. Guzman, a leading cancer researcher, examined the data regarding use of marijuana and cannabinoids in cancer treatment. He concluded that marijuana/cannabinoids can be useful in preventing or treating "chemotherapy-induced nausea and vomiting." He also noted that cannabinoids have potential as antitumor agents: "Regarding effectiveness, cannabinoids exert a notable antitumour activity... Regarding toxicity, cannabinoids not only show a good safety profile but also have palliative effects in patients with cancer, indicating that clinical trials with cannabinoids in cancer therapy are feasible."

(4) K. Nelson, et al., "A Phase II Study of Delta-9-Tetrahydrocannabinol for Appetite Stimulation in Cancer-Associated Anorexia," *Journal of Palliative Care* 10, no. 1 (1994): 14-8.

In this study of patients with anorexia due to advanced cancer, the researchers concluded, "THC is an effective appetite stimulant in patients with advanced cancer. It is well tolerated at low doses."

(5) Marta Duran, et al., "Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting," *Journal of Clinical Pharmacology* 70, no. 4 (2010): 656-63.

The researchers who conducted this double-blind, placebo-controlled clinical trial concluded that compared to the placebo, the whole plant cannabis (marijuana) medicine "added to standard antiemetic therapy was well tolerated and provided better protection against delayed CINV [chemotherapy-induced nausea and vomiting]."

(6) Kramer, Joan L. (2015). "Medical Marijuana for Cancer," *CA: A Cancer Journal for Clinicians,* 65(2): 109-122.

This literature review found significant evidence for marijuana use improving appetite, nausea, and pain. All but one of the studies analyzed noted an improvement in nausea, with smoked marijuana at least as effective as THC or synthetic cannabinoids. Additionally, the synthetic compound nabilone was found to produce more central nervous system side effects than marijuana or THC. The study also found a large consensus on the ability of marijuana to treat pain. Patients with a higher marijuana tolerance experienced greater pain tolerance with marijuana use. Marijuana was also shown to effectively improve appetite, with one study showing improvements in appetite for those with wasting syndrome.

(7) McAllister, Sean D., Murase Ryuichi, Christian, Rigel T., Lau, Darryl, Zielinksi, Anne J., Allison, Juanita, Almanza, Carolina, Pakdel, Arash, Lee, Jasmine, Limbad, Chandani, Liu, Yong, Debs, Robert J., Moore, Dan H. & Desprez, Pierre-Yves. (2011). "Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis," *Breast Cancer Research Treatment Journal* 129: 37-47.

Using human breast cancer cells grown in a culture, researchers observed CBD pathways to the down-regulation of inhibitors related to breast cancer. Using this, the researchers determined CBD acts as an inhibitor for human breast cancer. Similar results were observed when experimenting on immune competent mice, where treatment with CBD reduced both the size and mass of tumors.

HIV/AIDS References

(1) Donald Abrams, et al., "Short-Term Effects of Cannabinoids on Patients With HIV-1 Infection: A Randomized, Placebo-Controlled Clinical Trial," *Annals of Internal Medicine* 139, no. 4 (2003): 258-266.

This preliminary, short-term clinical trial, conducted over 21 days using 62 HIV-infected patients, was designed to examine the short-term safety of smoked marijuana and oral THC on HIV-infected patients, including potential interactions with HIV protease inhibitors, viral load, and CD4 and CD8 counts. Secondary endpoints included weight, caloric intake, and appetite. No safety concerns emerged with either treatment, and the authors concluded, "Our short-duration clinical trial suggests acceptable safety in a vulnerable immune-compromised patient population." Both the marijuana and oral THC groups gained significantly more weight than the placebo group.

(2) B.D. de Jong, et al., "Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea," *Journal of Acquired Immune Deficiency Syndromes* 38, no. 1 (2005): 43-6.

Use of illicit drugs is typically associated with poor adherence to medication regimens. This observational study sought to determine whether this common assumption applies to HIV/AIDS on antiretroviral therapy (ART). Marijuana-using patients who suffered moderate to severe nausea were far more likely to be adherent to ART than those suffering nausea who did not use marijuana (OR = 3.3). The authors concluded, "These data suggest that medicinal use of marijuana may facilitate, rather than impede, ART adherence for patients with nausea, in contrast of other illicit substances," particularly in the case of "use of smoked marijuana specifically for amelioration of nausea."

(3) M. Haney, et al., "Dronabinol and Marijuana in HIV-Positive Marijuana Smokers. Caloric Intake, Mood, and Sleep," *Journal of Acquired Immune Deficiency Syndromes* 45, no. 5 (2007): 545-54.

In this controlled clinical trial, both marijuana and oral THC (dronabinol) use resulted in increased caloric intake and body weight. Strikingly, a dronabinol dose "eight times current recommendations" was required to approximate the effect of relatively low-potency (3.9% THC) marijuana, and only the marijuana improved ratings of sleep. While both drugs produced some intoxication, researchers reported "little evidence of discomfort and no impairment of cognitive performance."

(See the section on chronic pain below for studies of marijuana for HIV-associated peripheral neuropathy.)

Hepatitis C References

(1) D.L. Sylvestre, B.J. Clements, and Y. Malibu, "Cannabis Use Improves Retention and Virological Outcomes in Patients Treated For Hepatitis C," *European Journal of Gastroenterology and Hepatology* 18 (2006): 1057-63.

A prospective observational study was conducted on 71 patients to define the impact of cannabis use during interferon/ribavirin treatment for the hepatitis C virus. Compared to non-users, marijuana users had three times the rate of sustained virological response, apparently due to better treatment adherence. The researchers stated, "[T] he use of cannabis during HCV treatment can improve adherence by increasing the duration of time that patients remain on therapy; this translates to reduced rates of post-treatment virological relapse."

(2) B. Fischer, et al., "Treatment For Hepatitis C Virus and Cannabis use in Illicit Drug User Patients: Implications and Questions," *European Journal of Gastroenterology and Hepatology* 18 (2006): 1039-42.

This commentary, published alongside the above study, placed the results in context, explaining how marijuana "may help address key challenges faced by drug users in HCV treatment (e.g. nausea, depression)."

Other References

(1) Richard W. Foltin, Marian W. Fischman, and Maryanne F. Byrne, "Effects of Smoked Marijuana on Food Intake and Body Weight of Humans Living in a Residential Laboratory," *Appetite* 11 (1988): 1-14.

This study, involving healthy volunteers living in a residential laboratory, documented marijuana's efficacy as an appetite stimulant. Compared to placebo, relatively weak marijuana cigarettes (2.3% THC) smoked at scheduled intervals resulted in a 40% increase in daily caloric intake.

(2) R. Layeeque, et al., "Prevention of Nausea and Vomiting Following Breast Surgery," *American Journal of Surgery* 191, no. 6 (2006): 767-72.

This retrospective review found that a prophylactic regimen combining oral THC with rectal prochlorperazine "significantly reduced the number and severity of episodes" of post-operative nausea and vomiting in breast surgical patients.

Severe, Debilitating Pain

Studies have shown that marijuana is effective in treating pain, including neuropathic pain, which is commonly seen in multiple sclerosis, HIV/AIDS, and other ailments, and notoriously resistant to treatment with conventional pain drugs. Research also suggests that marijuana use may allow reduced opioid doses when given in combination.

References

(1) Wilsey, Barth, et al., "Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain," *The Journal of Pain: Official Journal of the American Pain Society* 14.2 (2013): 136–148.

This double-blind, placebo-controlled study on 30 human subjects found that even low doses of vaporized marijuana were effective at alleviating treatment-resistant neuropathic pain. "Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours."

(2) Donald Abrams, et al., "Cannabinoid-opioid interaction in chronic pain," *Clinical Pharmacology & Therapeutics* (2011): 844-851.

This clinical trial involved 21 individuals with severe pain who were taking sustained-release morphine or oxycodone. It found that vaporized marijuana augmented the analgesic effects of opioids. The authors reported that the adding vaporized marijuana "may allow for opioid treatment at lower doses with fewer side effects."

(3) Mark Ware, et al., "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial," *Canadian Medical Association Journal* (2010): 694-701.

This trial found that "a single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated."

(4) Donald Abrams, et al., "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial," *Neurology* 68, no. 7 (2007): 515-21.

This clinical trial involved HIV/AIDS patients suffering from HIV-associated sensory neuropathy, a painful condition estimated to eventually afflict up to one third of HIV-infected persons. There are presently no FDA-approved treatments for this indication. Donald Abrams and his colleagues tested the efficacy of smoked marijuana on both HIV neuropathy and a type of laboratory-induced pain. Smoked marijuana produced an average 34% reduction in pain and was well tolerated.

(5) R.J. Ellis, et al., "Smoked Medicinal Cannabis For Neuropathic Pain in HIV: a Randomized, Crossover Clinical Trial," *Neuropsychopharmacology* 34, no. 3 (2009): 672-80.

This trial focused on patients with HIV-associated neuropathy refractory to at least two previous analgesic classes. Ellis and colleagues reported, "In the present experiment, cannabis reduced pain intensity and unpleasantness equally. Thus, as with opioids, cannabis does not rely on a relaxing or tranquilizing effect, (e.g. anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree. ... In general, side effects and changes in mood were inconsequential."

(6) B. Wilsey, et al., "A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain," *Journal of Pain* 9, no. 6 (2008): 506-21.

This study investigated the efficacy of smoked marijuana in patients suffering from neuropathic pain related to a variety of conditions, including multiple sclerosis, spinal cord injury, diabetes, and complex regional pain syndrome. Wilsey and colleagues concluded, "This study adds to a growing body of evidence that cannabis may be

effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs."

(7) David Baker, et al., "The Therapeutic Potential of Cannabis," *The Lancet Neurology* 2, no. 5 (2003): 291-8.

This review, written prior to publication of the clinical trials described above, discussed in detail the biochemical basis for marijuana's analgesic effects. It also discussed the drawbacks of oral dosing (taking a pill with cannabinoids), explaining that "oral administration is probably the least satisfactory route for cannabis owing to sequestration of cannabinoids into fat from which there is slow and variable release into plasma. In addition, significant first-pass metabolism in the liver, which degrades THC, contributes to the variability of circulating concentrations of orally administered cannabinoids, which makes dose titration more difficult and therefore increases the potential for adverse psychoactive effects. Smoking has been the route of choice for many cannabis users because it delivers a more rapid 'hit' and allows more accurate dose-titration."

(8) M.E. Lynch, J. Young, A.J. Clark, "A Case Series of Patients Using Medicinal Marihuana for Management of Chronic Pain Under the Canadian Marihuana Medical Access Regulations," *Journal of Pain and Symptom Management* 32, no. 5 (2006): 497-501.

This case series is based on 30 patients qualified to use medical marijuana under Canadian regulations, seen at a pain management center in Nova Scotia. All suffered from chronic, severe pain that had not responded to conventional approaches. On an 11-point scale, 93% reported pain relief equal to six or greater, and many reported relief of other symptoms such as spasticity, poor sleep, nausea, and vomiting. 70% reported being "able to decrease use of other medications that had been causing side effects (e.g., NSAIDs, opioids, and antidepressants)."

(9) Johnson, Jeremy R., Burnell-Nugent, Mary, Lossignol, Dominique, Ganae-Motan, Elena Doina, Potts, Richard & Fallon, Marie T. (2010). "Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC extract in Patients with Intractable Cancer-Related Pain," *Journal of Pain and Symptom Management* 39(2): 167-179.

This study compared the efficacy of a THC:CBD extract, a strictly THC extract, and a placebo for pain relief in patients suffering from intractable cancer-related pain. On the numerical rating scale for pain, the THC:CBD extract showed a statistically significant reduction in pain from the placebo, while the THC extract did not. A statistically significant odds ratio of 2:1 was shown between patients using the THC:CBD extract versus placebo for patients who experienced a reduction in pain of greater than 30%.

(10) Webb, Charles W. & Webb, Sandra M. (2014). "Therapeutic Benefits of Cannabis: A Patient Survey," *Hawai'i Journal of Medicine & Public Health* 73(4): 109-111.

Researchers handed out surveys to 100 patients returning for annual medical marijuana recertification in the state of Hawaii. Of the 94% of patients that responded, 97% used medical marijuana for pain relief with an average pain improvement from 7.8 to 2.8 on a ten-point scale. Additionally, 50% of the patients reported relief from anxiety, 45% reported relief from insomnia, and 71% reported no adverse side effects at all. The study concluded that medical cannabis has the potential to treat numerous medical conditions.

Glaucoma

Glaucoma is a leading cause of blindness, damaging the optic nerve, which is responsible for carrying images from the eye to the brain. High pressure within the eye is one of the main risk factors for this optic nerve damage. There currently is no cure for glaucoma. Marijuana helps relieve the pressure within the eye, thus preventing damage.

Although other drugs are considered first-line glaucoma treatments, some patients and physicians have found marijuana useful when conventional drugs fail. One of the three patients who still receive medical marijuana from the federal government – Elvy Musikka – is a glaucoma patient, who also successfully argued in a Florida court case that marijuana was medically necessary to maintaining her vision.

(1) J.E. Joy, S.J. Watson, and J.A. Benson, Marijuana and Medicine: Assessing the Science Base (National Academy Press, 1999).

"In a number of studies of healthy adults and glaucoma pressure, IOP (intra-ocular pressure) was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC — a reduction as good as that observed with most other medications available today."

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord, progressively reducing the ability of the brain to initiate and control muscle movement. Some research has shown that cannabinoids can delay the progression of ALS. Some ALS patients have indicated that medical marijuana has helped alleviate their symptoms, such as pain, appetite loss, depression, and drooling.

References

(1) Gregory T. Carter and Bill S. Rosen, "Marijuana in the Management of Amyotrophic Lateral Sclerosis," *American Journal of Hospice and Palliative Care* 18, no. 4 (2001): 264-69.

This review article, co-authored by a leading ALS and palliative medicine researcher from the University of Washington, concluded that marijuana may help with many symptoms of ALS, including pain, spasticity, drooling, dysautonomia, and wasting. The authors also discussed how marijuana's antioxidative and neuroprotective effects may prolong neuronal cell survival, and concluded, "In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS."

(2) E. de Lago, J. Fernández-Ruiz, "Cannabinoids and Neuroprotection in Motor-Related Disorders," *CNS and Neurological Disorders — Drug Targets* 6, no. 6 (2007): 377-87.

This review explored in detail the mechanisms of cannabinoid neuroprotection related to a variety of disorders, including ALS.

(3) Dagmar Amtmann, et al., "Survey of Cannabis Use in Patients With Amyotrophic Lateral Sclerosis," *American Journal of Hospice and Palliative Medicine*, March-April 2004.

This anonymous survey of 131 people with ALS found that 10 percent had reported using marijuana in the past year, reporting relief of multiple symptoms. The authors concluded, "...results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling."

Crohn's disease

Crohn's disease is marked by inflammation of the digestive tract, most commonly the lower part of the small intestine. It can cause severe abdominal pain, nausea, and weight loss – all symptoms that marijuana can help mitigate, as noted in other sections of this document. Preclinical research has demonstrated the role of the endocannabinoid system, the body's natural, marijuana-like chemicals, in protecting the GI tract, providing support for anecdotal reports of relief.

References

(1) J.E. Joy, S.J. Watson, and J.A. Benson, *Marijuana and Medicine: Assessing the Science Base* (National Academy Press, 1999).

"For patients ... who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

(2) F. Massa, M. Storr, and B. Lutz, "The Endocannabinoid System in the Physiology and Pathophysiology of the Gastrointestinal Tract," *Journal of Molecular Medicine* 83, no. 12 (2005): 944-54.

This review article noted, "Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Such protective activities are largely in agreement with anecdotal reports from folk medicine on the use of Cannabis sativa extracts by subjects suffering from various GI disorders."

(3) Timna Naftali, et al., "Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study," *Clinical Gastroenterology and Hepatology* (2013).

This placebo-controlled clinical trial found that complete remission was achieved in five out of 11 subjects who were administered cannabis, compared to one of the 10 who received a placebo. "A clinical response was observed in 10 of 11 subjects in the cannabis group and four of 10 in the placebo group. Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects." (*technical parentheticals within the quote deleted*)

(4) Adi Lahate, et al., "Impact of Cannabis Treatment on the Quality of Life, Weight, and Clinical Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Prospective Study," *Digestion* (2012).

This study found that inhaled cannabis improves quality of life in patients with Crohn's disease and ulcerative colitis. After three months of treatment, patients had a statistically significant increase in weight and improvement in clinical disease activity index. The data showed "a statistically significant improvement in almost all aspects of patients' daily life." This included "a statistically significant physical pain reduction during treatment, as well as improvement in mental distress …" In addition, none of the patients "complained of any side effect that disturbed their working ability. In fact, as was shown in the results, there was a statistically significant improvement in patients' ability to work after treatment."

(5) Timna Naftali, et al., "Treatment of Crohn's Disease with Cannabis: An Observational Study," *Israel Medical Association Journal* (2011).

This study of 30 patients found that 21 had significant improvement with cannabis treatment. "The mean number of bowel movements decreased from eight to

five a day and the need for other drugs was significantly reduced … the number of patients requiring steroid treatment was reduced from 26 to 4. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgery during an average period of 3 years of cannabis use." The authors noted the effects could be due to cannabis' anti-inflammatory properties. In addition, "Cannabinoids influence gastrointestinal motility and, in particular, have an anti-diarrheal effect …"

Agitation of Alzheimer's disease

In preliminary research, THC has been shown to reduce agitation in severely demented Alzheimer's patients. Preclinical research also suggests that marijuana components may help retard the progression of Alzheimer's disease.

References

(1) S. Walther, et al., "Delta-9-Tetrahydrocannabinol for Nighttime Agitation in Severe Dementia," *Psychopharmacology* (Berl) 185, no. 4 (2006): 524-8.

This open-label pilot study reported, "Compared to baseline, dronabinol led to a reduction in nocturnal motor activity (P=0.028). These findings were corroborated by improvements in Neuropsychiatric Inventory total score (P=0.027) as well as in subscores for agitation, aberrant motor, and nighttime behaviors (P<0.05). No side effects were observed."

(2) G. Esposito, et al., "The Marijuana Component Cannabidiol Inhibits Beta-Amyloid-Induced Tau Protein Hyperphosphorylation Through Wnt/beta-catenin Pathway Rescue in PC12 Cells," *Journal of Molecular Medicine* 84, no. 3 (2006): 253-8.

"Here, we report that cannabidiol inhibits hyperphosphorylation of tau protein in Abeta-stimulated PC12 neuronal cells, which is one of the most representative hallmarks in AD. ... These results provide new molecular insight regarding the neuroprotective effect of cannabidiol and suggest its possible role in the pharmacological management of AD, especially in view of its low toxicity in humans."

Multiple sclerosis, seizures, muscle spasms

Clinical trials involving whole plant marijuana and various marijuana extracts have found that patients reported relief of muscle stiffness, pain, and spasticity.

Considerable data from animal models as well as some human clinical evidence suggest a role for marijuana in the treatment of seizure disorders such as epilepsy.

Multiple Sclerosis References

(1) Jody Corey-Bloom, et al., "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial," *Canadian Medical Association Journal* 184, no. 10 (2012): 1143–1150.

This placebo-controlled, crossover trial of 37 participants with multiple sclerosis and spasticity found that smoked cannabis was superior to placebos in reducing pain and spasticity. The authors recommended that, "Future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact." There were no serious adverse events during the trial.

(2) J. Zajicek, et al., "Multiple Sclerosis and Extract of Cannabis: Results of the MUSEC trial," *Journal of Neurology, Neurosurgery & Psychiatry* 83: no 11 (2012): 1125-1132.

This double blind, placebo controlled, phrase III clinical trial found that patients found almost twice as much relief from muscle stiffness from oral cannabis extract than from the placebo.

(3) A Novotna, et al., "A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis," *European Journal of Neurology* 18, no. 9 (2011): 1122-1131.

This phase 3 double-blind, placebo-controlled study on patients whose multiple sclerosis spasticity was not fully alleviated by other therapies found that more than 47% had their spasticity improve by at least 20 during the first four weeks of the trial. This trial involved Sativex, which is a cannabis extract that is approved for multiple sclerosis spasticity in several European countries, New Zealand, and Canada, but which is not legally available to patients in the United States.

(4) J. Zajicek, et al., "Cannabinoids for Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis (CAMS Study): Multicentre Randomised Placebo-Controlled Trial," *The Lancet* 362 (2003): 1517-26.

This trial, using an oral cannabis extract, reported "evidence of a treatment effect on patient-reported spasticity and pain (p=0·003), with improvement in spasticity reported in 61% (n=121, 95% CI 54·6–68·2), 60% (n=108, 52·5– 66·8), and 46% (n=91, 39·0–52·9) of participants on cannabis extract, 9-THC, and placebo, respectively."

(5) D.T. Wade, et al., "Long-Term Use of a Cannabis-Based Medicine in the Treatment of Spasticity and Other Symptoms in Multiple Sclerosis," *Multiple Sclerosis* 12 (2006): 639-45.

In this long-term follow-up of a clinical trial of a marijuana-based oral spray, patients were followed for as much as 82 weeks. The marijuana spray demonstrated long-term relief of spasticity, pain, and bladder issues related to MS, "without unacceptable adverse effects."

(6) Collin, C., Davies, P., Mutiboko, I.K. & Ratclifee, S. (2007) "Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis," *European Journal of Neurology* 14: 290-296.

This double-blind study compared the effects of a placebo versus a whole plant based treatment containing THC and CBD. Over a six-week period of use, 40% of the subjects treated with cannabis saw a reduction in spasticity of more than 30% and 17.5% saw a reduction greater than 50%. A number of subjects also saw an increase in muscle power in their legs, and 57% of the subjects experienced a global improvement in symptoms. The authors noted surprise at the low dropout rate of subjects for such a high dosage of THC, which the authors attributed to the CBD in the medicine. The authors concluded that cannabis-based medications could be useful in symptomatic relief of spasticity for patients with MS.

(7) Flachenecker, Peter, Henze, Thomas & Zettl, Uwe K. (2014). "Long-Term Effectiveness and Safety of Nabiximols (Tetrahydrocannabidol/Cannabidiol Oromucosal Spray) in Clinical Practice," *European Neurology* 72: 95-102.

Multiple sclerosis patients taking nabiximols — a THC/CBD spray — were surveyed over a 12-month period. On a 10-point spasticity scale, a statistically significant average reduction from 6.0 to 4.8 was observed after the first month, with scores remaining constant for the remaining 11 months. Eighty-four percent of the subjects reported no adverse side effects. The authors concluded the data confirmed long-term efficacy of nabiximols for MS patients.

Epilepsy and Other References

(1) Alsasua del Valle, "Implication of Cannabinoids in Neurological Diseases," *Cellular and Molecular Neurobiology* 26, no. 4-6 (2006): 579-91

This wide-ranging review of the neurobiology of marijuana and its constituents in relation to neuroprotection and neurological disease noted, "It has been known for centuries that exogenous cannabinoids have anti-convulsant activity."

(2) K. Mortati, B. Dworetzky, and O. Devinsky, "Marijuana: an Effective Antiepileptic Treatment in Partial Epilepsy? A Case Report and Review of the Literature," *Reviews in Neurological Diseases* 4, no. 2 (2007): 103-6.

Mortati and colleagues reported the case of a 45-year-old male with cerebral palsy and epilepsy "who showed marked improvement with the use of marijuana."The authors reviewed the current literature and concluded, "Although more data are needed, animal studies and clinical experience suggest that marijuana or its active constituents may have a place in the treatment of partial epilepsy."

(3) D.W. Gross, et al., "Marijuana Use and Epilepsy: Prevalence in Patients of a Tertiary Care Epilepsy Center," *Neurology* 62, no. 11 (2004): 2095-7.

In this patient survey, of 28 epileptic patients who actively used marijuana, 68% reported that it improved severity of seizures and 54% reported improvement of seizure frequency. None reported that it worsened these symptoms.

Post Traumatic Stress Disorder

Post-traumatic stress disorder involves a person developing characteristic symptoms — such as flashbacks, numbing, and avoidance — after personally experiencing an extremely traumatic stressor. Available treatments are often not effective. Unfortunately, there has been limited research on whole plant marijuana and PTSD, including due to the U.S. federal government refusing to provide marijuana to an FDA-approved and institutional review board-approved study. However, there are clinical trials are ongoing in Israel, where an open pilot study found marijuana effective at alleviating symptoms of combat veterans. In addition, other human and animal evidence supports the therapeutic potential of cannabis and cannabinoids in treating PTSD symptoms.

References

(1) Torsten Passie, et al., "Mitigation of post-traumatic stress symptom by Cannabis resin: A review of the clinical and neurobiological evidence," *Drug Testing and Analysis* (2012): 649-659

This is a case report of a 19-year-old patient who had severe PTSD, including panic attacks and self-mutilation. He discovered that his major symptoms were dramatically reduced by smoking cannabis resin. As the abstract explains, "The major part of this review is concerned with the clinical and preclinical neurobiological evidence in order to offer a potential explanation of these effects on symptom reduction in PTSD." It noted, "Evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and antidepressive effects."

(2) George Fraser, "The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD)," *CNS Neuroscience & Therapeutics* 15, no 1. (2009): 84-88.

This study involved administering a naboline — a prescription drug made of a synthetic cannabinoid (component of marijuana) to patients with treatment-resistant nightmares who had PTSD. They reported, "The majority of patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time, the quality of sleep, and the reduction of day-time flashbacks and nightsweats were also noted by some patients."

(3) Eti Ganon-Elaza and Irit Akirav, "Cannabinoids Prevent the Development of Behavioral and Endocrine Alterations in a Rat Model of Intense Stress," *Neuropsychopharmacology* (2012): 456–466.

In this study, synthetic marijuana was given to rats after a traumatic event. It was able to block symptoms of PTSD after the rodents were exposed to extreme stress. All of the rats experienced anxiety, but symptoms of PTSD disappeared in the group given marijuana within the two or 24-hour time frame. The findings concluded that, "cannabinoids could serve as a pharmacological treatment of stress- and trauma-related disorder."

(4) George R. Greer M.D., Charles S. Grob M.D. & Adam L. Halberstadt Ph.D. (2014). "PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program," *Journal of Psychoactive Drugs* 46(1): 73-77.

In 2011, 34% of patients participating in New Mexico's medical cannabis program were diagnosed with PTSD. Authors evaluated patients based on the Clinician-Administered PTSD Score (CAPS). The results showed a statistically significant decline in the CAPS scores for patients using cannabis across all major categories in the CAPS evaluation. Based on these conclusions, the authors showed that cannabis is associated with a reduction in PTSD symptoms for some patients and supported a placebo-controlled study for further research.

(5) Papini, Santiago, Sullivan, Gregory M., Hein, Denise A., Shvil, Erel & Neria, Yuval. (2015). "Toward a translational approach to targeting the endocannabinoid system in posttraumatic stress disorder: A critical review of preclinical research," *Biological Psychology* 104: 8-18.

This study trained mice to develop fear-based responses to certain stimuli and then examined the effects of cannabinoids on the treatment of PTSD developed through previous conditioning. The study confirmed previous research that disruption of CB1 receptors impairs fear extinction (the ability of an organism to stop reacting negatively to stimuli after the negative consequences of that stimuli cease). The study also found

some success in treating rats with CB1 agonists during extinction therapy and found similar results for humans. The study concluded that using CB1 agonists could be used to improve the effectiveness of extinction therapy for those with PTSD or for those at risk for developing PTSD.

(6) Roitman, Pablo, Mechoulam, Raphael, Cooper-Kazas, Rena & Shalev, Arieh. (2014). "Preliminary, Open-Label, Pilot Study PTSD," *Clinical Drug Investigation* 34: 587-591.

This study examined the effects of orally ingested THC for 10 subjects with post-traumatic stress disorder. Patients experienced only mild side effects like dry mouth or dizziness in some cases, and none of the side effects were severe enough to cause the patients to drop out of the study. The data showed a statistically significant relationship between using THC to treat PTSD and an improvement in overall severity of sleep quality, nightmare frequency, and PTSD hyperarousal symptoms like feelings of tenseness or being easily startled. The authors recommend further research based on the results of the pilot study.

Vaporization as an Alternative to Smoking

One often-mentioned objection to medical use of marijuana is the respiratory risk associated with smoking. For this reason, the Institute of Medicine urged development of a "nonsmoked, rapid-onset cannabinoid delivery system." Published research suggests that vaporization — in which marijuana is heated to the point where cannabinoid vapors are released, but not to the point of combustion — represents a viable solution to this problem.

References

(1) A. Hazekamp, et al., "Evaluation of a Vaporizing Device (Volcano) for the Pulmonary Administration of Tetrahydrocannabinol," *Journal of Pharmaceutical Sciences* 95, no. 6 (2006): 1308-17.

This laboratory test of a commercially available vaporizer known as the Volcano used language striking similar to that of the Institute of Medicine, concluding, "Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients."

(2) D.I. Abrams, et al., "Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study," *Clinical Pharmacology and Therapeutics* 282, no. 5 (2007): 572-8.

In this clinical trial, again using the Volcano vaporizer, volunteers were randomly assigned to either smoke or vaporize marijuana of three different strengths.

Vaporization was comparable to smoking in terms of THC delivery, but dramatically reduced the amount of carbon monoxide, indicating "little or no exposure to gaseous combustion toxins." The researchers concluded that vaporization "therefore is expected to be much safer than smoking marijuana cigarettes."

(3) M. Earleywine and S.S. Barnwell, "Decreased Respiratory Symptoms in Cannabis Users Who Vaporize," *Harm Reduction Journal* 4, no. 11 (2007).

This internet sample of nearly 7,000 participants compared self-reported respiratory symptoms among marijuana users whose primary method was smoking with those whose primary method was vaporization, reporting, "use of a vaporizer predicted fewer respiratory symptoms even when age, sex, cigarette smoking, and amount of cannabis used were taken into account."

(4) Earleywine, Mitch & van Dam, Nicholas T. (2010). "Case studies in cannabis vaporization," *Addiction Research and Theory,* 18(3): 243-249.

This study found four cannabis smokers reporting negative respiratory symptoms and asked them to begin using a vaporizer. After one month of use, the smokers self-reported dramatic improvements in respiratory symptoms and lung function. The authors concluded that vaporization can improve respiratory-related side effects of cannabis use and recommended further study.

Exhibit 4

Marijuana and Medicine

Assessing the Science Base

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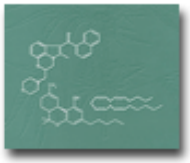
Executive Summary



Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite "scientific evidence" to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids (see the Statement of Task on page 9). That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state "medical marijuana" initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona's referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, most of which lie outside the scope of this report. Controversies concerning the nonmedical use of marijuana spill over into the medical marijuana debate and obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on social issues, the study team found substantial consensus among experts in the relevant disciplines on the scientific evidence about potential medical uses of marijuana.

This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Throughout this report, *marijuana* refers to unpurified plant substances, including leaves or flower tops whether consumed by ingestion or smoking. References to the "effects of marijuana" should be understood to include the composite effects of its various components; that is, the effects of tetrahydrocannabinol (THC), which is the primary psychoactive ingredient in marijuana, are included among its effects, but not all the effects of marijuana are necessarily due to THC. *Cannabinoids* are the group of compounds related to THC, whether found in the marijuana plant, in animals, or synthesized in chemistry laboratories.

Three focal concerns in evaluating the medical use of marijuana are:

1. Evaluation of the effects of isolated cannabinoids;

2. Evaluation of the risks associated with the medical use of marijuana; and

3. Evaluation of the use of smoked marijuana.

EFFECTS OF ISOLATED CANNABINOIDS

Cannabinoid Biology

Much has been learned since the 1982 IOM report *Marijuana and Health*. Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. In addition, too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That all changed with the identification and characterization of cannabinoid receptors in the 1980s and 1990s. During the past 16 years, science has advanced greatly and can tell us much more about the potential medical benefits of cannabinoids.

Conclusion: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).

Conclusion: The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

Recommendation 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to

have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Efficacy of Cannabinoid Drugs

The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation. The therapeutic effects of cannabinoids are best established for THC, which is generally one of the two most abundant of the cannabinoids in marijuana. (Cannabidiol is generally the other most abundant cannabinoid.)

The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications. However, people vary in their responses to medications, and there will likely always be a subpopulation of patients who do not respond well to other medications. The combination of cannabinoid drug effects (anxiety reduction, appetite stimulation, nausea reduction, and pain relief) suggests that cannabinoids would be moderately well suited for particular conditions, such as chemotherapy-induced nausea and vomiting and AIDS wasting.

Defined substances, such as purified cannabinoid compounds, are preferable to plant products, which are of variable and uncertain composition. Use of defined cannabinoids permits a more precise evaluation of their effects, whether in combination or alone. Medications that can maximize the desired effects of cannabinoids and minimize the undesired effects can very likely be identified.

Although most scientists who study cannabinoids agree that the pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public for medical use. Cannabinoid-based drugs will only become available if public investment in cannabinoid drug research is sustained and if there is enough incentive for private enterprise to develop and market such drugs.

Conclusion: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

Influence of Psychological Effects on Therapeutic Effects

The psychological effects of THC and similar cannabinoids pose three issues for the therapeutic use of cannabinoid drugs. First, for some patients--particularly older patients with no previous marijuana experience--the psychological effects are disturbing. Those

patients report experiencing unpleasant feelings and disorientation after being treated with THC, generally more severe for oral THC than for smoked marijuana. Second, for conditions such as movement disorders or nausea, in which anxiety exacerbates the symptoms, the antianxiety effects of cannabinoid drugs can influence symptoms indirectly. This can be beneficial or can create false impressions of the drug effect. Third, for cases in which symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy; for example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite.

> **Conclusion:** The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.
>
> **Recommendation 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.**

RISKS ASSOCIATED WITH MEDICAL USE OF MARIJUANA

Physiological Risks

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. The harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse. When interpreting studies purporting to show the harmful effects of marijuana, it is important to keep in mind that the majority of those studies are based on *smoked* marijuana, and cannabinoid effects cannot be separated from the effects of inhaling smoke from burning plant material and contaminants.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance. It is, therefore, inadvisable to operate any vehicle or potentially dangerous equipment while under the influence of marijuana, THC, or any cannabinoid drug with comparable effects. In addition, a minority of marijuana users experience dysphoria, or unpleasant feelings. Finally, the short-term immunosuppressive effects are not well established but, if they exist, are not likely great enough to preclude a legitimate medical use.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking and the effects of THC. Marijuana smoking is associated with abnormalities of cells lining the human respiratory tract. Marijuana smoke, like tobacco smoke, is associated with increased risk of cancer, lung

damage, and poor pregnancy outcomes. Although cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer, proof that habitual marijuana smoking does or does not cause cancer awaits the results of well-designed studies.

> **Conclusion:** Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

> **Recommendation 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.**

Marijuana Dependence and Withdrawal

A second concern associated with chronic marijuana use is dependence on the psychoactive effects of THC. Although few marijuana users develop dependence, some do. Risk factors for marijuana dependence are similar to those for other forms of substance abuse. In particular, anti-social personality and conduct disorders are closely associated with substance abuse.

> **Conclusion:** A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.

Marijuana as a "Gateway" Drug

Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana--usually before they are of legal age.

In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, "gateway" to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use.

Finally, there is a broad social concern that sanctioning the medical use of marijuana might increase its use among the general population. At this point there are no convincing data to support this concern. The existing data are consistent with the idea that this would

not be a problem if the medical use of marijuana were as closely regulated as other medications with abuse potential.

> **Conclusion:** Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

USE OF SMOKED MARIJUANA

Because of the health risks associated with smoking, smoked marijuana should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern. Further, despite the legal, social, and health problems associated with smoking marijuana, it is widely used by certain patient groups.

> **Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.**

The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the possible development of nonsmoked rapid-onset cannabinoid delivery systems. However, it will likely be many years before a safe and effective cannabinoid delivery system, such as an inhaler, is available for patients. In the meantime there are patients with debilitating symptoms for whom smoked marijuana might provide relief. The use of smoked marijuana for those patients should weigh both the expected efficacy of marijuana and ethical issues in patient care, including providing information about the known and suspected risks of smoked marijuana use.

> **Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:**
>
> - **failure of all approved medications to provide relief has been documented,**
> - **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
> - **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
> - **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a**

submission by a physician to provide marijuana to a patient for a specified use.

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n*-of-1 clinical trials (single-patient trials), in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions.

STATEMENT OF TASK

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

Specific Issues

Specific issues to be addressed fall under three broad categories: science base, therapeutic use, and economics.

Science Base

- Review of the neuroscience related to marijuana, particularly the relevance of new studies on addiction and craving
- Review of the behavioral and social science base of

marijuana use, particularly an assessment of the relative risk of progression to other drugs following marijuana use
- Review of the literature determining which chemical components of crude marijuana are responsible for possible therapeutic effects and for side effects

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups
- Efficacy and side effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Differential effects of various forms of marijuana that relate to age or type of disease

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Assessment of differences between marijuana and existing medications in terms of access and availability

RECOMMENDATIONS

Recommendation 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect.

Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of

developing rapid-onset, reliable, and safe delivery systems.

The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

Recommendation 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

Recommendation 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid

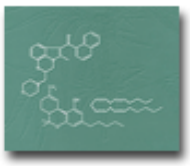
delivery systems.

Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

1

Introduction



This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Scientific data on controversial subjects are commonly misinterpreted, overinterpreted, and misrepresented, and the medical marijuana debate is no exception. We have tried to present the scientific studies in such a way as to reveal their strengths and limitations. One of the goals of this report is to help people to understand the scientific data, including the logic behind the scientific conclusions, so it goes into greater detail than previous reports on the subject. In many cases, we have explained why particular studies are inconclusive and what sort of evidence is needed to support particular claims about the harms or benefits attributed to marijuana. Ideally, this report will enable the thoughtful reader to interpret new information about marijuana that will continue to emerge rapidly well after this report is published.

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, which lie outside the scope of this report. Controversies concerning nonmedical use of marijuana spill over onto the medical marijuana debate and tend to obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on the social issues, the study team found substantial consensus, among experts in the relevant disciplines, on the scientific evidence bearing on potential medical use. This report analyzes science, not the law. As in any policy debate, the value of scientific analysis is that it can provide a foundation for further discussion. Distilling scientific evidence does not in itself solve a policy problem. What it can do is illuminate the common ground, bringing to light fundamental differences out of the shadows of misunderstanding and misinformation that currently prevail. Scientific analysis cannot be the end of the debate, but it should at least provide the basis for an honest and informed discussion.

Our analysis of the evidence and arguments concerning the medical use of marijuana focuses on the strength of the supporting evidence and does not refer to the motivations of people who put forth the evidence and arguments. That is, it is not relevant to scientific validity whether an argument is put forth by someone who believes that all marijuana use should be legal or by someone who believes that any marijuana use is highly damaging to individual users and to society as a whole. Nor does this report comment on the degree to which scientific analysis is compatible with current regulatory policy. Although many have argued that current drug laws pertaining to marijuana are inconsistent with scientific

data, it is important to understand that decisions about drug regulation are based on a variety of moral and social considerations, as well as on medical and scientific ones.

Even when a drug is used only for medical purposes, value judgments affect policy decisions concerning its medical use. For example, the magnitude of a drug's expected medical benefit affects regulatory judgments about the acceptability of risks associated with its use. Also, although a drug is normally approved for medical use only on proof of its "safety and efficacy," patients with life-threatening conditions are sometimes (under protocols for "compassionate use") allowed access to unapproved drugs whose benefits and risks are uncertain. Value judgments play an even more substantial role in regulatory decisions concerning drugs, such as marijuana, that are sought and used for nonmedical purposes. Then policymakers must take into account not only the risks and benefits associated with medical use but also possible interactions between the regulatory arrangements governing medical use and the integrity of the legal controls set up to restrict nonmedical use.

It should be clear that many elements of drug control policy lie outside the realm of biology and medicine. Ultimately, the complex moral and social judgments that underlie drug control policy must be made by the American people and their elected officials. A goal of this report is to evaluate the biological and medical factors that should be taken into account in making those judgments.

HOW THIS STUDY WAS CONDUCTED

Information was gathered through scientific workshops, site visits, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops--in Irvine, California; New Orleans, Louisiana; and Washington, D.C.--were open to the public and included scientific presentations and reports, mostly from patients and their families, about their experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics (listed in Appendix B). Selection of the experts was based on recommendations by their peers, who ranked them among the most accomplished scientists and the most knowledgeable about marijuana and cannabinoids in their own fields. In addition, advocates for (John Morgan) and against (Eric A. Voth) the medical use of marijuana were invited to present scientific evidence in support of their positions.

Information presented at the scientific workshops was supplemented by analysis of the scientific literature and evaluating the methods used in various studies and the validity of the authors' conclusions. Different kinds of clinical studies are useful in different ways: results of a controlled double-blind study with adequate sample sizes can be expected to apply to the general population from which study subjects were drawn; an isolated case report can suggest further studies but cannot be presumed to be broadly applicable; and survey data can be highly informative but are generally limited by the need to rely on self-reports of drug use and on unconfirmed medical diagnoses. This report relies mainly on the most relevant and methodologically rigorous studies available and treats the results

of more limited studies cautiously. In addition, study results are presented in such a way as to allow thoughtful readers to judge the results themselves.

The Institute of Medicine (IOM) appointed a panel of nine experts to advise the study team on technical issues. These included neurology and the treatment of pain (Howard Fields); regulation of prescription drugs (J. Richard Crout); AIDS wasting and clinical trials (Judith Feinberg); treatment and pathology of multiple sclerosis (Timothy Vollmer); drug dependence among adolescents (Thomas Crowley); varieties of drug dependence (Dorothy Hatsukami); internal medicine, health care delivery, and clinical epidemiology (Eric B. Larson); cannabinoids and marijuana pharmacology (Billy R. Martin); and cannabinoid neuroscience (Steven R. Childers).

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for comment from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations--particularly those opposed to the medical use of marijuana--felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

The study team visited four cannabis buyers' clubs in California (the Oakland Cannabis Buyers' Cooperative, the San Francisco Cannabis Cultivators Club, the Los Angeles Cannabis Resource Center, and Californians Helping Alleviate Medical Problems, or CHAMPS) and two HIV/AIDS clinics (AIDS Health Care Foundation in Los Angeles and Louisiana State University Medical Center in New Orleans). We listened to many individual stories from the buyers' clubs about using marijuana to treat a variety of symptoms and heard clinical observations on the use of Marinol to treat AIDS patients. Marinol is the brand name for dronabinol, which is Δ^9-tetrahydrocannabinol (THC) in pill form and is available by prescription for the treatment of nausea associated with chemotherapy and AIDS wasting.

MARIJUANA TODAY

The Changing Legal Landscape

In the 20th century, marijuana has been used more for its euphoric effects than as a medicine. Its psychological and behavioral effects have concerned public officials since the drug first appeared in the southwestern and southern states during the first two decades of the century. By 1931, at least 29 states had prohibited use of the drug for nonmedical purposes.[3] Marijuana was first regulated at the federal level by the Marijuana Tax Act of 1937, which required anyone producing, distributing, or using marijuana for medical purposes to register and pay a tax and which effectively prohibited nonmedical use of the drug. Although the act did not make medical use of marijuana illegal, it did make it expensive and inconvenient. In 1942, marijuana was removed from the U.S.

Pharmacopoeia because it was believed to be a harmful and addictive drug that caused psychoses, mental deterioration, and violent behavior.

In the late 1960s and early 1970s, there was a sharp increase in marijuana use among adolescents and young adults. The current legal status of marijuana was established in 1970 with the passage of the Controlled Substances Act, which divided drugs into five schedules and placed marijuana in Schedule I, the category for drugs with high potential for abuse and no accepted medical use (see Appendix C, Scheduling Definitions). In 1972, the National Organization for the Reform of Marijuana Legislation (NORML), an organization that supports decriminalization of marijuana, unsuccessfully petitioned the Bureau of Narcotics and Dangerous Drugs to move marijuana from Schedule I to Schedule II. NORML argued that marijuana is therapeutic in numerous serious ailments, less toxic, and in many cases more effective than conventional medicines.[13] Thus, for 25 years the medical marijuana movement has been closely linked with the marijuana decriminalization movement, which has colored the debate. Many people criticized that association in their letters to IOM and during the public workshops of this study. The argument against the medical use of marijuana presented most often to the IOM study team was that "the medical marijuana movement is a Trojan horse"; that is, it is a deceptive tactic used by advocates of marijuana decriminalization who would exploit the public's sympathy for seriously ill patients.

Since NORML's petition in 1972, there have been a variety of legal decisions concerning marijuana. From 1973 to 1978, 11 states adopted statutes that decriminalized use of marijuana, although some of them recriminalized marijuana use in the 1980s and 1990s. During the 1970s, reports of the medical value of marijuana began to appear, particularly claims that marijuana relieved the nausea associated with chemotherapy. Health departments in six states conducted small studies to investigate the reports. When the AIDS epidemic spread in the 1980s, patients found that marijuana sometimes relieved their symptoms, most dramatically those associated with AIDS wasting. Over this period a number of defendants charged with unlawful possession of marijuana claimed that they were using the drug to treat medical conditions and that violation of the law was therefore justified (the so-called medical necessity defense). Although most courts rejected these claims, some accepted them.[8]

Against that backdrop, voters in California and Arizona in 1996 passed two referenda that attempted to legalize the medical use of marijuana under particular conditions. Public support for patient access to marijuana for medical use appears substantial; public opinion polls taken during 1997 and 1998 generally reported 60—70 percent of respondents in favor of allowing medical uses of marijuana.[15] However, those referenda are at odds with federal laws regulating marijuana, and their implementation raises complex legal questions.

Despite the current level of interest, referenda and public discussions have not been well informed by carefully reasoned scientific debate. Although previous reports have all called for more research, the nature of the research that will be most helpful depends greatly on the specific health conditions to be addressed. And while there have been

important recent advances in our understanding of the physiological effects of marijuana, few of the recent investigators have had the time or resources to permit detailed analysis. The results of those advances, only now beginning to be explored, have significant implications for the medical marijuana debate.

Several months after the passage of the California and Arizona medical marijuana referendums, the Office of National Drug Control Policy (ONDCP) asked whether IOM would conduct a scientific review of the medical value of marijuana and its constituent compounds. In August 1997, IOM formally began the study and appointed John A. Benson Jr. and Stanley J. Watson Jr. to serve as principal investigators for the study. The charge to IOM was to review the medical use of marijuana and the harms and benefits attributed to it (details are given in Appendix D).

Medical Marijuana Legislation Among the States

The 1996 California referendum known as Proposition 215 allowed seriously ill Californians to obtain and use marijuana for medical purposes without criminal prosecution or sanction. A physician's recommendation is needed. Under the law, physicians cannot be punished or denied any right or privilege for recommending marijuana to patients who suffer from any illness for which marijuana will provide relief.

The 1996 Arizona referendum known as Proposition 200 was largely about prison reform but also gave physicians the option to prescribe controlled substances, including those in Schedule I (e.g., marijuana), to treat the disease or relieve the suffering of seriously or terminally ill patients. Five months after the referendum was passed, it was stalled whenArizona legislators voted that all prescription medications must be approved by the Food and Drug Administration, and marijuana is not so approved. In November 1998, Arizona voters passed a second referendum designed to allow physician's to prescribe marijuana as medicine, but this is still at odds with federal law.[8]

As of summer 1998, eight states--California, Connecticut, Louisiana, New Hampshire, Ohio, Vermont, Virginia, and Wisconsin--had laws that permit physicians to prescribe marijuana for medical purposes or to allow a medical necessity defense.[8] In November 1998, five states--Arizona, Alaska, Oregon, Nevada, and Washington--passed medical marijuana ballot initiatives. The District of Columbia also voted on a medical marijuana initiative, but was barred from counting the

votes because an amendment designed to prohibit them from doing so was added to the federal appropriations bill; however, exit polls suggested that a majority of voters had approved the measure.

MARIJUANA AND MEDICINE

Marijuana plants have been used since antiquity for both herbal medication and intoxication. The current debate over the medical use of marijuana is essentially a debate over the value of its medicinal properties relative to the risk posed by its use.

Marijuana's use as an herbal remedy before the 20th century is well documented.[1,10,11] However, modern medicine adheres to different standards from those used in the past. The question is not whether marijuana can be used as an herbal remedy but rather how well this remedy meets today's standards of efficacy and safety. We understand much more than previous generations about medical risks. Our society generally expects its licensed medications to be safe, reliable, and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not tolerated. That refers not only to prescription and over-the-counter drugs but also to vitamin supplements and herbal remedies purchased at the grocery store. For example, the essential amino acid *l*-tryptophan was widely sold in health food stores as a natural remedy for insomnia until early 1990 when it became linked to an epidemic of a new and potentially fatal illness (eosinophilia-myalgia syndrome).[9,12] When it was removed from the market shortly thereafter, there was little protest, despite the fact that it was safe for the vast majority of the population. The 1,536 cases and 27 deaths were later traced to contaminants in a batch produced by a single Japanese manufacturer.

Although few herbal medicines meet today's standards, they have provided the foundation for modern Western pharmaceuticals. Most current prescriptions have their roots either directly or indirectly in plant remedies.[7] At the same time, most current prescriptions are synthetic compounds that are only distantly related to the natural compounds that led to their development. Digitalis was discovered in foxglove, morphine in poppies, and taxol in the yew tree. Even aspirin (acetylsalicylic acid) has its counterpart in herbal medicine: for many generations, American Indians relieved headaches by chewing the bark of the willow tree, which is rich in a related form of salicylic acid.

Although plants continue to be valuable resources for medical advances, drug development is likely to be less and less reliant on plants and more reliant on the tools of

modern science. Molecular biology, bioinformatics software, and DNA array-based analyses of genes and chemistry are all beginning to yield great advances in drug discovery and development. Until recently, drugs could only be *discovered*; now they can be *designed*. Even the discovery process has been accelerated through the use of modern drug-screening techniques. It is increasingly possible to identify or isolate the chemical compounds in a plant, determine which compounds are responsible for the plant's effects, and select the most effective and safe compounds--either for use as purified substances or as tools to develop even more effective, safer, or less expensive compounds.

Yet even as the modern pharmacological toolbox becomes more sophisticated and biotechnology yields an ever greater abundance of therapeutic drugs, people increasingly seek alternative, low-technology therapies.[4,5] In 1997, 46 percent of Americans sought nontraditional medicines and spent over 27 billion unreimbursed dollars; the total number of visits to alternative medicine practitioners appears to have exceeded the number of visits to primary care physicians.[5,6] Recent interest in the medical use of marijuana coincides with this trend toward self-help and a search for "natural" therapies. Indeed, several people who spoke at the IOM public hearings in support of the medical use of marijuana said that they generally preferred herbal medicines to standard pharmaceuticals. However, few alternative therapies have been carefully and systematically tested for safety and efficacy, as is required for medications approved by the FDA (Food and Drug Administration).[2]

WHO USES MEDICAL MARIJUANA?

There have been no comprehensive surveys of the demographics and medical conditions of medical marijuana users, but a few reports provide some indication. In each case, survey results should be understood to reflect the situation in which they were conducted and are not necessarily characteristic of medical marijuana users as a whole. Respondents to surveys reported to the IOM study team were all members of "buyers' clubs," organizations that provide their members with marijuana, although not necessarily through direct cash transactions. The atmosphere of the marijuana buyers' clubs ranges from that of the comparatively formal and closely regulated Oakland Cannabis Buyers' Cooperative to that of a "country club for the indigent," as Denis Peron described the San Francisco Cannabis Cultivators Club (SFCCC), which he directed.

John Mendelson, an internist and pharmacologist at the University of California, San Francisco (UCSF) Pain Management Center, surveyed 100 members of the SFCCC who were using marijuana at least weekly. Most of the respondents were unemployed men in their forties. Subjects were paid $50 to participate in the survey; this might have encouraged a greater representation of unemployed subjects. All subjects were tested for drug use. About half tested positive for marijuana only; the other half tested positive for drugs in addition to marijuana (23% for cocaine and 13% for amphetamines). The predominant disorder was AIDS, followed by roughly equal numbers of members who reported chronic pain, mood disorders, and musculoskeletal disorders (Table 1.1).

The membership profile of the San Francisco club was similar to that of the Los Angeles Cannabis Resource Center (LACRC), where 83% of the 739 patients were men, 45% were 36—45 years old, and 71% were HIV positive. Table 1.2 shows a distribution of conditions somewhat different from that in SFCCC respondents, probably because of a different membership profile. For example, cancer is generally a disease that occurs late in life; 34 (4.7%) of LACRC members were over 55 years old; only 2% of survey respondents in the SFCCC study were over 55 years old.

Jeffrey Jones, executive director of the Oakland Cannabis Buyers' Cooperative, reported that its largest group of patients is HIV-positive men in their forties. The second-largest group is patients with chronic pain.

Among the 42 people who spoke at the public workshops or wrote to the study team, only six identified themselves as members of marijuana buyers' clubs. Nonetheless, they presented a similar profile: HIV/AIDS was the predominant disorder, followed by chronic pain (Tables 1.3 and 1.4). All HIV/AIDS patients reported that marijuana relieved nausea and vomiting and improved their appetite. About half the patients who reported using marijuana for chronic pain also reported that it reduced nausea and vomiting.

Note that the medical conditions referred to are only those reported to the study team or to interviewers; they cannot be assumed to represent complete or accurate diagnoses. Michael Rowbotham, a neurologist at the UCSF Pain Management Center, noted that many pain patients referred to that center arrive with incorrect diagnoses or with pain of unknown origin. At that center the patients who report medical benefit from marijuana say that it does not reduce their pain but enables them to cope with it.

Most--not all--people who use marijuana to relieve medical conditions have previously used it recreationally. An estimated 95% of the LACRC members had used marijuana before joining the club. It is important to emphasize the absence of comprehensive information on marijuana use before its use for medical conditions. Frequency of prior use almost certainly depends on many factors, including membership in a buyers' club, membership in a population sector that uses marijuana more often than others (for example, men 20—30 years old), and the medical condition being treated with marijuana (for example, there are probably relatively fewer recreational marijuana users among cancer patients than among AIDS patients).

Patients who reported their experience with marijuana at the public workshops said that marijuana provided them with great relief from symptoms associated with disparate diseases and ailments, including AIDS wasting, spasticity from multiple sclerosis, depression, chronic pain, and nausea associated with chemotherapy. Their circumstances and symptoms were varied, and the IOM study team was not in a position to make medical evaluations or confirm diagnoses. Three representative cases presented to the IOM study team are presented in Box 1.1; the stories have been edited for brevity, but each case is presented in the patient's words and with the patient's permission.

The variety of stories presented left the study team with a clear view of people's beliefs about how marijuana had helped them. But this collection of anecdotal data, although useful, is limited. We heard many positive stories but no stories from people who had tried marijuana but found it ineffective. This is a fraction with an unknown denominator. For the numerator we have a sample of positive responses; for the denominator we have no idea of the total number of people who have tried marijuana for medical purposes. Hence, it is impossible to estimate the clinical value of marijuana or cannabinoids in the general population based on anecdotal reports. Marijuana clearly seems to relieve some symptoms for some people--even if only as a placebo effect. But what is the balance of harmful and beneficial effects? That is the essential medical question that can be answered only by careful analysis of data collected under controlled conditions.

CANNABIS AND THE CANNABINOIDS

Marijuana is the common name for *Cannabis sativa*, a hemp plant that grows throughout temperate and tropical climates. The most recent review of the constituents of marijuana lists 66 cannabinoids (Table 1.5).[16] But that does not mean there are 66 different cannabinoid effects or interactions. Most of the cannabinoids are closely related; they fall into only 10 groups of closely related cannabinoids, many of which differ by only a single chemical moiety and might be midpoints along biochemical pathways--that is, degradation products, precursors, or byproducts.[16,18] Δ^9-tetrahydrocannabinol (Δ^9-THC) is the primary psychoactive ingredient; depending on the particular plant, either THC or cannabidiol is the most abundant cannabinoid in marijuana (Figure 1.1). Throughout this report, THC is used to indicate Δ^9-THC. In the few cases where variants of THC are discussed, the full names are used. All the cannabinoids are lipophilic--they are highly soluble in fatty fluids and tissues but not in water. Indeed, THC is so lipophilic that it is aptly described as "greasy."

Throughout this report, *marijuana* refers to unpurified plant extracts, including leaves and flower tops, regardless of how they are consumed--whether by ingestion or by smoking. References to the effects of marijuana should be understood to include the composite effects of its various components; that is, the effects of THC are included among the effects of marijuana, but not all the effects of marijuana are necessarily due to THC. Discussions concerning *cannabinoids* refer only to those particular compounds and not to the plant extract. This distinction is important; it is often blurred or exaggerated.

Cannabinoids are produced in epidermal glands on the leaves (especially the upper ones), stems, and the bracts that support the flowers of the marijuana plant. Although the flower itself has no epidermal glands, it has the highest cannabinoid content anywhere on the plant, probably because of the accumulation of resin secreted by the supporting bracteole (the small leaf-like part below the flower). The amounts of cannabinoids and their relative abundance in a marijuana plant vary with growing conditions, including humidity, temperature, and soil nutrients (reviewed in Pate, 1994[14]). The chemical stability of cannabinoids in harvested plant material is also affected by moisture, temperature, sunlight, and storage. They degrade under any storage condition.

ORGANIZATION OF THE REPORT

Throughout the report, steps that might be taken to fill the gaps in understanding both the potential harms and benefits of marijuana and cannabinoid use are identified. Those steps include identifying knowledge gaps, promising research directions, and potential therapies based on scientific advances in cannabinoid biology.

Chapter 2 reviews basic cannabinoid biology and provides a foundation to understand the medical value of marijuana or its constituent cannabinoids. In consideration of the physician's first rule, "first, do no harm," the potential harms attributed to the medical use of marijuana are reviewed before the potential medical benefits. Chapter 3 reviews the risks posed by marijuana use, with emphasis on medical use.

Chapter 4 analyzes the most credible clinical data relevant to the medical use of marijuana. It reviews what is known about the physiological mechanisms underlying particular conditions (for example, chronic pain, vomiting, anorexia, and muscle spasticity), what is known about the cellular actions of cannabinoids, and the levels of proof needed to show that marijuana is an effective treatment for specific symptoms. It does not analyze the historical literature; history is informative in enumerating uses of marijuana, but it does not provide the sort of information needed for a scientifically sound evaluation of the efficacy and safety of marijuana for clinical use. Because marijuana is advocated primarily as affording relief from the symptoms of disease rather than as a cure, this chapter is organized largely by symptoms as opposed to disease categories. Finally, chapter 4 compares the conclusions of this report with those of other recent reports on the medical use of marijuana.

Chapter 5 describes the process of and analyzes the prospects for cannabinoid drug development.

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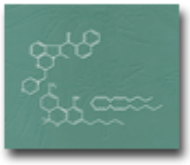
Cannabinoids and Animal Physiology

INTRODUCTION



Much has been learned since the publication of the 1982 Institute of Medicine (IOM) report *Marijuana and Health*.[1] Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. Too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That is no longer true. During the past 16 years, there have been major advances in what basic science discloses about the potential medical benefits of cannabinoids, the group of compounds related to THC. Many variants are found in the marijuana plant, and other cannabinoids not found in the plant have been chemically synthesized. Sixteen years ago it was still a matter of debate as to whether THC acted nonspecifically by affecting the fluidity of cell membranes or whether a specific pathway of action was mediated by a receptor that responded selectively to THC (Table 2.1).

Basic science is the wellspring for developing new medications and is particularly important for understanding a drug that has as many effects as marijuana. Even committed advocates of the medical use of marijuana do not claim that all the effects of marijuana are desirable for every medical use. But they do claim that the combination of specific effects of marijuana enhances its medical value. An understanding of those specific effects is what basic science can provide. The multiple effects of marijuana can be singled out and studied with the goals of evaluating the medical value of marijuana and cannabinoids in specific medical conditions, as well as minimizing unwanted side effects. An understanding of the basic mechanisms through which cannabinoids affect physiology permits more strategic development of new drugs and designs for clinical trials that are most likely to yield conclusive results.

Research on cannabinoid biology offers new insights into clinical use, especially given the scarcity of clinical studies that adequately evaluate the medical value of marijuana. For example, despite the scarcity of substantive clinical data, basic science has made it clear that cannabinoids can affect pain transmission and, specifically, that cannabinoids interact with the brain's endogenous opioid system, an important system for the medical treatment of pain (see chapter 4).

The cellular machinery that underlies the response of the body and brain to cannabinoids involves an intricate interplay of different systems. This chapter reviews the components of that machinery with enough detail to permit the reader to compare what is known about basic biology with the medical uses proposed for marijuana. For some

readers that will be too much detail. Those readers who do not wish to read the entire chapter should, nonetheless, be mindful of the following key points in this chapter:

- The most far reaching of the recent advances in cannabinoid biology are the identification of two types of cannabinoid receptors (CB_1 and CB_2) and of anandamide, a substance naturally produced by the body that acts at the cannabinoid receptor and has effects similar to those of THC. The CB_1 receptor is found primarilàúin the brain and mediates the psychological effects of THC. The CB_2 receptor is associated with the immune system; its role remains unclear.
- The physiological roles of the brain cannabinoid system in humans are the subject of much active research and are not fully known; however, cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- Animal research has shown that the potential for cannabinoid dependence exists, and cannabinoid withdrawal symptoms can be observed. However, both appear to be mild compared to dependence and withdrawal seen with other drugs.
- Basic research in cannabinoid biology has revealed a variety of cellular pathways through which potentially therapeutic drugs could act on the cannabinoid system. In addition to the known cannabinoids, such drugs might include chemical derivatives of plant-derived cannabinoids or of endogenous cannabinoids such as anandamide but would also include noncannabinoid drugs that act on the cannabinoid system.

This chapter summarizes the basics of cannabinoid biology--as known today. It thus provides a scientific basis for interpreting claims founded on anecdotes and for evaluating the clinical studies of marijuana presented in chapter 4.

The Value of Animal Studies

Much of the research into the effects of cannabinoids on the brain is based on animal studies. Many speakers at the public workshops associated with this study argued that animal studies of marijuana are not relevant to humans. Animal studies are not a substitute for clinical trials, but they are a necessary complement. Ultimately, every biologically active substance exerts its effects at the cellular and molecular levels, and the evidence has shown that this is remarkably consistent among mammals, even those as different in body and mind as rats and humans. Animal studies typically provide information about how drugs work that would not be obtainable in clinical studies. At the same time, animal studies can never inform us completely about the full range of psychological and physiological effects of marijuana or cannabinoids on humans.

The Active Constituents of Marijuana

Δ^9-THC and Δ^8-THC are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana. Because Δ^9-THC is much more abundant than Δ^8-THC, the psychoactivity of marijuana has been attributed largely to the effects of Δ^9-THC. 11-OH-Δ^9-THC is the primary product of Δ^9-THC metabolism by the liver and is about three times as potent as Δ^9-THC.[128]

There have been considerably fewer experiments with cannabinoids other than Δ^9-THC, although a few studies have been done to examine whether other cannabinoids modulate the effects of THC or mediate the nonpsychological effects of marijuana. Cannabidiol (CBD) does not have the same psychoactivity as THC, but it was initially reported to attenuate the psychological response to THC in humans;[81,177] however, later studies reported that CBD did not attenuate the psychological effects of THC.[11,69] One double-blind study of eight volunteers reported that CBD can block the anxiety induced by high doses of THC (0.5 mg/kg).[177] There are numerous anecdotal reports claiming that marijuana with relatively higher ratios of THC:CBD is less likely to induce anxiety in the user than marijuana with low THC:CBD ratios; but, taken together, the results published thus far are inconclusive.

The most important effect of CBD seems to be its interference with drug metabolism, including Δ^9-THC metabolism in the liver.[14,114] It exerts that effect by inactivating cytochrome P450s, which are the most important class of enzymes that metabolize drugs. Like many P450 inactivators, CBD can also induce P450s after repeated doses.[13] Experiments in which mice were treated with CBD followed by THC showed that CBD treatment was associated with a substantial increase in brain concentrations of THC and its major metabolites, most likely because it decreased the rate of clearance of THC from the body.[15]

In mice, THC inhibits the release of luteinizing hormone, the pituitary hormone that triggers the release of testosterone from the testes; this effect is increased when THC is given with cannabinol or CBD.[113]

Cannabinol also lowers body temperature and increases sleep duration in mice.[175] It is considerably less active than THC in the brain, but studies of immune cells have shown that it can modulate immune function (see "Cannabinoids and the Immune System" later in this chapter).

The Pharmacological Toolbox

A researcher needs certain key tools in order to understand how a drug acts on the brain. To appreciate the importance of these tools, one must first understand some basic principles of drug action. All recent studies have indicated that the behavioral effects of THC are receptor mediated.[27] Neurons in the brain are activated when a compound binds to its receptor, which is a protein typically located on the cell surface. Thus, THC will exert its effects only after binding to its receptor. In general, a given receptor will accept only particular classes of compounds and will be unaffected by other compounds.

Compounds that activate receptors are called *agonists*. Binding to a receptor triggers an event or a series of events in the cell that results in a change in the cell's activity, its gene regulation, or the signals that it sends to neighboring cells (Figure 2.1). This agonist-induced process is called signal transduction.

Another set of tools for drug research, which became available only recently for cannabinoid research, are the *receptor antagonists*, so-called because they selectively bind to a receptor that would have otherwise been available for binding to some other compound or drug. Antagonists block the effects of agonists and are tools to identify the functions of a receptor by showing what happens when its normal functions are blocked. Agonists and antagonists are both *ligands*; that is, they bind to receptors. Hormones, neurotransmitters, and drugs can all act as ligands. Morphine and naloxone provide a good example of how agonists and antagonists interact. A large dose of morphine acts as an agonist at opioid receptors in the brain and interferes with, or even arrests, breathing. Naloxone, a powerful opioid antagonist, blocks morphine's effects on opiate receptors, thereby allowing an overdose victim to resume breathing normally. Naloxone itself has no effect on breathing.

Another key tool involves identifying the receptor protein and determining how it works. That makes it possible to locate where a drug activates its receptor in the brain--both the general region of the brain and the cell type where the receptor is located. The way to find a receptor for a drug in the brain is to make the receptor "visible" by attaching a radioactive or fluorescent marker to the drug. Such markers show where in the brain a drug binds to the receptor, although this is not necessarily the part of the brain where the drug ultimately has its greatest effects.

Because drugs injected into animals must be dissolved in a water-based solution, it is easier to deliver water-soluble molecules than to deliver fat-soluble (lipophilic) molecules such as THC. THC is so lipophilic that it can stick to glass and plastic syringes used for injection. Because it is lipophilic, it readily enters cell membranes and thus can cross the blood brain barrier easily. (This barrier insulates the brain from many blood-borne substances.) Early cannabinoid research was hindered by the lack of potent cannabinoid ligands (THC binds to its cannabinoid receptors rather weakly) and because they were not readily water soluble. The synthetic agonist CP 55,940, which is more water soluble than THC, was the first useful research tool for studying cannabinoid receptors because of its high potency and ability to be labeled with a radioactive molecule, which enabled researchers to trace its activity.

CANNABINOID RECEPTORS

The cannabinoid receptor is a typical member of the largest known family of receptors: the G protein-coupled receptors with their distinctive pattern in which the receptor molecule spans the cell membrane seven times (Figure 2.2). For excellent recent reviews of cannabinoid receptor biology, see Childers and Breivogel,[27] Abood and Martin,[1] Felder and Glass,[43] and Pertwee.[124] Cannabinoid receptor ligands bind *reversibly* (they bind to the receptor briefly and then dissociate) and *stereoselectively* (when there are molecules that are mirror images of each other, only one version activates the receptor). Thus far, two cannabinoid receptor subtypes (CB_1 and CB_2) have been identified, of which only CB_1 is found in the brain.

The cell responds in a variety of ways when a ligand binds to the cannabinoid receptor (Figure 2.3). The first step is activation of G proteins, the first components of the signal transduction pathway. That leads to changes in several intracellular components--such as cyclic AMP and calcium and potassium ions--which ultimately produce the changes in cell functions. The final result of cannabinoid receptor stimulation depends on the particular type of cell, the particular ligand, and the other molecules that might be competing for receptor binding sites. Different agonists vary in binding *potency*, which determines the effective dose of the drug, and *efficacy*, which determines the maximal strength of the signal that they transmit to the cell. The potency and efficacy of THC are both relatively lower than those of some synthetic cannabinoids; in fact, synthetic compounds are generally more potent and efficacious than endogenous agonists.

CB_1 receptors are extraordinarily abundant in the brain. They are more abundant than most other G protein-coupled receptors and 10 times more abundant than *mu* opioid receptors, the receptors responsible for the effects of morphine.[148]

The cannabinoid receptor in the brain is a protein referred to as CB_1. The peripheral receptor (outside the nervous system), CB_2, is most abundant on cells of the immune system and is not generally found in the brain.[43,124] Although no other receptor subtypes have been identified, there is a genetic variant known as CB_1A (such variants are somewhat different proteins that have been produced by the same genes via alternative processing). In some cases, proteins produced via alternative splicing have different effects on cells. It is not yet known whether there are any functional differences between the two, but the structural differences raise the possibility.

CB_1 and CB_2 are similar, but not as similar as members of many other receptor families are to each other. On the basis of a comparison of the sequence of amino acids that make up the receptor protein, the similarity of the CB_1 and CB_2 receptors is 44% (Figure 2.2). The differences between the two receptors indicate that it should be possible to design therapeutic drugs that would act only on one or the other receptor and thus would activate or attenuate (block) the appropriate cannabinoid receptors. This offers a powerful method for producing biologically selective effects. In spite of the difference between the receptor subtypes, most cannabinoid compounds bind with similar affinity[2] to both CB_1 and CB_2 receptors. One exception is the plant-derived compound CBD, which appears to have greater binding affinity for CB_2 than for CB_1,[112] although another research group has failed to substantiate that observation.[129] Other exceptions include the synthetic compound WIN 55,212-2, which shows greater affinity for CB_2 than CB_1, and the endogenous ligands, anan-damide and 2-AG, which show greater affinity for CB_1 than CB_2.[43] The search for compounds that bind to only one or the other of the cannabinoid receptor types has been under way for several years and has yielded a number of compounds that are useful research tools and have potential for medical use.

Cannabinoid receptors have been studied most in vertebrates, such as rats and mice. However, they are also found in invertebrates, such as leeches and mollusks.[156] The evolutionary history of vertebrates and invertebrates diverged more than 500 million years ago, so cannabinoid receptors appear to have been conserved throughout evolution

at least this long. This suggests that they serve an important and basic function in animal physiology. In general, cannabinoid receptor molecules are similar among different species.[124] Thus, cannabinoid receptors likely fill many similar functions in a broad range of animals, including humans.

THE ENDOGENOUS CANNABINOID SYSTEM

For any drug for which there is a receptor, the logical question is, "Why does this receptor exist?" The short answer is that there is probably an endogenous agonist (that is, a compound that is naturally produced in the brain) that acts on that receptor. The long answer begins with a search for such compounds in the area of the body that produces the receptors and ends with a determination of the natural function of those compounds. So far, the search has yielded several endogenous compounds that bind selectively to cannabinoid receptors. The best studied of them are anandamide[37] and arachidonyl glycerol (2-AG).[108] However, their physiological roles are not yet known.

Initially, the search for an endogenous cannabinoid was based on the premise that its chemical structure would be similar to that of THC; that was reasonable, in that it was really a search for another "key" that would fit into the cannabinoid receptor "keyhole," thereby activating the cellular message system. One of the intriguing discoveries in cannabinoid biology was how chemically different THC and anandamide are. A similar search for endogenous opioids (endorphins) also revealed that their chemical structure is very different from the plant-derived opioids, opium and morphine.

Further research has uncovered a variety of compounds with quite different chemical structures that can activate cannabinoid receptors (Table 2.2 and Figure 2.4). It is not yet known exactly how anandamide and THC bind to cannabinoid receptors. Knowing this should permit more precise design of drugs that selectively activate the endogenous cannabinoid systems.

Anandamide

The first endogenous cannabinoid to be discovered was arachidonyl-ethanolamine, named anandamide from the Sanskrit word *ananda*, meaning "bliss."[37] Compared with THC, anandamide has only moderate affinity for CB_1 receptor and is rapidly metabolized by amidases (enzymes that remove amide groups). Despite its short duration of action, anand-amide shares most of the pharmacological effects of THC.[37,152] Rapid degradation of active molecules is a feature of neurotransmitter systems that allows them control of signal timing by regulating the abundance of signaling molecules. It creates problems for interpreting the results of many experiments and might explain why *in vivo* studies with anandamide injected into the brain have yielded conflicting results.

Anandamide appears to have both central (in the brain) and peripheral (in the rest of the body) effects. The precise neuroanatomical localization of anandamide and the enzymes that synthesize it are not yet known. This information will provide essential clues to the natural role of anan-damide and an understanding of the brain circuits in

which it is a neurotransmitter. The importance of knowing specific brain circuits that involve anandamide (and other endogenous cannabinoid ligands) is that such circuits are the pivotal elements for regulating specific brain functions, such as mood, memory, and cognition. Anandamide has been found in numerous regions of the human brain: hippocampus (and parahippocampic cortex), striatum, and cerebellum; but it has not been precisely identified with specific neuronal circuits. CB_1 receptors are abundant in these regions, and this further implies a physiological role for endogenous cannabinoids in the brain functions controlled by these areas. But substantial concentrations of anandamide are also found in the thalamus, an area of the brain that has relatively few CB_1 receptors.[124]

Anandamide has also been found outside the brain. It has been found in spleen tissue, which also has high concentrations of CB_2 receptors, and small amounts have been detected in heart tissue.[44]

In general, the affinity of anandamide for cannabinoid receptors is only one-fourth to one-half that of THC (see Table 2.3). The differences depend on the cells or tissue that are tested and on the experimental conditions, such as the binding assay used (reviewed by Pertwee[124]).

The molecular structure of anandamide is relatively simple, and it can be formed from arachidonic acid and ethanolamine. Arachidonic acid is a common precursor of a group of biologically active molecules known as eicosanoids, including prostaglandins.[3] Although anandamide can be synthesized in a variety of ways, the physiologically relevant pathway seems to be through enzymatic cleavage of *N*-arachidonyl-phosphatidyl-ethanolamine (NAPE), which yields anandamide and phosphatidic acid (reviewed by Childers and Breivogel[27]).

Anandamide can be inactivated in the brain via two mechanisms. In one it is enzymatically cleaved to yield arachidonic acid and ethanolamine--the reverse of what was initially proposed as its primary mode of synthesis. In the other it is inactivated through neuronal uptake--that is, by being transported into the neuron, which prevents its continuing activation of neighboring neurons.

Other Endogenous Agonists

Several other endogenous compounds that are chemically related to anandamide and that bind to cannabinoid receptors have been discovered, one of which is 2-AG.[108] 2-AG is closely related to anandamide and is even more abundant in the brain. At the time of this writing, all known endogenous cannabinoid receptor agonists (including anandamide) were eicosanoids, which are arachidonic acid metabolites. Arachidonic acid (a free fatty acid) is released via hydrolysis of membrane phospholipids.

Other, noneicosanoid, compounds that bind cannabinoid receptors have recently been isolated from brain tissue, but they have not been identified, and their biological effects

are under investigation. This is a fast-moving field of research, and no review over six months old will be fully up to date.

The endogenous compounds that bind to cannabinoid receptors probably perform a broad range of natural functions in the brain. This neural signaling system is rich and complex and has many subtle variations, many of which await discovery. In the next few years much more will probably be known about these naturally occurring cannabinoids.

Some effects of cannabinoid agonists are receptor independent. For example, both THC and CBD can be neuroprotective through their antioxidative activity; that is, they can reduce the toxic forms of oxygen that are released when cells are under stress.[54] Other likely examples of receptor-independent cannabinoid activity are modulation of activation of membrane-bound enzymes (such as ATPase), arachidonic acid release, and perturbation of membrane lipids. An important caution in interpreting those reports is that concentrations of THC or CBD used in cellular studies, such as these, are generally much higher than the concentrations of THC or CBD in the body that would likely be achieved by smoking marijuana.

Novel Targets for Therapeutic Drugs

Drugs that alter the natural biology of anandamide or other endogenous cannabinoids might have therapeutic uses (Table 2.4). For example, drugs that selectively inhibit neuronal uptake of anandamide would increase the brain's own natural cannabinoids, thereby mimicking some of the effects of THC. A number of important psychotherapeutic drugs act by inhibiting neurotransmitter uptake. For example, antidepressants like fluoxetine (Prozac) inhibit serotonin uptake and are known as selective serotonin reuptake inhibitors, or SSRIs. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis. Some antihypertensive drugs work by inhibiting enzymes involved in the synthesis of endogenous hypertensive agents. For example, anti-converting enzyme (ACE) inhibitors are used in hypertensive patients to interfere with the conversion of angiotensin I, which is inactive, to the active hormone, angiotensin II.

SITES OF ACTION

Cannabinoid receptors are particularly abundant in some areas of the brain. The normal biology and behavior associated with these brain areas are consistent with the behavioral effects produced by cannabinoids (Table 2.5 and Figure 2.5). The highest receptor density is found in cells of the basal ganglia that project locally and to other brain regions. These cells include the substantia nigra pars reticulata, entopeduncular nucleus, and globus pallidus, regions that are generally involved in coordinating body movements. Patients with Parkinson's or Huntington's disease tend to have impaired functions in these regions.

CB_1 receptors are also abundant in the putamen, part of the relay system within the basal ganglia that regulates body movements; the cerebellum, which coordinates body

movements; the hippocampus, which is involved in learning, memory, and response to stress; and the cerebral cortex, which is concerned with the integration of higher cognitive functions.

CB_1 receptors are found on various parts of neurons, including the axon, cell bodies, terminals, and dendrites.[57,165] Dendrites are generally the "receiving" part of a neuron, and receptors on axons or cell bodies generally modulate other signals. Axon terminals are the "sending" part of the neuron.

Cannabinoids tend to inhibit neurotransmission, although the results are somewhat variable. In some cases, cannabinoids diminish the effects of the inhibitory neurotransmitter, g-aminobutyric acid (GABA);[144] in other cases, cannabinoids can augment the effects of GABA.[120] The effect of activating a receptor depends on where it is found on the neuron: if cannabinoid receptors are presynaptic (on the "sending" side of the synapse) and inhibit the release of GABA, cannabinoids would diminish GABA effects; the net effect would be stimulation. However, if cannabinoid receptors are postsynaptic (on the "receiving" side of the synapse) and on the same cell as GABA receptors, they will probably mimic the effects of GABA; in that case, the net effect would be inhibition.[120,144,160]

CB_1 is the predominant brain cannabinoid receptor. CB_2 receptors have not generally been found in the brain, but there is one isolated report suggesting some in mouse cerebellum.[150] CB_2 is found primarily on cells of the immune system. CB_1 receptors are also found in immune cells, but CB_2 is considerably more abundant there (Table 2.6) (reviewed by Kaminski[80] in 1998).

As can be appreciated in the next section, the presence of cannabinoid systems in key brain regions is strongly tied to the functions and pathology associated with those regions. The clinical value of cannabinoid systems is best understood in the context of the biology of these brain regions.

CANNABINOID RECEPTORS AND BRAIN FUNCTIONS

Motor Effects

Marijuana affects psychomotor performance in humans. The effects depend both on the nature of the task and the experience with marijuana. In general, effects are clearest in steadiness (body sway and hand steadiness) and in motor tasks that require attention. The results of testing cannabinoids in rodents are much clearer.

Cannabinoids clearly affect movement in rodents, but the effects depend on the dose: low doses stimulate and higher doses inhibit locomotion.[111,159] Cannabinoids mainly inhibit the transmission of neural signals, and they inhibit movement through their actions on the basal ganglia and cerebellum, where cannabinoid receptors are particularly abundant (Figure 2.6). Cannabinoid receptors are also found in the neurons that project

from the striatum and subthalamic nucleus, which inhibit and stimulate movement, respectively.[58,101]

Cannabinoids decrease both the inhibitory and stimulatory inputs to the substantia nigra and therefore might provide dual regulation of movement at this nucleus. In the substantia nigra, cannabinoids decrease transmission from both the striatum and the subthalamic nucleus.[141] The globus pallidus has been implicated in mediating the cataleptic effects of large doses of cannabinoids in rats.[126] (Catalepsy is a condition of diminished responsiveness usually characterized by trancelike states and waxy rigidity of the muscles.) Several other brain regions--the cortex, the cerebellum, and the neural pathway from cortex to striatum--are also involved in the control of movement and contain abundant cannabinoid receptors.[52,59,101] They are therefore possible additional sites that might underlie the effects of cannabinoids on movement.

Memory Effects

One of the primary effects of marijuana in humans is disruption of short-term memory.[68] That is consistent with the abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory. The effects of THC resemble a temporary hippocampal lesion.[63] Deadwyler and colleagues have demonstrated that cannabinoids decrease neuronal activity in the hippocampus and its inputs.[23,24,83] *In vitro*, several cannabinoid ligands and endogenous cannabinoids can block the cellular processes associated with memory formation.[29,30,116,157,163] Furthermore, cannabinoid agonists inhibit release of several neurotransmitters: acetylcholine from the hippocampus,[49-51] norepinephrine from human and guinea pig (but not rat or mouse) hippocampal slices,[143] and glutamate in cultured hippocampal cells.[144] Cholinergic and noradrenergic neurons project into the hippocampus, but circuits within the hippocampus are glutamatergic.[4] Thus, cannabinoids could block transmission both into and within the hippocampus by blocking presynaptic neurotransmitter release.

Pain

After nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medical use for marijuana. Recent research presented below has shown intriguing parallels with anecdotal reports of the modulating effects of cannabinoids on pain--both the effects of cannabinoids acting alone and the effects of their interaction with opioids.

Behavioral Studies

Cannabinoids reduce reactivity to acute painful stimuli in laboratory animals. In rodents, cannabinoids reduced the responsiveness to pain induced through various stimuli, including thermal, mechanical, and chemical stimuli.[12,19,46,72,96,154,174] Cannabinoids were comparable with opiates in potency and efficacy in these experiments.[12,72]

Cannabinoids are also effective in rodent models of chronic pain. Herzberg and co-workers found that cannabinoids can block allodynia and hyperalgesia associated with neuropathic pain in rats.[62] This is an important advance because chronic pain frequently results in a series of neural changes that increase suffering due to allodynia (pain elicited by stimuli that are normally innocuous), hyperalgesia (abnormally increased reactivity to pain), and spontaneous pain; furthermore, some chronic pain syndromes are not amenable to therapy, even with the most powerful narcotic analgesics.[10]

Pain perception is controlled mainly by neurotransmitter systems within the central nervous system, and cannabinoids clearly play a role in the control of pain in those systems.[45] However, pain-relieving and pain-preventing mechanisms also occur in peripheral tissues, and endogenous cannabinoids appear to play a role in peripheral tissues. Thus, the different cannabinoid receptor subtypes might act synergistically. Experiments in which pain is induced by injecting dilute formalin into a mouse's paw have shown that anandamide and palmitylethanolamide (PEA) can block peripheral pain.[22,73] Anandamide acts primarily at the CB_1 receptor, whereas PEA has been proposed as a possible CB_2 agonist; in short, there might be a biochemical basis for their independent effects. When injected together, the analgesic effect is stronger than that of either alone. That suggests an important strategy for the development of a new class of analgesic drug: a mixture of CB_1 and CB_2 agonists. Because there are few, if any, CB_2 receptors in the brain, it might be possible to develop drugs that enhance the peripheral analgesic effect while minimizing the psychological effects.

Neural Sites of Altered Responsiveness to Painful Stimuli

The brain and spinal cord mediate cannabinoid analgesia. A number of brain areas participate in cannabinoid analgesia and support the role of descending pathways (neural pathways that project from the brain to the spinal cord).[103,105] Although more work is needed to produce a comprehensive map of the sites of cannabinoid analgesia, it is clear that the effects are limited to particular areas, most of which have an established role in pain.

Specific sites where cannabinoids act to affect pain processing include the periaqueductal gray,[104] rostral ventral medulla,[105,110] thalamic nucleus submedius,[102] thalamic ventroposterolateral nucleus,[102] dorsal horn of the spinal cord,[64,65] and peripheral sensory nerves.[64-66,131] Those nuclei also participate in opiate analgesia. Although similar to opiate analgesia, cannabinoid analgesia is not mediated by opioid receptors; morphine and cannabinoids sometimes act synergistically, and opioid antagonists generally have no effect on cannabinoid-induced analgesia.[171] However, a *kappa*-receptor antagonist has been shown to attenuate spinal, but not supraspinal, cannabinoid analgesia.[153,170,171] (*Kappa* opioid receptors constitute one of the three major types of opioid receptors; the other two types are *mu* and *delta* receptors.)

Neurophysiology and Neurochemistry of Cannabinoid Analgesia

Because of the marked effects of cannabinoids on motor function, behavioral studies in animals alone cannot provide sufficient grounds for the conclusion that cannabinoids depress pain perception. Motor behavior is typically used to measure responses to pain, but this behavior is itself affected by cannabinoids. Thus, experimental results include an unmeasured combination of cannabinoid effects on motor and pain systems. The effects on specific neural systems, however, can be measured at the neurophysiological and neurochemical levels. Cannabinoids decrease the response of immediate-early genes (genes that are activated in the early or immediate stage of response to a broad range of cellular stimuli) to noxious stimuli in the spinal cord, decrease response of pain neurons in the spinal cord, and decrease the responsiveness of pain neurons in the ventral posterolateral nucleus of the thalamus.[67,102] Those changes are mediated by cannabinoid receptors, are selective for pain neurons, and are unrelated to changes in skin temperature or depth of anesthesia, and they follow the time course of the changes in behavioral responses to painful stimuli but not the time course of motor changes.[67] On-cells and off-cells in the rostral ventral medulla control pain transmission at the level of the spinal cord, and cannabinoids also modulate their responses in a manner that is very similar to that of morphine.[110]

Endogenous Cannabinoids Modulate Pain

Endogenous cannabinoids can modulate pain sensitivity through both central and peripheral mechanisms. For example, animal studies have shown that pain sensitivity can be increased when endogenous cannabinoids are blocked from acting at CB_1 receptors.[22,62,110,130,158] Administration of cannabinoid antagonists in either the spinal cord[130] or paw[22] increase the sensitivity of animals to pain. In addition, there is evidence that cannabinoids act at the site of injury to reduce peripheral inflammation.[131]

Current data suggest that the endogenous cannabinoid analgesic system might offer protection against the long-lasting central hyperalgesia and allodynia that sometimes follow skin or nerve injuries.[130,158] These results raise the possibility that therapeutic interventions that alter the levels of endogenous cannabinoids might be useful for managing pain in humans.

CHRONIC EFFECTS OF THC

Most substances of abuse produce tolerance, physical dependence, and withdrawal symptoms. *Tolerance* is the most common response to repetitive use of a drug and is the condition in which, after repeated exposure to a drug, increasing doses are needed to achieve the same effect. *Physical dependence* develops as a result of a resetting of homeostatic mechanisms in response to repeated drug use. Tolerance, dependence, and withdrawal are not peculiar to drugs of abuse. Many medicines that are not addicting can produce these types of effects; examples of such medications include clonidine, propranolol, and tricyclic antidepressants. The following sections discuss what is known about the biological mechanisms that underlie tolerance, reward, and dependence; clinical studies about those topics are discussed in chapter 3.

Tolerance

Chronic administration of cannabinoids to animals results in tolerance to many of the acute effects of THC, including memory disruption,[34] decreased locomotion,[2,119] hypothermia,[42,125] neuroendocrine effects,[134] and analgesia.[4] Tolerance also develops to the cardiovascular and psychological effects of THC and marijuana in humans (see also discussion in chapter 3).[55,56,76]

Tolerance to cannabinoids appears to result from both *pharmacokinetic* changes (how the drug is absorbed, distributed, metabolized, and excreted) and *pharmacodynamic* changes (how the drug interacts with target cells). Chronic treatment with the cannabinoid agonist, CP 55,940, increases the activity of the microsomal cytochrome P450 oxidative system,[31] the system through which drugs are metabolized in the liver; this suggests pharmacokinetic tolerance. Chronic cannabinoid treatment also produces changes in brain cannabinoid receptors and cannabinoid receptor mRNA concentrations--an indication that pharmacodynamic effects are important as well.

Most studies have found that brain cannabinoid receptor concentrations usually decrease after prolonged exposure to agonists,[42,119,136,138] although some studies have reported increases[137] or no changes[2] in receptor binding in brain. Differences among studies could be due to the particular agonist tested, the assay used, the brain region examined, or the treatment time. For example, the THC analogue, levonantradol, produces a greater desensitization of adenylyl cyclase inhibition than does THC in cultured neuroblastoma cells.[40] This might be explained by differences in efficacy between these two agonists.[18,147] A time course study revealed differences among brain regins in the rates and magnitudes of receptor down regulation.[16] Those findings suggest that tolerance to different effects of cannabinoids develops at different rates.

Chronic treatment with THC also produces variable effects on cannabinoid-mediated signal transduction systems. It produces substantial desensitization of cannabinoid-activated G proteins in a number of rat brain regions.[147] The time course of this desensitization varies across brain regions.[16]

It is difficult to extend the findings of short-term animal studies to human marijuana use. To simulate long-term use, higher doses are used in animal studies than are normally achieved by smoking marijuana. For example, the average human will feel "high" after injection of THC at a level of 0.06 mg/kg,[118] compared with the 10—20 mg/kg per day used in many chronic rat studies. At the same time, doses of marijuana needed to observe behavioral changes in rats (usually changes in locomotor behavior) are substantially higher than doses at which people feel "high." The pharmacokinetics of THC distribution in the body are also dramatically different between rats and humans and depend heavily on whether it is inhaled, injected, or swallowed. It is likely that some of the same biochemical adaptations to chronic cannabinoid administration occur in laboratory animals and humans, but the magnitude of the effects in humans might be less than that in animals in proportion to the doses used.

Reward and Dependence

Experimental animals that are given the opportunity to self-administer cannabinoids generally do not choose to do so, which has led to the conclusion that they are not reinforcing and rewarding.[38] However, behavioral[95] and brain stimulation[94] studies have shown that THC can be rewarding to animals. The behavioral study used a "place preference" test, in which an animal is given repeated doses of a drug in one place, and is then given a choice between a place where it received the drug and a place where it did not. The animals chose the place where they received the THC. These rewarding effects are highly dose dependent. In all models studied, cannabinoids are only rewarding at midrange; doses that are too low are not rewarding; doses that are too high can be aversive. Mice will self-administer the cannabinoid agonist WIN 55,212-2 but only at low doses.[106] This effect is specifically mediated by CB_1 receptors and indicates that stimulation of those receptors is rewarding to the mice. Antagonism of cannabinoid receptors is also rewarding in rats; in conditioned place preference tests, animals show a preference for the place they receive the cannabinoid antagonist SR 141716A at both low and high doses.[140] Cannabinoids increase dopamine concentrations in the mesolimbic dopamine system of rats, a pathway associated with reinforcement.[25,39,161] However, the mechanism by which THC increases dopa-mine concentrations appears to be different from that of other abused drugs[51] (see chapter 3 for further discussion of reinforcement). THC-induced increases in dopamine are due to increases in the firing rate of dopamine cells in the ventral tegmental area by Δ^9-THC.[47] However, these increases in firing rate in the ventral tegmental area could not be explained by increases in the firing of the A10 dopamine cell group, where other abused drugs have been shown to act.[51]

Physical dependence on cannabinoids has been observed only under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given the CB_1 antagonist SR 141716A.[3,166] The addition of the antagonist accentuates any withdrawal effect by competing with the agonist at receptor sites; that is, the antagonist helps to clear agonists off and keep them off receptor sites. This suggests that, under normal cannabis use, the long half-life and slow elimination from the body of THC and the residual bioactivity of its metabolite, 11-OH-THC, can prevent substantial abstinence symptoms. The precipitated withdrawal produced by SR 141716A has some of the characteristics of opiate withdrawal, but it is not affected by opioid antagonists, and it affects motor systems differently. An earlier study with monkeys also suggested that abrupt cessation of chronic THC is associated with withdrawal symptoms.[8] Monkeys in that study were trained to work for food after which they were given THC on a daily basis; when the investigators stopped administering THC, the animals stopped working for food.

A study in rats indicated that the behavioral cannabinoid withdrawal syndrome is consistent with the consequences of withdrawal from other drugs of abuse in that it correlates with the effects of stimulation of central amygdaloid corticotropin-releasing hormone release.[135] However, the withdrawal syndrome for cannabinoids and the corresponding increase in corticotropin-releasing hormone are observed only after administration of the CB_1 antagonist SR 141716A to cannabinoid-tolerant animals.[3,166]

The implications of data based on precipitated withdrawal in animals for human cannabinoid abuse have not been established.[166] Furthermore, acute administration of THC also produces increases in corticotropin-releasing hormone and adrenocorticotropin release; both are stress-related hormones.[71] This set of withdrawal studies may explain the generally aversive effects of cannabinoids in animals and could indicate that the increase in corticotropin-releasing hormone is merely a rebound effect. Thus, cannabinoids appear to be conforming to some of the neurobiological effects of other drugs abused by humans, but the underlying mechanisms of these actions and their value for determining the reinforcement and dependence liability of cannabinoids in humans remain undetermined.

CANNABINOIDS AND THE IMMUNE SYSTEM

The human body protects itself from invaders, such as bacteria and viruses through the elaborate and dynamic network of organs and cells referred to as the immune system. Cannabinoids, especially THC, can modulate the function of immune cells in various ways--in some cases enhancing and in others diminishing the immune response[85] (summarized in Table 2.7). However, the natural function of cannabinoids in the immune system is not known. Immune cells respond to cannabinoids in a variety of ways, depending on such factors as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation, and type of cell function. Although the chronic effects of cannabinoids on the immune system have not been studied, based on acute exposure studies in experimental animals it appears that THC concentrations that modulate immunological responses are higher than those required for psycho-activity.

The CB_2 receptor gene, which is not expressed in the brain, is particularly abundant in immune tissues, with an expression level 10—100 times higher than that of CB_1. In spleen and tonsils the CB_2 mRNA[5] content is equivalent to that of CB_1 mRNA in the brain.[48] The rank order, from high to low, of CB_2 mRNA levels in immune cells is B-cells > natural killer cells >> monocytes > polymorphonuclear neutrophil cells > T8 cells > T4 cells. In tonsils the CB_2 receptors appear to be restricted to B-lymphocyte-enriched areas. In contrast, CB_1 receptors are mainly expressed in the central nervous system and, to a lesser extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.

Cannabinoid Receptors and Intracellular Action in Immune Cells

CB_2 appears to be the predominant gene expressed in resting leukocytes.[78,112] The level of CB_1 gene activity is normally low in resting cells but increases with cell activation.[32] Thus the CB_1 receptor might be important only when immune responses are stimulated, but the physiological relevance of this observation remains to be determined. Some of the cannabinoid effects observed in immune systems, especially at high drug concentrations, are likely mediated through nonreceptor mechanisms, but these have not yet been identified.[4]

Ligand binding to either CB_1 or CB_2 inhibits adenylate cyclase, an enzyme that is responsible for cAMP production and is, thus, an integral aspect of intracellular signal transduction (see Figure 2.3).[53,79,91,122,139,151,167] Increases in intracellular cAMP concentrations lead to immune enhancement, and decreases lead to an inhibition of the immune response.[77] Cannabinoids inhibit the rise in intracellular cAMP that normally results from leukocyte activation, and this might be the pathway through which cannabinoids suppress immune cell functions.[28,74,167] In addition, cannabinoids activate other molecular pathways such as the nuclear factor-kB pathway, and therefore these signals might be modified in drug-treated immune cells.[33,74]

T and B Cells

When stimulated by antigen, lymphocytes (see Box 2.1) first proliferate and then mature or differentiate to become potent effector cells, such as B cells that release antibodies or T cells that release cytokines. The normal T-cell proliferation that is seen when human lymphocytes and mouse splenocytes (spleen cells) are exposed to antigens and mitogens[6] can be inhibited by THC, 11-OH-THC, cannabinol, and 2-AG, as well as synthetic cannabinoid agonists such as CP 55,940; WIN 55,212-2; and HU-210.[61,89,93,99,127,155] In contrast, one study testing anandamide revealed little or no effect on T cell proliferation.[93]

However, these drug effects are variable and depend on experimental conditions, such as the experimental drug dose used, the mitogen used, the percentage of serum in the culture, and the timing of cannabinoid drug exposure. In general, lower doses of cannabinoids increase proliferation and higher doses suppress proliferation. Doses that are effective in suppressing immune function are typically greater than 10 µM in cell culture studies and greater than 5 mg/kg in whole-animal studies.[85] By comparison, at 0.05 mg/kg, people will experience the full psychoactive effects of THC; however, because of their high metabolic rates, small rodents frequently require drug doses that are 100-fold higher than doses needed for humans to achieve comparable drug effects. Thus, the immune effects of doses of cannabinoids higher than those ever experienced by humans should be interpreted with caution.[93]

As with T cells, B cell proliferation can be suppressed by various cannabinoids, such as THC, 11-OH-THC, and 2-AG, but B cell proliferation is more inhibited at lower drug concentrations than T cell proliferation.[89,93] Conversely, low doses of THC, CP 55,940 and WIN 55,212-2 *increase* B cell proliferation in cultured human cells exposed to mitogen.[35] This effect possibly involves the CB_2 receptor, because the effect appears to be the same when the CB_1 receptor was blocked by the antagonist SR 141716A (which does not block the CB_2 receptor). The reason for the differences in B cell responsiveness to cannabinoids is probably due to differences in cell type and source; for example, B cells collected from mouse spleen might respond to cannabinoids somewhat differently than B cells from human tonsils.

Natural Killer Cells

Repeated injections of relatively low doses of THC (3 mg/kg/day[1217]) or two injections of a high dose (40 mg/kg[86]) suppress the ability of NK cells to destroy foreign cells in rats and mice. THC can also suppress cytolytic activity of the NK cells in cell cultures; 11-OH-THC is even more potent.[86] In contrast, THC concentrations below 10 µM had no effect on NK cell activity in mouse cell cultures.[98]

Macrophages

Macrophages perform various functions, including phagocytosis (ingestion and destruction of foreign substances), cytolysis, antigen presentation to lymphocytes, and production of active proteins involved in destroying microorganisms, tissue repair, and modulation of immune cells. Those functions can be suppressed by THC doses similar to those capable of modulating lymphocyte functions (see above).[88,109]

Cytokines

Cytokines are proteins produced by immune cells. When released from the producing cell, they can alter the function of other cells they come in contact with. In a sense they are like hormones. Thus, cannabinoids can either increase or decrease cytokine production depending upon experimental conditions.

Some cytokines, such as interferon-γ and interleukin-2 (IL-2), are produced by T helper-1 (Th1) cells. These cytokines help to activate cell-mediated immunity and the killer cells that eliminate microorganisms from the body (see Box 2.1). When injected into mice, THC suppresses the production of those cytokines that modulate the host response to infection (see below).[115] Cannabinoids also modulate interferons induced by viral infection,[21] as well as other interferon inducers.[85] Furthermore, in human cell cultures, interferon production can be increased by low concentrations but decreased by high concentrations of either THC or CBD.[168] In addition to Th1 cytokines, cannabinoids modulate the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6).[145,176] At 8 mg/kg, THC can increase the *in vivo* mobilization of serum acute-phase cytokines, including IL-1, TNF, and IL-6.[90] Finally, although these studies suggest that cannabinoids can induce an increase in cytokines, other studies suggest that they can also suppress cytokine production.[85] The different results might be due to different cell culture conditions or because different cell lines were studied.

Antibody Production

Antibody production is an important measure of humoral immune function as contrasted with cellular (cell-mediated) immunity. Antibody production can be suppressed in mice injected with relatively low doses of THC (>5 mg/kg) or HU-210 (>0.05 mg/kg) and in mouse spleen cell cultures exposed to a variety of cannabinoids, including THC, 11-OH-THC, cannabinol, cannabidiol, CP 55,940, or HU-210.[5,6,61,78,79,84,85,142,164] However, the inhibition of antibody response by cannabinoids was only observed when antibody-forming cells were exposed to T-cell-dependent

antigens (the responses require functional T cells and macrophages as accessory cells). Conversely, antibody responses to several T-cell-independent antigens were not inhibited by THC; this suggests that B cells are relatively insensitive to inhibition by cannabinoids.[142]

Resistance to Infection in Animals Exposed to Cannabinoids

Evaluation of bacterial infections in mice that received injections of THC can suppress resistance to infection, although the effect depends on the dose and timing of drug administration. Mice pretreated with THC (8 mg/kg) one day before infection with a sublethal dose of the pneumonia-causing bacteria *Legionella pneumophilia* and then treated again one day after the infection with THC developed symptoms of cytokine-mediated septic shock and died; control mice that were not pretreated with THC became immune to repeated infection and survived the bacterial challenge.[90] If only one injection of THC was given or doses less than 5 mg/kg were used, all the mice survived the initial infection but failed to survive later challenge with a lethal dose of the bacteria; hence, these mice failed to develop immune memory in response to the initial sublethal infection.[87] Note that these are very high doses and are considerably higher than doses experienced by marijuana users (see Figure 3.1).[115] In rats, doses of 4.0 mg/kg THC are aversive.[95]

Few studies have been done to evaluate the effect of THC on viral infections, and this subject needs further study.[20] Compared to healthy animals, THC might have greater immunosuppressive effects in animals whose immune systems are severely weakened. For example, a very high dose of THC (100 mg/kg) given two days before and after herpes simplex virus infection was shown to be a cofactor with the virus in advancing the progression to death in an immunodeficient mouse model infected with a leukemia virus.[85] However, THC given as a single dose (100 mg/kg) two days before herpes simplex virus infection did not promote the progression to death. Hence, whether THC is immunosuppressive probably depends on the timing of THC exposure relative to an infection.

Antiinflammatory Effects

As discussed above, cannabinoid drugs can modulate the production of cytokines, which are central to inflammatory processes in the body. In addition, several studies have shown directly that cannabinoids can be antiinflammatory. For example, in rats with autoimmune encephalomyelitis (an experimental model used to study multiple sclerosis), cannabinoids were shown to attenuate the signs and the symptoms of central nervous system damage.[100,172] (Some believe that nerve damage associated with multiple sclerosis is caused by an inflammatory reaction.) Likewise, the cannabinoid, HU-211, was shown to suppress brain inflammation that resulted from closed-head injury[146] or infectious meningitis[7] in studies on rats. HU-211 is a synthetic cannabinoid that does not bind to cannabinoid receptors and is not psychoactive;[7] thus, without direct evidence, the effects of marijuana cannot be assumed to include those of HU-211. CT-3, another atypical cannabinoid, suppresses acute and chronic joint inflammation in animals.[178] It is a

nonpsychoactive synthetic derivative of 11-THC-oic acid (a breakdown product of THC) and does not appear to bind to cannabinoid receptors.[129] Cannabichromene, a cannabinoid found in marijuana, has also been reported to have antiinflammatory properties.[173] No mechanism of action for possible antiinflammatory effects of cannabinoids has been identified, and the effects of these atypical cannabinoids and effects of marijuana are not yet established.

It is interesting to note that two reports of cannabinoid-induced analgesia are based on the ability of the endogenous cannabinoids, anan-damide and PEA, to reduce pain associated with local inflammation that was experimentally induced by subcutaneous injections of dilute formalin.[22,73] Both THC and anandamide can increase serum levels of ACTH and corticosterone in animals.[169] Those hormones are involved in regulating many responses in the body, including those to inflammation. The possible link between experimental cannabinoid-induced analgesia and reported antiinflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs but has not yet been established.

Conclusions Regarding Effects on the Immune System

Cell culture and animal studies have established cannabinoids as immunomodulators--that is, they increase some immune responses and decrease others. The variable responses depend on such experimental factors as drug dose, timing of delivery, and type of immune cell examined.

Cannabinoids affect multiple cellular targets in the immune system and a variety of effector functions. Many of the effects noted above appear to occur at concentrations over 5 µM *in vitro* and over 5 µg/kg *in vivo*.[8] By comparison, a 5-mg injection of THC into a person (about 0.06 mg/kg) is enough to produce strong psychoactive effects. It should be emphasized, however, that little is known about the immune effects of chronic low- dose exposure to cannabinoids.

Another issue in need of further clarification involves the potential usefulness of cannabinoids as therapeutic agents in inflammatory diseases. Glucocorticoids have historically been used for these diseases, but nonpsychotropic cannabinoids potentially have fewer side effects and might thus offer an improvement over glucocorticoids in treating inflammatory diseases.

CONCLUSIONS AND RECOMMENDATIONS

Given the progress of the past 15 years in understanding the effects of cannabinoids, research in the next decade is likely to reveal even more. It is interesting to compare how little we know about cannabinoids with how much we know about opiates. Table 2.8 suggests good reason for optimism about the future of cannabinoid drug development. Now that many of the basic tools of cannabinoid pharmacology and biology have been developed, one can expect to see rapid advances that can begin to match what is known of opiate systems in the brain.

Despite the tremendous progress in understanding the pharmacology and neurobiology of brain cannabinoid systems, this field is still in its early developmental stages. A key focus for future study is the neurobiology of endogenous cannabinoids; establishing the precise brain localization (in which cells and where) of cannabinoids, cellular storage and release mechanisms, and uptake mechanisms will be crucial in determining the biological role of this system. Technology needed to establish the biological significance of these systems will be broad based and include such research tools as the transgenic or gene knockout mice, as has already been accomplished for various opioid-receptor types.[26] In 1997, both CB_1 and CB_2 knockout mice were generated by a team of scientists at the National Institutes of Health, and a group in France has developed another strain of CB_1 knockout mice.[92]

Several research tools will greatly aid such investigations, in particular a greater selection of agonists and antagonists that permit discrimination in activation between CB_1 and CB_2 and hydrophilic agonists that can be delivered to animals or cells more effectively than hydrophobic compounds. In the area of drug development, future progress should continue to provide more specific agonists and antagonists for CB_1 and CB_2 receptors, with varying potential for therapeutic uses.

There are certain areas that will provide keys to a better understanding of the potential therapeutic value of cannabinoids. For example, basic biology indicates a role for cannabinoids in pain and control of movement, which is consistent with a possible therapeutic role in these areas. The evidence is relatively strong for the treatment of pain and, intriguing although less well established, for movement disorders. The neuroprotective properties of cannabinoids might prove therapeutically useful, although it should be noted that this is a new area and other, better studied, neuroprotective drugs have not yet been shown to be therapeutically useful. Cannabinoid research is clearly relevant not only to drug abuse but also to understanding basic human biology. Further, it offers the potential for the discovery and development of new therapeutically useful drugs.

Conclusion: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines, such as diazepam (Valium).

Conclusion: The different cannabinoid receptor types found in the body appear to play different roles in normal physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

Recommendation: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

This chapter has summarized recent progress in understanding the basic biology of cannabinoids and provides a foundation for the next two chapters which review studies on the potential health risks (chapter 3) and benefits of marijuana use (chapter 4).

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Notes

[1] The field of neuroscience has grown substantially since the publication of the 1982 IOM report. The number of members in the Society for Neuroscience provides a rough measure of the growth in research and knowledge about the brain: as of the middle of 1998, there were over 27,000 members, more than triple the number in 1982.

[2] *Affinity* is a measure of how avidly a compound binds to a receptor. The higher the affinity of a compound, the higher its potency; that is, lower doses are needed to produce its effects.

[3] Eicosanoids all contain a chain of 20 carbon atoms and are named after *eikosi*, the Greek word for 20.

[4] Neurons are often defined by the primary neurotransmitter released at their terminals. Thus, *cholinergic* neurons release acetylcholine, *noradrenergic* neurons release noradrenalin (also known as norepinephrine), and *glutamergic* neurons release glutamate.

[5] After a gene is transcribed, it is often spliced and modified into mRNA, or message RNA. The CB-2 mRNA is the gene "message" that moves from the cell nucleus into the cytoplasm where it will be translated into the receptor protein.

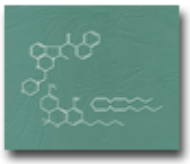
[6] Mitogens are substances that stimulate cell division (mitosis) and cell transformation.

[7] While 3 mg/kg would be a high dose for humans (see Table 3.1), in rodents, it is a low dose for immunological effects and a moderate dose for behavioral effects.

[8] *In vitro* studies are those in which animal cells or tissue are removed and studied outside the animal; *in vivo* studies are those in which experiments are conducted in the whole animal.

3

First, Do No Harm: Consequences of Marijuana Use and Abuse



Primum non nocere. This is the physician's first rule: whatever treatment a physician prescribes to a patient--first, that treatment must not harm the patient.

The most contentious aspect of the medical marijuana debate is not whether marijuana can alleviate particular symptoms but rather the degree of harm associated with its use. This chapter explores the negative health consequences of marijuana use, first with respect to drug abuse, then from a psychological perspective, and finally from a physiological perspective.

THE MARIJUANA "HIGH"

The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and sleepiness (see reviews by Adams and Martin, 1996,[1] Hall and Solowij,[59] and Hall et al. [60]). A characteristic feature of a marijuana "high" is a distortion in the sense of time associated with deficits in short-term memory and learning. A marijuana smoker typically has a sense of enhanced physical and emotional sensitivity, including a feeling of greater interpersonal closeness. The most obvious behavioral abnormality displayed by someone under the influence of marijuana is difficulty in carrying on an intelligible conversation, perhaps because of an inability to remember what was just said even a few words earlier.

The high associated with marijuana is not generally claimed to be integral to its therapeutic value. But mood enhancement, anxiety reduction, and mild sedation can be desirable qualities in medications--particularly for patients suffering pain and anxiety. Thus, although the psychological effects of marijuana are merely side effects in the treatment of some symptoms, they might contribute directly to relief of other symptoms. They also must be monitored in controlled clinical trials to discern which effect of cannabinoids is beneficial. These possibilities are discussed later under the discussions of specific symptoms in chapter 4.

The effects of various doses and routes of delivery of THC are shown in Table 3.1.

Adverse Mood Reactions

Although euphoria is the more common reaction to smoking marijuana, adverse mood reactions can occur. Such reactions occur most frequently in inexperienced users after large doses of smoked or oral marijuana. They usually disappear within hours and respond well to reassurance and a supportive environment. Anxiety and paranoia are the most common acute adverse reactions;[59] others include panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.[1,40,66,69] Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.[145] Those observations are particularly relevant for the use of medical marijuana in people who have not previously used marijuana.

DRUG DYNAMICS

There are many misunderstandings about drug abuse and dependence (see reviews by O'Brien[114] and Goldstein[54]). The terms and concepts used in this report are as defined in the most recent *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[3] the most influential system in the United States for diagnoses of mental disorders, including substance abuse (see Box 3.1). Tolerance, dependence, and withdrawal are often presumed to imply abuse or addiction, but this is not the case. Tolerance and dependence are *normal* physiological adaptations to repeated use of any drug. The correct use of prescribed medications for pain, anxiety, and even hypertension commonly produces tolerance and some measure of physiological dependence.

Even a patient who takes a medicine for appropriate medical indications and at the correct dosage can develop tolerance, physical dependence, and withdrawal symptoms if the drug is stopped abruptly rather than gradually. For example, a hypertensive patient receiving a beta-adrenergic receptor blocker, such as propranolol, might have a good therapeutic response; but if the drug is stopped abruptly, there can be a withdrawal syndrome that consists of tachycardia and a rebound increase in blood pressure to a point that is temporarily higher than before administration of the medication began.

Because it is an illegal substance, some people consider any use of marijuana as substance abuse. However, this report uses the medical definition; that is, substance abuse is a maladaptive pattern of repeated substance use manifested by recurrent and significant adverse consequences.[3] Substance abuse and dependence are both diagnoses of pathological substance use. Dependence is the more serious diagnosis and implies compulsive drug use that is difficult to stop despite significant substance-related problems (see Box 3.2).

Reinforcement

Drugs vary in their ability to produce good feelings in users, and the more strongly reinforcing a drug is, the more likely it will be abused (G. Koob, Institute of Medicine (IOM) workshop). Marijuana is indisputably reinforcing for many people. The reinforcing properties of even so mild a stimulant as caffeine are typical of reinforcement by addicting drugs (reviewed by Goldstein[54] in 1994). Caffeine is reinforcing for many people at low doses (100—200 mg, the average amount of caffeine in one to two cups of

coffee) and is aversive at high doses (600 mg, the average amount of caffeine in six cups of coffee). The reinforcing effects of many drugs are different for different people. For example, caffeine was most reinforcing for test subjects who scored lowest on tests of anxiety but tended not to be reinforcing for the most anxious subjects.

As an argument to dispute the abuse potential of marijuana, some have cited the observation that animals do not willingly self-administer THC, as they will cocaine. Even if that were true, it would not be relevant to human use of marijuana. The value in animal models of drug self-administration is not that they are necessary to show that a drug is reinforcing but rather that they provide a model in which the effects of a drug can be studied. Furthermore, THC is indeed rewarding to animals at some doses but, like many reinforcing drugs, is aversive at high doses (4.0 mg/kg).[93] Similar effects have been found in experiments conducted in animals outfitted with intravenous catheters that allow them to self-administer WIN 55,212, a drug that mimics the effects of THC.[100]

A specific set of neural pathways has been proposed to be a "reward system" that underlies the reinforcement of drugs of abuse and other pleasurable stimuli.[51] Reinforcing properties of drugs are associated with their ability to increase concentrations of particular neurotransmitters in areas that are part of the proposed brain reward system. The median forebrain bundle and the nucleus accumbens are associated with brain reward pathways.[88] Cocaine, amphetamine, alcohol, opioids, nicotine, and THC[144] all increase extracellular fluid dopamine in the nucleus accumbens region (reviewed by Koob and Le Moal[88] and Nestler and Aghajanian[110] in 1997). However, it is important to note that brain reward systems are not strictly "drug reinforcement centers." Rather, their biological role is to respond to a range of positive stimuli, including sweet foods and sexual attraction.

Tolerance

The rate at which tolerance to the various effects of any drug develops is an important consideration for its safety and efficacy. For medical use, tolerance to some effects of cannabinoids might be desirable. Differences in the rates at which tolerance to the multiple effects of a drug develops can be dangerous. For example, tolerance to the euphoric effects of heroin develops faster than tolerance to its respiratory depressant effects, so heroin users tend to increase their daily doses to reach their desired level of euphoria, thereby putting themselves at risk for respiratory arrest. Because tolerance to the various effects of cannabinoids might develop at different rates, it is important to evaluate independently their effects on mood, motor performance, memory, and attention, as well as any therapeutic use under investigation.

Tolerance to most of the effects of marijuana can develop rapidly after only a few doses, and it also disappears rapidly. Tolerance to large doses has been found to persist in experimental animals for long periods after cessation of drug use. Performance impairment is less among people who use marijuana heavily than it is among those who use marijuana only occasionally,[29,104,124] possibly because of tolerance. Heavy users tend to reach higher plasma concentrations of THC than light users after similar doses of

THC, arguing against the possibility that heavy users show less performance impairment because they somehow absorb less THC (perhaps due to differences in smoking behavior).[95]

There appear to be variations in the development of tolerance to the different effects of marijuana and oral THC. For example, daily marijuana smokers participated in a residential laboratory study to compare the development of tolerance to THC pills and to smoked marijuana.[61,62] One group was given marijuana cigarettes to smoke four times per day for four consecutive days; another group was given THC pills on the same schedule. During the four-day period, both groups became tolerant to feeling "high" and what they reported as a "good drug effect." In contrast, neither group became tolerant to the stimulatory effects of marijuana or THC on appetite. "Tolerance" does not mean that the drug no longer produced the effects but simply that the effects were less at the end than at the beginning of the four-day period. The marijuana smoking group reported feeling "mellow" after smoking and did not show tolerance to this effect; the group that took THC pills did not report feeling "mellow." The difference was also reported by many people who described their experiences to the IOM study team.

The oral and smoked doses were designed to deliver roughly equivalent amounts of THC to a subject. Each smoked marijuana dose consisted of five 10-second puffs of a marijuana cigarette containing 3.1% THC; the pills contained 30 mg of THC. Both groups also received placebo drugs during other four-day periods. Although the dosing of the two groups was comparable, different routes of administration resulted in different patterns of drug effect. The peak effect of smoked marijuana is usually felt within minutes and declines sharply after 30 minutes[68,95]; the peak effect of oral THC is usually not felt until about an hour and lasts for several hours.[118]

Withdrawal

A distinctive marijuana and THC withdrawal syndrome has been identified, but it is mild and subtle compared with the profound physical syndrome of alcohol or heroin withdrawal.[31,74] The symptoms of marijuana withdrawal include restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping (Table 3.2). In addition to those symptoms, two recent studies noted several more. A group of adolescents under treatment for conduct disorders also reported fatigue and illusions or hallucinations after marijuana abstinence (this study is discussed further in the section on "Prevalence and Predictors of Dependence on Marijuana and Other Drugs").[31] In a residential study of daily marijuana users, withdrawal symptoms included sweating and runny nose, in addition to those listed above.[62] A marijuana withdrawal syndrome, however, has been reported only in a group of adolescents in treatment for substance abuse problems[31] and in a research setting where subjects were given marijuana or THC daily.[62,74]

Withdrawal symptoms have been observed in carefully controlled laboratory studies of people after use of both oral THC and smoked marijuana.[61,62] In one study, subjects were given very high doses of oral THC: 180—210 mg per day for 10—20 days, roughly

equivalent to smoking 9—10 2% THC cigarettes per day.[74] During the abstinence period at the end of the study, the study subjects were irritable and showed insomnia, runny nose, sweating, and decreased appetite. The withdrawal symptoms, however, were short lived. In four days they had abated. The time course contrasts with that in another study in which lower doses of oral THC were used (80—120 mg/day for four days) and withdrawal symptoms were still near maximal after four days.[61,62]

In animals, simply discontinuing chronic heavy dosing of THC does not reveal withdrawal symptoms, but the "removal" of THC from the brain can be made abrupt by another drug that blocks THC at its receptor if administered when the chronic THC is withdrawn. The withdrawal syndrome is pronounced, and the behavior of the animals becomes hyperactive and disorganized.[153] The half-life of THC in brain is about an hour.[16,24] Although traces of THC can remain in the brain for much longer periods, the amounts are not physiologically significant. Thus, the lack of a withdrawal syndrome when THC is abruptly withdrawn without administration of a receptor-blocking drug is probably not due to a prolonged decline in brain concentrations.

Craving

Craving, the intense desire for a drug, is the most difficult aspect of addiction to overcome. Research on craving has focused on nicotine, alcohol, cocaine, and opiates but has not specifically addressed marijuana.[115] Thus, while this section briefly reviews what is known about drug craving, its relevance to marijuana use has not been established.

Most people who suffer from addiction relapse within a year of abstinence, and they often attribute their relapse to craving.[58] As addiction develops, craving increases even as maladaptive consequences accumulate. Animal studies indicate that the tendency to relapse is based on changes in brain function that continue for months or years after the last use of the drug.[115] Whether neurobiological conditions change during the manifestation of an abstinence syndrome remains an unanswered question in drug abuse research.[88] The "liking" of sweet foods, for example, is mediated by opioid forebrain systems and by brain stem systems, whereas "wanting" seems to be mediated by ascending dopamine neurons that project to the nucleus accumbens.[109]

Anticraving medications have been developed for nicotine and alcohol. The antidepressant, bupropion, blocks nicotine craving, while naltrexone blocks alcohol craving.[115] Another category of addiction medication includes drugs that block other drugs' effects. Some of those drugs also block craving. For example, methadone blocks the euphoric effects of heroin and also reduces craving.

MARIJUANA USE AND DEPENDENCE

Prevalence of Use

Millions of Americans have tried marijuana, but most are not regular users. In 1996, 68.6 million people--32% of the U.S. population over 12 years old--had tried marijuana

or hashish at least once in their lifetime, but only 5% were current users.[132] Marijuana use is most prevalent among 18- to 25-year-olds and declines sharply after the age of 34 (Figure 3.1).[77,132] Whites are more likely than blacks to use marijuana in adolescence, although the difference decreases by adulthood.[132]

Most people who have used marijuana did so first during adolescence. Social influences, such as peer pressure and prevalence of use by peers, are highly predictive of initiation into marijuana use.[9] Initiation is not, of course, synonymous with continued or regular use. A cohort of 456 students who experimented with marijuana during their high school years were surveyed about their reasons for initiating, continuing, and stopping their marijuana use.[9] Students who began as heavy users were excluded from the analysis. Those who did not become regular marijuana users cited two types of reasons for discontinuing. The first was related to health and well-being; that is, they felt that marijuana was bad for their health or for their family and work relationships. The second type was based on age-related changes in circumstances, including increased responsibility and decreased regular contact with other marijuana users. Among high school students who quit, parental disapproval was a stronger influence than peer disapproval in discontinuing marijuana use. In the initiation of marijuana use, the reverse was true. The reasons cited by those who continued to use marijuana were to "get in a better mood or feel better." Social factors were not a significant predictor of continued use. Data on young adults show similar trends. Those who use drugs in response to social influences are more likely to stop using them than those who also use them for psychological reasons.[80]

The age distribution of marijuana users among the general population contrasts with that of medical marijuana users. Marijuana use generally declines sharply after the age of 34 years, whereas medical marijuana users tend to be over 35. That raises the question of what, if any, relationship exists between abuse and medical use of marijuana; however, no studies reported in the scientific literature have addressed this question.

Prevalence and Predictors of Dependence on Marijuana and Other Drugs

Many factors influence the likelihood that a particular person will become a drug abuser or an addict; the user, the environment, and the drug are all important factors (Table 3.3).[114] The first two categories apply to potential abuse of any substance; that is, people who are vulnerable to drug abuse for individual reasons and who find themselves in an environment that encourages drug abuse are initially likely to abuse the most readily available drug--regardless of its unique set of effects on the brain.

The third category includes drug-specific effects that influence the abuse liability of a particular drug. As discussed earlier in this chapter, the more strongly reinforcing a drug is, the more likely that it will be abused. The abuse liability of a drug is enhanced by how quickly its effects are felt, and this is determined by how the drug is delivered. In general, the effects of drugs that are inhaled or injected are felt within minutes, and the effects of drugs that are ingested take a half hour or more.

The proportion of people who become addicted varies among drugs. Table 3.4 shows estimates for the proportion of people among the general population who used or became dependent on different types of drugs. The proportion of users that ever became dependent includes anyone who was *ever* dependent--whether it was for a period of weeks or years--and thus includes more than those who are currently dependent. Compared to most other drugs listed in this table, dependence among marijuana users is relatively rare. This might be due to differences in specific drug effects, the availability of or penalties associated with the use of the different drugs, or some combination.

Daily use of most illicit drugs is extremely rare in the general population. In 1989, daily use of marijuana among high school seniors was less than that of alcohol (2.9% and 4.2%, respectively).[76]

Drug dependence is more prevalent in some sectors of the population than in others. Age, gender, and race or ethnic group are all important.[8] Excluding tobacco and alcohol, the following trends of drug dependence are statistically significant:[8] Men are 1.6 times as likely than women to become drug dependent, non-Hispanic whites are about twice as likely as blacks to become drug dependent (the difference between non-Hispanic and Hispanic whites was not significant), and people 25—44 years old are more than three times as likely as those over 45 years old to become drug dependent.

More often than not, drug dependence co-occurs with other psychiatric disorders. Most people with a diagnosis of drug dependence disorder also have a diagnosis of a another psychiatric disorder (76% of men and 65% of women).[76] The most frequent co-occurring disorder is alcohol abuse; 60% of men and 30% of women with a diagnosis of drug dependence also abuse alcohol. In women who are drug dependent, phobic disorders and major depression are almost equally common (29% and 28%, respectively). Note that this study distinguished only between alcohol, nicotine and "other drugs"; marijuana was grouped among "other drugs." The frequency with which drug dependence and other psychiatric disorders co-occur might not be the same for marijuana and other drugs that were included in that category.

A strong association between drug dependence and antisocial personality or its precursor, conduct disorder, is also widely reported in children and adults (reviewed in 1998 by Robins[126]). Although the causes of the association are uncertain, Robins recently concluded that it is more likely that conduct disorders generally lead to substance abuse than the reverse.[126] Such a trend might, however, depend on the age at which the conduct disorder is manifested.

A longitudinal study by Brooks and co-workers noted a significant relationship between adolescent drug use and disruptive disorders in young adulthood; except for earlier psychopathology, such as childhood conduct disorder, the drug use preceded the psychiatric disorders.[18] In contrast with use of other illicit drugs and tobacco, moderate (less than once a week and more than once a month) to heavy marijuana use did not predict anxiety or depressive disorders; but it was similar to those other drugs in predicting antisocial personality disorder. The rates of disruptive disorders increased with

increased drug use. Thus, heavy drug use among adolescents can be a warning sign for later psychiatric disorders; whether it is an early manifestation of or a cause of those disorders remains to be determined.

Psychiatric disorders are more prevalent among adolescents who use drugs--including alcohol and nicotine--than among those who do not.[79] Table 3.5 indicates that adolescent boys who smoke cigarettes daily are about 10 times as likely to have a psychiatric disorder diagnosis as those who do not smoke. However, the table does not compare intensity of use among the different drug classes. Thus, although *daily* cigarette smoking among adolescent boys is more strongly associated with psychiatric disorders than is any use of illicit substances, it does not follow that this comparison is true for every amount of cigarette smoking.[79]

Few marijuana users become dependent on it (Table 3.4), but those who do encounter problems similar to those associated with dependence on other drugs.[19,143] Dependence appears to be less severe among people who use only marijuana than among those who abuse cocaine or those who abuse marijuana with other drugs (including alcohol).[19,143]

Data gathered in 1990—1992 from the National Comorbidity Study of over 8,000 persons 15—54 years old indicate that 4.2% of the general population were dependent on marijuana at some time.[8] Similar results for the frequency of substance abuse among the general population were obtained from the Epidemiological Catchment Area Program, a survey of over 19,000 people. According to data collected in the early 1980s for that study, 4.4% of adults have, at one time, met the criteria for marijuana dependence. In comparison, 13.8% of adults met the criteria for alcohol dependence and 36.0% for tobacco dependence. After alcohol and nicotine, marijuana was the substance most frequently associated with a diagnosis of substance dependence.

In a 15-year study begun in 1979, 7.3% of 1,201 adolescents and young adults in suburban New Jersey at some time met the criteria for marijuana dependence; this indicates that the rate of marijuana dependence might be even higher in some groups of adolescents and young adults than in the general population.[71] Adolescents meet the criteria for drug dependence at lower rates of marijuana use than do adults, and this suggests that they are more vulnerable to dependence than adults[25] (see Box 3.2).

Youths who are already dependent on other substances are particularly vulnerable to marijuana dependence. For example, Crowley and co-workers[31] interviewed a group of 229 adolescent patients in a residential treatment program for delinquent, substance-involved youth and found that those patients were dependent on an average of 3.2 substances. The adolescents had previously been diagnosed as dependent on at least one substance (including nicotine and alcohol) and had three or more conduct disorder symptoms during their life. About 83% of those who had used marijuana at least six times went on to develop marijuana dependence. About equal numbers of youths in the study had a diagnosis of marijuana dependence and a diagnosis of alcohol dependence; fewer were nicotine dependent. Comparisons of dependence potential between different drugs should be made cautiously. The probability that a particular drug will be abused is

influenced by many factors, including the specific drug effects and availability of the drug.

Although parents often state that marijuana caused their children to be rebellious, the troubled adolescents in the study by Crowley and co-workers developed conduct disorders *before* marijuana abuse. That is consistent with reports that the more symptoms of conduct disorders children have, the younger they begin drug abuse,[127] and that the earlier they begin drug use, the more likely it is to be followed by abuse or dependence.[125]

Genetic factors are known to play a role in the likelihood of abuse for drugs other than marijuana,[7,129] and it is not unexpected that genetic factors play a role in the marijuana experience, including the likelihood of abuse. A study of over 8,000 male twins listed in the Vietnam Era Twin Registry indicated that genes have a statistically significant influence on whether a person finds the effects of marijuana pleasant.[97] Not surprisingly, people who found marijuana to be pleasurable used it more often than those who found it unpleasant. The study suggested that, although social influences play an important role in the initiation of use, individual differences--perhaps associated with the brain's reward system--influence whether a person will continue using marijuana. Similar results were found in a study of female twins.[86] Family and social environment strongly influenced the likelihood of ever using marijuana but had little effect on the likelihood of heavy use or abuse. The latter were more influenced by genetic factors. Those results are consistent with the finding that the degree to which rats find THC rewarding is genetically based.[92]

In summary, although few marijuana users develop dependence, some do. But they appear to be less likely to do so than users of other drugs (including alcohol and nicotine), and marijuana dependence appears to be less severe than dependence on other drugs. Drug dependence is more prevalent in some sectors of the population than others, but no group has been identified as particularly vulnerable to the drug-specific effects of marijuana. Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear to be more likely than the general population to become dependent on marijuana.

If marijuana or cannabinoid drugs were approved for therapeutic uses, it would be important to consider the possibility of dependence, particularly for patients at high risk for substance dependence. Some controlled substances that are approved medications produce dependence after long-term use; this, however, is a normal part of patient management and does not generally present undue risk to the patient.

Progression from Marijuana to Other Drugs

The fear that marijuana use might cause, as opposed to merely precede, the use of drugs that are more harmful is of great concern. To judge from comments submitted to the IOM study team, it appears to be of greater concern than the harms directly related to marijuana itself. The discussion that marijuana is a "gateway" drug implicitly recognizes that other illicit drugs might inflict greater damage to health or social relations than

marijuana. Although the scientific literature generally discusses drug use progression between a variety of drug classes, including alcohol and tobacco, the public discussion has focused on marijuana as a "gateway" drug that leads to abuse of more harmful illicit drugs, such as cocaine and heroin.

There are strikingly regular patterns in the progression of drug use from adolescence to adulthood. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug that most people encounter. Not surprisingly, most users of other illicit drugs used marijuana first.[81,82] In fact, most drug users do not begin their drug use with marijuana--they begin with alcohol and nicotine, usually when they are too young to do so legally.[82,90]

The gateway analogy evokes two ideas that are often confused. The first, more often referred to as the "stepping stone" hypothesis, is the idea that progression from marijuana to other drugs arises from pharmacological properties of marijuana itself.[82] The second is that marijuana serves as a gateway to the world of illegal drugs in which youths have greater opportunity and are under greater social pressure to try other illegal drugs. The latter interpretation is most often used in the scientific literature, and it is supported, although not proven, by the available data.

The stepping stone hypothesis applies to marijuana only in the broadest sense. People who enjoy the effects of marijuana are, logically, more likely to be willing to try other mood-altering drugs than are people who are not willing to try marijuana or who dislike its effects. In other words, many of the factors associated with a willingness to use marijuana are, presumably, the same as those associated with a willingness to use other illicit drugs. Those factors include physiological reactions to the drug effect, which are consistent with the stepping stone hypothesis, but also psychosocial factors, which are independent of drug-specific effects. There is no evidence that marijuana serves as a stepping stone on the basis of its particular physiological effect. One might argue that marijuana is generally used before other illicit mood-altering drugs, in part, because its effects are milder; in that case, marijuana is a stepping stone only in the same sense as taking a small dose of a particular drug and then increasing that dose over time is a stepping stone to increased drug use.

Whereas the stepping stone hypothesis presumes a predominantly physiological component of drug progression, the gateway theory is a social theory. The latter does not suggest that the pharmacological qualities of marijuana make it a risk factor for progression to other drug use. Instead, the legal status of marijuana makes it a gateway drug.[82]

Psychiatric disorders are associated with substance dependence and are probably risk factors for progression in drug use. For example, the troubled adolescents studied by Crowley and co-workers[31] were dependent on an average of 3.2 substances, and this suggests that their conduct disorders were associated with increased risk of progressing from one drug to another. Abuse of a single substance is probably also a risk factor for later multiple drug use. For example, in a longitudinal study that examined drug use and

dependence, about 26% of problem drinkers reported that they first used marijuana after the onset of alcohol-related problems (R. Pandina, IOM workshop). The study also found that 11% of marijuana users developed chronic marijuana problems; most also had alcohol problems.

Intensity of drug use is an important risk factor in progression. Daily marijuana users are more likely than their peers to be extensive users of other substances (for review, see Kandel and Davies[78]). Of 34- to 35-year- old men who had used marijuana 10—99 times by the age 24—25, 75% never used any other illicit drug; 53% of those who had used it more than 100 times did progress to using other illicit drugs 10 or more times. [78] Comparable proportions for women are 64% and 50%.

The factors that best predict use of illicit drugs other than marijuana are probably the following: age of first alcohol or nicotine use, heavy marijuana use, and psychiatric disorders. However, progression to illicit drug use is not synonymous with heavy or persistent drug use. Indeed, although the age of onset of use of licit drugs (alcohol and nicotine) predicts later illicit drug use, it does *not* appear to predict persistent or heavy use of illicit drugs.[90]

Data on the gateway phenomenon are often overinterpreted. For example, one study reports that "marijuana's role as a gateway drug appears to have increased."[55] It was a retrospective study based on interviews of drug abusers who reported smoking crack or injecting heroin daily. The data from the study provide no indication of what proportion of marijuana users become serious drug abusers; rather, they indicate that serious drug abusers usually use marijuana before they smoke crack or inject heroin. Only a small percentage of the adult population uses crack or heroin daily; during the five-year period from 1993 to 1997, an average of three people per 1,000 used crack and about two per 1,000 used heroin in the preceding month.[132]

Many of the data on which the gateway theory is based do not measure dependence; instead, they measure use--even once-only use. Thus, they show only that marijuana users are more likely to use other illicit drugs (even if only once) than are people who never use marijuana, not that they become dependent or even frequent users. The authors of these studies are careful to point out that their data should not be used as evidence of an inexorable *causal* progression; rather they note that identifying stage-based user groups makes it possible to identify the specific risk factors that predict movement from one stage of drug use to the next--the real issue in the gateway discussion.[25]

In the sense that marijuana use typically precedes rather than follows initiation into the use of other illicit drugs, it is indeed a gateway drug. However, it does not appear to be a gateway drug to the extent that it is the *cause* or even that it is the most significant predictor of serious drug abuse; that is, care must be taken not to attribute cause to association. The most consistent predictors of serious drug use appear to be the intensity of marijuana use and co-occurring psychiatric disorders or a family history of psychopathology (including alcoholism).[78,83]

An important caution is that data on drug use progression pertain to *nonmedical* drug use. It does not follow from those data that if marijuana were available by prescription for *medical* use, the pattern of drug use would be the same. Kandel and co-workers also included nonmedical use of prescription psychoactive drugs in their study of drug use progression.[82] In contrast with the use of alcohol, nicotine, and illicit drugs, there was not a clear and consistent sequence of drug use involving the abuse of prescription psychoactive drugs. The current data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse among medical marijuana users. Whether the medical use of marijuana might encourage drug abuse among the general community--not among medical marijuana users themselves but among others simply because of the fact that marijuana would be used for medical purposes--is another question.

LINK BETWEEN MEDICAL USE AND DRUG ABUSE

Almost everyone who spoke or wrote to the IOM study team about the potential harms posed by the medical use of marijuana felt that it would send the wrong message to children and teenagers. They stated that information about the harms caused by marijuana is undermined by claims that marijuana might have medical value. Yet many of our powerful medicines are also dangerous medicines. These two facets of medicine--effectiveness and risk--are inextricably linked.

The question here is not whether marijuana can be both harmful and helpful but whether the perception of its benefits will increase its abuse. For now any answer to the question remains conjecture. Because marijuana is not an approved medicine, there is little information about the consequences of its medical use in modern society. Reasonable inferences might be drawn from some examples. Opiates, such as morphine and codeine, are an example of a class of drugs that is both abused to great harm and used to great medical benefit, and it would be useful to examine the relationship between their medical use and their abuse. In a "natural experiment" during 1973—1978 some states decriminalized marijuana, and others did not. Finally, one can examine the short-term consequences of the publicity surrounding the 1996 medical marijuana campaign in California and ask whether it had any measurable impact on marijuana consumption among youth in California; the consequences of "message" that marijuana might have medical use are examined below.

Medical Use and Abuse of Opiates

Two highly influential papers published in the 1920s and 1950s led to widespread concern among physicians and medical licensing boards that liberal use of opiates would result in many addicts (reviewed by Moulin and co-workers[106] in 1996). Such fears have proven unfounded; it is now recognized that fear of producing addicts through medical treatment resulted in needless suffering among patients with pain as physicians needlessly limited appropriate doses of medications.[27,44] Few people begin their drug addiction problems with misuse of drugs that have been prescribed for medical use.[114]

Opiates are carefully regulated in the medical setting, and diversion of medically prescribed opiates to the black market is not generally considered to be a major problem.

No evidence suggests that the use of opiates or cocaine for medical purposes has increased the perception that their illicit use is safe or acceptable. Clearly, there are risks that patients will abuse marijuana for its psychoactive effects and some likelihood of diversion of marijuana from legitimate medical channels into the illicit market. But those risks do not differentiate marijuana from many accepted medications that are abused by some patients or diverted from medical channels for nonmedical use. Medications with abuse potential are placed in Schedule II of the Controlled Substances Act, which brings them under stricter control, including quotas on the amount that can be legally manufactured (see chapter 5 for discussion of the Controlled Substances Act). That scheduling also signals to physicians that a drug has abuse potential and that they should monitor its use by patients who could be at risk for drug abuse.

Marijuana Decriminalization

Monitoring the Future, the annual survey of values and lifestyles of high school seniors, revealed that high school seniors in decriminalized states reported using no more marijuana than did their counterparts in states where marijuana was not decriminalized.[72] Another study reported somewhat conflicting evidence indicating that decriminalization had increased marijuana use.[105] That study used data from the Drug Awareness Warning Network (DAWN), which has collected data on drug-related emergency room (ER) cases since 1975. There was a greater increase from 1975 to 1978 in the proportion of ER patients who had used marijuana in states that had decriminalized marijuana in 1975—1976 than in states that had not decriminalized it (Table 3.6). Despite the greater increase among decriminalized states, the proportion of marijuana users among ER patients by 1978 was about equal in states that had and states that had not decriminalized marijuana. That is because the non-decriminalized states had higher rates of marijuana use *before* decriminalization. In contrast with marijuana use, rates of other illicit drug use among ER patients were substantially higher in states that did not decriminalize marijuana use. Thus, there are different possible reasons for the greater increase in marijuana use in the decriminalized states. On the one hand, decriminalization might have led to an increased use of marijuana (at least among people who sought health care in hospital ERs). On the other hand, the lack of decriminalization might have encouraged greater use of drugs that are even more dangerous than marijuana.

The differences between the results for high school seniors from the Monitoring the Future study and the DAWN data are unclear, although the author of the latter study suggests that the reasons might lie in limitations inherent in how the DAWN data are collected.[105]

In 1976, the Netherlands adopted a policy of toleration for possession of up to 30 g of marijuana. There was little change in marijuana use during the seven years after the policy change, which suggests that the change itself had little effect; however, in 1984, when Dutch "coffee shops" that sold marijuana commercially spread throughout

Amsterdam, marijuana use began to increase.[98] During the 1990s, marijuana use has continued to increase in the Netherlands at the same rate as in the United States and Norway--two countries that strictly forbid marijuana sale and possession. Furthermore, during this period, approximately equal percentages of American and Dutch 18 year olds used marijuana; Norwegian 18 year olds were about half as likely to have used marijuana. The authors of this study conclude that there is little evidence that the Dutch marijuana depenalization policy led to increased marijuana use, although they note that commercialization of marijuana might have contributed to its increased use. Thus, there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use.

The Medical Marijuana Debate

The most recent National Household Survey on Drug Abuse showed that among people 12—17 years old the perceived risk associated with smoking marijuana once or twice a week had decreased significantly between 1996 and 1997.[132] (Perceived risk is measured as the percentage of survey respondents who report that they "perceive great risk of harm" in using a drug at a specified frequency.) At first glance, that might seem to validate the fear that the medical marijuana debate of 1996--before passage of the California medical marijuana referendum in November 1997--had sent a message that marijuana use is safe. But a closer analysis of the data shows that Californian youth were an exception to the national trend. In contrast to the national trend, the perceived risk of marijuana use did not change among California youth between 1996 and 1997.[1321] In summary, there is no evidence that the medical marijuana debate has altered adolescents' perceptions of the risks associated with marijuana use.[132]

PSYCHOLOGICAL HARMS

In assessing the relative risks and benefits related to the medical use of marijuana, the psychological effects of marijuana can be viewed both as unwanted side effects and as potentially desirable end points in medical treatment. However, the vast majority of research on the psychological effects of marijuana has been in the context of assessing the drug's intoxicating effects when it is used for nonmedical purposes. Thus, the literature does not directly address the effects of marijuana taken for medical purposes.

There are some important caveats to consider in attempting to extrapolate from the research mentioned above to the medical use of marijuana. The circumstances under which psychoactive drugs are taken are an important influence on their psychological effects. Furthermore, research protocols to study marijuana's psychological effects in most instances were required to use participants who already had experience with marijuana. People who might have had adverse reactions to marijuana either would choose not to participate in this type of study or would be screened out by the investigator. Therefore, the incidence of adverse reactions to marijuana that might occur in people with no marijuana experience cannot be estimated from such studies. A further complicating factor concerns the dose regimen used for laboratory studies. In most instances, laboratory research studies have looked at the effects of single doses of

marijuana, which might be different from those observed when the drug is taken repeatedly for a chronic medical condition.

Nonetheless, laboratory studies are useful in suggesting what psychological functions might be studied when marijuana is evaluated for medical purposes. Results of laboratory studies indicate that acute and chronic marijuana use has pronounced effects on mood, psychomotor, and cognitive functions. These psychological domains should therefore be considered in assessing the relative risks and therapeutic benefits related to marijuana or cannabinoids for any medical condition.

Psychiatric Disorders

A major question remains as to whether marijuana can produce lasting mood disorders or psychotic disorders, such as schizophrenia. Georgotas and Zeidenberg[52] reported that smoking 10—22 marijuana cigarettes per day was associated with a gradual waning of the positive mood and social facilitating effects of marijuana and an increase in irritability, social isolation, and paranoid thinking. Inasmuch as smoking *one* cigarette is enough to make a person feel "high" for about 1—3 hours,[68,95,118] the subjects in that study were taking very high doses of marijuana. Reports have described the development of apathy, lowered motivation, and impaired educational performance in heavy marijuana users who do not appear to be behaviorally impaired in other ways.[121,122] There are clinical reports of marijuana-induced psychosis-like states (schizophrenia-like, depression, and/or mania) lasting for a week or more.[112] Hollister suggests that, because of the varied nature of the psychotic states induced by marijuana, there is no specific "marijuana psychosis." Rather, the marijuana experience might trigger latent psychopathology of many types.[66] More recently, Hall and colleagues[60] concluded that "there is reasonable evidence that heavy cannabis use, and perhaps acute use in sensitive individuals, can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomanic symptoms predominate." Regardless of which of those interpretations is correct, the two reports agree that there is little evidence that marijuana alone produces a psychosis that persists after the period of intoxication.

Schizophrenia

The association between marijuana and schizophrenia is not well understood. The scientific literature indicates general agreement that heavy marijuana use can precipitate schizophrenic episodes but not that marijuana use can cause the underlying psychotic disorder.[59,96,151] As noted earlier, drug abuse is common among people with psychiatric disorders. Estimates of the prevalence of marijuana use among schizophrenics vary considerably but are in general agreement that it is at least as great as that among the general population.[134] Schizophrenics prefer the effects of marijuana to those of alcohol and cocaine,[35] which they seem to use less often than does the general population.[134] The reasons for this are unknown, but it raises the possibility that schizophrenics might obtain some symptomatic relief from moderate marijuana use. But overall, compared with the general population, people with schizophrenia or with a family history of schizophrenia

are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids.

Cognition

As discussed earlier, acutely administered marijuana impairs cognition.[60,66,112] Positron emission tomography (PET) imaging allows investigators to measure the acute effects of marijuana smoking on active brain function. Human volunteers who perform auditory attention tasks before and after smoking a marijuana cigarette show impaired performance while under the influence of marijuana; this is associated with substantial reduction in blood flow to the temporal lobe of the brain, an area that is sensitive to such tasks.[116,117] Marijuana smoking increases blood flow in other brain regions, such as the frontal lobes and lateral cerebellum.[101,155] Earlier studies purporting to show structural changes in the brains of heavy marijuana users[22] have not been replicated with more sophisticated techniques.[28,89]

Nevertheless, recent studies[14,122] have found subtle defects in cognitive tasks in heavy marijuana users after a brief period (19—24 hours) of marijuana abstinence. Longer term cognitive deficits in heavy marijuana users have also been reported.[140] Although these studies have attempted to match heavy marijuana users with subjects of similar cognitive abilities before exposure to marijuana use, the adequacy of this matching has been questioned.[133] The complex methodological issues facing research in this area are well reviewed in an article by Pope and colleagues.[121] Care must be exercised so that studies are designed to differentiate between changes in brain function caused the effects of marijuana and by the illness for which marijuana is being given. AIDS dementia is an obvious example of this possible confusion. It is also important to determine whether repeated use of marijuana at therapeutic dosages produces any irreversible cognitive effects.

Psychomotor Performance

Marijuana administration has been reported to affect psychomotor performance on a number of tasks. The review by Chait and Pierri[23] not only details the studies that have been done but also points out the inconsistencies among studies, the methodological shortcomings of many studies, and the large individual differences among the studies attributable to subject, situational, and methodological factors. Those factors must be considered in studies of psychomotor performance when participants are involved in a clinical trial of the efficacy of marijuana. The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana include body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test. A study of experienced airplane pilots showed that even 24 hours after a single marijuana cigarette their performance on flight simulator tests was impaired.[163] Before the tests, however, they told the study investigators that they were sure their performance would be unaffected.

Cognitive impairments associated with acutely administered marijuana limit the activities that people would be able to do safely or productively. For example, no one under the influence of marijuana or THC should drive a vehicle or operate potentially dangerous equipment.

Amotivational Syndrome

One of the more controversial effects claimed for marijuana is the production of an "amotivational syndrome." This syndrome is not a medical diagnosis, but it has been used to describe young people who drop out of social activities and show little interest in school, work, or other goal-directed activity. When heavy marijuana use accompanies these symptoms, the drug is often cited as the cause, but no convincing data demonstrate a causal relationship between marijuana smoking and these behavioral characteristics.[23] It is not enough to observe that a chronic marijuana user lacks motivation. Instead, relevant personality traits and behavior of subjects must be assessed before and after the subject becomes a heavy marijuana user. Because such research can only be done on subjects who become heavy marijuana users on their own, a large population study--such as the Epidemiological Catchment Area study described earlier in this chapter--would be needed to shed light on the relationship between motivation and marijuana use. Even then, although a causal relationship between the two could, in theory, be dismissed by an epidemiological study, causality could not be proven.

Summary

Measures of mood, cognition, and psychomotor performance should be incorporated into clinical trials evaluating the efficacy of marijuana or cannabinoid drugs for a given medical condition. Ideally, participants would complete mood assessment questionnaires at various intervals throughout the day for a period before; every week during; and, where appropriate, after marijuana therapy. A full psychological screening of research participants should be conducted to determine whether there is an interaction between the mood-altering effects of chronic marijuana use and the psychological characteristics of the subjects. Similarly, the cognitive and psychomotor functioning should be assessed before and regularly during the course of a chronic regimen of marijuana or cannabinoid treatment to determine the extent to which tolerance to the impairing effects of marijuana develops and to monitor whether new problems develop.

When compared with changes produced by either placebo or an active control medication, the magnitude of desirable therapeutic effects and the frequency and magnitude of adverse psychological side effects of marijuana could be determined. That would allow a more thorough assessment of the risk:benefit ratio associated with the use of marijuana for a given indication.

> **Conclusion:** The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria, can influence their potential therapeutic value. Those effects are potentially undesirable in some patients and situations and

beneficial in others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.

Recommendation: Psychological effects of cannabinoids, such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

PHYSIOLOGICAL HARMS: TISSUE AND ORGAN DAMAGE

Many people who spoke to the IOM study team in favor of the medical use of marijuana cited the absence of marijuana overdoses as evidence that it is safe. Indeed, epidemiological data indicate that in the general population marijuana use is not associated with increased mortality.[138] However, other serious health outcomes should be considered, and they are discussed below.

It is important to keep in mind that most of the studies that report physiological harm resulting from marijuana use are based on the effects of marijuana smoking. Thus, we emphasize that the effects reported cannot be presumed to be caused by THC alone or even in combination with other cannabinoids found in marijuana. It is likely that smoke is a major cause of the reported effects. In most studies the methods used make it impossible to weigh the relative contributions of smoke versus cannabinoids.

Immune System

The relationship between marijuana and the immune system presents many facets, including potential benefits and suspected harms. This section reviews the evidence on suspected harms to the immune system caused by marijuana use.

Despite the many claims that marijuana suppresses the human immune system, the health effects of marijuana-induced immunomodulation are still unclear. Few studies have been done with animals or humans to assess the effects of marijuana exposure on host resistance to bacteria, viruses, or tumors.

Human Studies

Several approaches have been used to determine the effects of marijuana on the human immune system. Each has serious limitations, which are discussed below.

Assays of Leukocytes from Marijuana Smokers. One of the more common approaches has been to isolate peripheral blood leukocytes from people who have smoked marijuana in order to evaluate the immune response of those cells in vitro--most often by measuring mitogen-induced cell proliferation, a normal immune response. Almost without exception, this approach has failed to demonstrate any reduction in leukocyte function. The major problem with the approach is that after blood samples are drawn from the study subjects the leukocytes must be isolated from whole blood before they are tested. That is done by high-speed centrifugation followed by extensive washing of the cells,

which removes the cannabinoid; perhaps for this reason no adverse effects have been demonstrated in peripheral blood leukocytes from marijuana smokers.[75,91,123,160]

Leukocyte Responses to THC. Another approach is to isolate peripheral blood leukocytes from healthy control subjects who do not smoke marijuana and then to measure the effect of THC on the ability of these cells to proliferate in response to mitogenic stimulation *in vitro*. One important difference between leukocytes isolated from a marijuana smoker, as described above, and leukocyte cell cultures to which THC has been added directly is in the cannabinoid composition. Marijuana smoke contains many distinct cannabinoid compounds of which THC is just one. Moreover, the immunomodulatory activity of many of the other cannabinoid compounds has never been tested, and it is now known that at least one of those--cannabinol (CBN)--has greater activity on the immune system than on the central nervous system,[64] so it is unclear whether the profile of activity observed with THC accurately represents the effects of marijuana smoke on immune competence. Likewise, the extent to which different cannabinoids in combination exhibit additive, synergistic, or antagonistic effects with respect to immunomodulatory activity is unclear. The issue is complicated by the fact that leukocytes express both types of cannabinoid receptors: CB_1 and CB_2.

An additional factor that might affect the immunomodulatory activity of cannabinoids in leukocytes is metabolism. Leukocytes have very low levels of the cytochrome P-450 drug-metabolizing enzymes,[20] so the metabolism of cannabinoids is probably different between *in vivo* and *in vitro* exposure. That last point is pertinent primarily to investigations of chronic, not acute, cannabinoid exposure.

Human-Derived Cell Lines. A third approach for investigating the effects of cannabinoids on human leukocytes has been to study human-derived cell lines.[2] As described above, the cell lines are treated *in vitro* with cannabinoids to test their responses to different stimuli. Although cell lines are a convenient source of human cells, the problems described above apply here as well. In addition, the cell lines might not be the same as the original cells. For example, cell lines do not necessarily have the same number of cannabinoid receptors as the original human cells.

Rodent Studies

The most widely used approach is to evaluate the effects of cannabinoids in rodents, using rodent-derived cells *in vitro*. The rationale is that the human and rodent immune systems are remarkably similar, and it is assumed that the effects produced by cannabinoids on the rodent immune system will be similar to those produced in humans. Although no substantial species differences in immune system sensitivity to cannabinoids have been reported, the possibility should be considered.

Summary

The complete effect of marijuana smoking on immune function remains unknown. More important, it is not known whether smoking leads to increased rates of infections,

tumors, allergies, or autoimmune responses. The problem is how to duplicate the "normal" marijuana smoking pattern while removing other potential immunomodulating lifestyle factors, such as alcohol and tobacco use. Epidemiological studies are needed to determine whether marijuana users have a higher incidence of such diseases, as infections, tumors, allergies, and autoimmune diseases. Studies on resistance to bacterial and viral infection are clearly needed and should involve the collaboration of immunologists, infectious disease specialists, oncologists, and pharmacologists.

Marijuana Smoke

Tobacco is the predominant cause of such lung diseases as cancer and emphysema, and marijuana smoke contains many of the components of tobacco smoke.[69] Thus, it is important to consider the relationship between habitual marijuana smoking and some lung diseases.

Given a cigarette of comparable weight, as much as four times the amount of tar can be deposited in the lungs of marijuana smokers as in the lungs of tobacco smokers.[162] The difference is due primarily to the differences in filtration and smoking technique between tobacco and marijuana smokers. Marijuana cigarettes usually do not have filters, and marijuana smokers typically develop a larger puff volume, inhale more deeply, and hold their breath several times longer than tobacco smokers.[119] However, a marijuana cigarette smoked recreationally typically is not packed as tightly as a tobacco cigarette, and the smokable substance is about half that in a tobacco cigarette. In addition, tobacco smokers generally smoke considerably more cigarettes per day than do marijuana smokers.

Cellular Damage

Lymphocytes: T and B Cells. Human studies of the effect of marijuana smoking on immune cell function are not all consistent with cannabinoid cell culture and animal studies. For example, antibody production was decreased in a group of hospitalized patients who smoked marijuana for four days (12 cigarettes/day), but the decrease was seen in only one subtype of humoral antibody (IgG), whereas two other subtypes (IgA and IgM) remained normal and one (IgE) was increased.[108] In addition, T cell proliferation was normal in the blood of a group of marijuana smokers, although closer evaluation showed an increase in one subset of T cells[161] and a decrease in a different subset (CD8).[157] It appears that marijuana use is associated with intermittent disturbances in T and B cell function, but the magnitude is small and other measures are often normal.[87]

Macrophages. Alveolar macrophages are the principal immune-effector cells in the lung and are primarily responsible for protecting the lung against infectious microorganisms, inhaled foreign substances, and tumor cells. They are increased during tissue inflammation. In a large sample of volunteers, habitual marijuana smokers had twice as many alveolar macrophages as nonsmokers, and smokers of both marijuana and tobacco had twice as many again.[11] Marijuana smoking also reduced the ability of alveolar macrophages to kill fungi, such as *Candida albicans*;[3] pathogenic bacteria, such as

Staphylococcus aureus; and tumor target cells. The reduction in ability to destroy fungal organisms was similar to that seen in tobacco smokers. The inability to kill pathogenic bacteria was not seen in tobacco smokers.[10] Furthermore, marijuana smoking depressed production of proinflammatory cytokines, such as TNF-I and IL-6, but not of immunosuppressive cytokines.[10] Cytokines are important regulators of macrophage function, so this marijuana-related decrease in inflammatory cytokine production might be a mechanism whereby marijuana smokers are less able to destroy fungal and bacterial organisms, as well as tumor cells.

The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungi, bacteria, and tumor cells and to release proinflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defense. Therefore, the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with preexisting immune deficits--including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients).

Bronchial and Pulmonary Damage

Animal Studies. A number of animal studies have revealed respiratory tract changes and diseases associated with marijuana smoking, but others have not. Extensive damage to the smaller airways, which are the major site of chronic obstructive pulmonary disease (COPD),[4] and acute and chronic pneumonia have been observed in various species exposed to different doses of marijuana smoke.[41,42,128] In contrast, rats exposed to increasing doses of marijuana smoke for one year did not show any signs of COPD, whereas rats exposed to tobacco smoke did.[67]

Chronic Bronchitis and Respiratory Illness. Results of human studies suggest that there is a greater chance of respiratory illness in people who smoke marijuana. In a survey of outpatient medical visits at a large health maintenance organization (HMO), marijuana users were more likely to seek help for respiratory illnesses than people who smoked neither marijuana or tobacco.[120] However, the incidence of seeking help for respiratory illnesses was not higher in those who smoked marijuana for 10 years or more than in those who smoked for less than 10 years. One explanation for this is that people who experience respiratory symptoms are more likely to quit smoking and that people who continue to smoke constitute a set of survivors who do not develop or are indifferent to such symptoms. One limitation of this study is that no data were available on the use of cocaine, which when used with marijuana could contribute to the observed differences. Another limitation is that the survey relied on self-reporting; tobacco, alcohol, and marijuana use might have been under-reported (S. Sidney, IOM workshop).

When marijuana smokers were compared with nonsmokers and tobacco smokers in a group of 446 volunteers, 15—20% of the marijuana smokers reported symptoms of chronic bronchitis, including chronic cough and phlegm production,[146] and 20—25% of the tobacco smokers reported symptoms of chronic bronchitis. Despite a marked disparity in the amount of each substance smoked per day (three or four joints of marijuana versus

more than 20 cigarettes of tobacco), the difference in the percentages of tobacco smokers and marijuana smokers experiencing symptoms of chronic bronchitis was statistically insignificant.[146] Similar findings were reported by Bloom and co-workers,[15] who noted an additive effect of smoking both marijuana and tobacco.

Bronchial Tissue Changes. Habitual marijuana smoking is associated with changes in the lining of the human respiratory tract. Many marijuana or tobacco smokers have increased redness (erythema) and swelling (edema) of the airway tissues and increased mucous secretions.[43,56] In marijuana smokers the number and size of small blood vessels in the bronchial wall are increased, tissue edema is present, and the normal ciliated cells[5] lining the inner surface of the bronchial wall are largely replaced by mucous-secreting goblet cells. The damage is greater in people who smoke both marijuana and tobacco.[130] Overproduction of mucus by the increased numbers of mucous-secreting cells in the presence of decreased numbers of ciliated cells tends to leave coughing as the only major mechanism to remove mucus from the airways; this might explain the relatively high proportion of marijuana smokers who complain of chronic cough and phlegm production.[148]

A 1998 study has shown that both marijuana and tobacco smokers have significantly more cellular and molecular abnormalities in bronchial epithelium cells than nonsmokers; these changes are associated with increased risk of cancer.[12] The tobacco-only smokers in that study smoked an average of 25 cigarettes per day, whereas the marijuana-only smokers smoked an average of 21 marijuana cigarettes per week. Although the marijuana smokers smoked far fewer cigarettes, their cellular abnormalities were equivalent to or greater than those seen in tobacco smokers. This and earlier studies have shown that such abnormalities are greatest in people who smoke both marijuana and tobacco; hence, marijuana and tobacco smoke might have additive effects on airway tissue.[12,43,56] Tenant[150] found similar results in U.S. servicemen who suffered from respiratory symptoms and were heavy hashish smokers. (Hashish is the resin from the marijuana plant.)

Chronic Obstructive Pulmonary Disease. In the absence of epidemiological data, indirect evidence, such as nonspecific airway hyperresponsiveness and measures of lung function, offers an indicator of the vulnerability of marijuana smokers to COPD.[154] For example, the methacholine provocative challenge test, used to evaluate airway hyperresponsiveness, showed that tobacco smokers develop more airway hyperresponsiveness. But no such correlation has been shown between marijuana smoking and airway hyperresponsiveness.

There is conflicting evidence on whether regular marijuana use harms the small airways of the lungs. Bloom and co-workers found that an average of one joint smoked per day significantly impaired the function of small airways.[15] But Tashkin and co-workers[146] did not observe such damage among heavier marijuana users (three to four joints per day for at least 10 years), although they noted a narrowing of large central airways. Tashkin and co-workers' long-term study, which adjusted for age-related decline in lung function (associated with an increased risk for developing COPD), showed an

accelerated rate of decline in tobacco smokers but not in marijuana smokers.[147] Thus, the question of whether usual marijuana smoking habits are enough to cause COPD remains open.

Conclusion. Chronic marijuana smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cells lining the bronchial passageways, some of which may be premalignant. These respiratory symptoms are similar to those of tobacco smokers, and the combination of marijuana and tobacco smoking augments these effects. At the time of this writing, it had not been established whether chronic smoking marijuana causes COPD, but there is probably an association.

HIV/AIDS Patients

The relationship between marijuana smoking and the natural course of AIDS is of particular concern because HIV patients are the largest group who report using marijuana for medical purposes. Marijuana use has been linked both to increased risk of progression to AIDS in HIV-seropositive patients and to increased mortality in AIDS patients.

For unknown reasons, marijuana use is associated with increased mortality among men with AIDS but not among the general population.[138] (The relative risk of AIDS mortality for current marijuana users in this 12-year study was 1.90, indicating that almost twice as many marijuana users died of AIDS as did noncurrent marijuana users.) Never-married men used twice as much marijuana as married men and accounted for 83% of the AIDS deaths in the study. The authors of the study note that, while marital status is insufficient to adjust for lifestyle factors--particularly, homosexual behavior--a substantial proportion of the never-married men with AIDS were probably homosexuals or bisexuals. That raises the possibility that the association of marijuana use with AIDS deaths might be related to indirect factors, such as use of other drugs or high-risk sexual behavior, both of which increase risks of infection to which AIDS patients are more susceptible. The higher mortality of AIDS patients who were current marijuana users also raises the question of whether this was because patients increased their use of marijuana at the endstages of the disease to treat their symptoms. However, the association between marijuana use and AIDS deaths was similar even when the subjects who died earliest in the first five years of this 12-year study, and who were presumably the most sick, were excluded from the analysis. In summary, it is premature to conclude what the underlying causes of this association might be.

For the general population, the mortality associated with marijuana use was lower than that associated with cigarette smoking, and tobacco smoking was not an independent risk factor in AIDS mortality. The authors of the study described above concluded that therapeutic use of marijuana did not contribute to the increased mortality among men with AIDS.

Marijuana use has been associated with a higher prevalence of HIV seropositivity in cross-sectional studies,[84] but the relationship of marijuana to the progression to AIDS in HIV-seropositive patients is a reasonable question. It remains unclear whether marijuana

smoking is an independent risk factor in the progression of AIDS in HIV-seropositive men. Marijuana use did not increase the risk of AIDS in HIV-seropositive men in the Multicenter AIDS Cohort Study, in which 1,795 HIV-seropositive men were studied for 18 months,[84] or in the San Francisco Men's Health Study, in which 451 HIV-seropositive men were studied for six years.[34] In contrast, the Sydney AIDS Project in Australia, in which 386 HIV-seropositive men were studied for 12 months,[152] reported that marijuana use was associated with increased risk of progression to AIDS. The results of the Sydney study are less reliable than those of the other two studies noted; it was the shortest of the studies and, according to the 1993 definition of AIDS, many of the subjects probably already had AIDS at the beginning of the study.[6]

The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity.[111] Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking either suppresses the immune system[33] or exposes patients to an added burden of pathogens.[21] In summary, patients with preexisting immune deficits due to AIDS should be expected to be vulnerable to serious harm caused by smoking marijuana. The relative contribution of marijuana smoke versus THC or other cannabinoids is not known.

Carcinogenicity

The gas and tar phases of marijuana and tobacco smoke contain many of the same compounds. Furthermore, the tar phase of marijuana smoke contains higher concentrations of polycyclic aromatic hydrocarbons (PAHs), such as the carcinogen benzopyrene. The higher content of carcinogenic PAHs in marijuana tar and the greater deposition of this tar in the lung might act in conjunction to amplify the exposure of a marijuana smoker to carcinogens. For those reasons the carcinogenicity of marijuana smoke is an important concern.

It is more difficult to collect the epidemiological data necessary to establish or refute the link between marijuana smoke and cancer than that between tobacco smoke and cancer. Far fewer people smoke only marijuana than only tobacco, and marijuana smokers are more likely to underreport their smoking.

Case Studies. Results of several case series suggest that marijuana might play a role in the development of human respiratory cancer. Reports indicate an unexpectedly large proportion of marijuana users among people with lung cancer[141,149] and cancers of the upper aerodigestive tract--that is, the oral cavity, pharynx, larynx, and esophagus--that occur before the age of 45.[36,39,149] Respiratory tract cancers associated with heavy tobacco and alcohol consumption are not usually seen before the age of 60,[154] and the occurrence of such cancers in marijuana users younger than 60 suggests that long-term marijuana smoking potentiates the effects of other risk factors, such as tobacco smoking, and is a more potent risk factor than tobacco and alcohol use in the early development of respiratory cancers. Most studies lack the necessary comparison groups to calculate the isolated effect of marijuana use on cancer risk. Many marijuana smokers also smoke

tobacco, so when studies lack information regarding cigarette smoking status, there is no way to separate the effects of marijuana smoke and tobacco smoke.

Epidemiological Evidence. As of this writing, Sidney and co-workers[139] had conducted the only epidemiological study to evaluate the association between marijuana use and cancer. The study included a cohort of about 65,000 men and women 15—49 years old. Marijuana users were defined as those who had used marijuana on six or more occasions. Among the 1,421 cases of cancer in this cohort, marijuana use was associated only with an increased risk of prostate cancer in men who did not smoke tobacco. In these relatively young HMO clients, no association was found between marijuana use and other cancers, including all tobacco-related cancers, colorectal cancer, and melanoma. The major limitation associated with interpreting this study is that the development of lung cancer requires a long exposure to smoking, and most marijuana users quit before this level of exposure is achieved. In addition, marijuana use has been widespread in the United States only since the late 1960s; therefore, despite the large cohort size there might not have been a sufficient number of heavy or long-term marijuana smokers to reveal an effect.

Cellular and Molecular Studies. In contrast with clinical studies, cellular and molecular studies have provided strong evidence that marijuana smoke is carcinogenic. Cell culture studies implicate marijuana smoke in the development of cancer. Prolonged exposure of hamster lung cell cultures to marijuana smoke led to malignant transformations,[94] and exposure of human lung explants to marijuana smoke resulted in chromosomal and DNA alterations.[154] The tar from marijuana smoke also induced mutations similar to those produced by tar from the same quantity of tobacco in a common bacterial assay for mutagenicity.[158]

Molecular studies also implicate marijuana smoke as a carcinogen. Proto-oncogenes and tumor suppressor genes are a group of genes that affect cell growth and differentiation. Normally, they code for proteins that control cellular proliferation. Once mutated or activated, they produce proteins that cause cells to multiply rapidly and out of control, and this results in tumors or cancer.[7] When the production of these proteins was evaluated in tissue biopsies taken from marijuana, tobacco, and marijuana plus tobacco smokers, and nonsmokers, two of them (EGFR and Ki-67) were markedly higher in the marijuana smokers than in the nonsmokers and the tobacco smokers. Moreover, the effects of marijuana and tobacco were additive.[131] Thus, in relatively young smokers of marijuana, particularly those who smoke both marijuana and tobacco, marijuana is implicated as a risk factor for lung cancer.

DNA alterations are known to be early events in the development of cancer, and have been observed in the lymphocytes of pregnant marijuana smokers and in those of their newborns.[4] This is an important study because the investigators were careful to exclude tobacco smokers--a problem in previous studies that cited mutagenic effects of marijuana smoke.[26,53,63,142] The same investigators found similar effects in previous studies among tobacco smokers,[5,6] so the effects cannot be attributed solely to THC or other cannabinoids. Although it can be determined only by experiment, it is likely that the

smoke contents--other than cannabinoids--are responsible for a large part of the mutagenic effect.

Preliminary findings suggest that marijuana smoke activates cytochrome P4501Al (CYP1Al), the enzyme that converts PAHs, such as benz[α]pyrene, into active carcinogens.[99] Bronchial epithelial cells in tissue biopsies taken from marijuana smokers show more binding to CYP1A1 antibodies than do comparable cells in biopsies from nonsmokers (D. Tashkin, IOM workshop). That suggests that there is more of CYP1A1 itself in the bronchial cells of marijuana smokers, but different experimental methods will be needed to establish that possibility.

Conclusions

There is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use. However, cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer. More definitive evidence that habitual marijuana smoking leads or does not lead to respiratory cancer awaits the results of well-designed case control epidemiological studies. It has been 30 years since the initiation of widespread marijuana use among young people in our society, and such studies should now be feasible.

The following studies or activities would be useful in providing data that could more precisely define the health risks of smoking marijuana.

1. **Case control studies to determine whether marijuana use is associated with an increased risk of respiratory cancer.** Despite the lack of compelling epidemiological evidence, findings from the biochemical, cellular, immunological, genetic, tissue, and animal studies cited above strongly suggest that marijuana is a risk factor for human cancer. What is required to address that hypothesis more convincingly is a population-based case control study of sufficiently large numbers of people with lung cancer and upper aerodigestive tumors (cancers of the oral cavity and pharynx, larynx, and esophagus), as well as noncancer controls, to demonstrate a statistically significant association, if one exists. Because of the long period required for induction of human carcinomas and the infrequent use of marijuana in the general U.S. population before 1966, no epidemiological studies so far have been extensive enough to measure the association between marijuana and cancer adequately. However, epidemiological investigation of this association is probably possible now in that some 30 years have elapsed since the start of widespread marijuana use in the United States among teenagers and young adults.

2. **Molecular markers of respiratory cancer progression in marijuana smokers**. If an epidemiological association between marijuana use and risk of respiratory cancer is demonstrated, studies would be warranted to explore the presence of molecular markers--such as TP53, p16, NATZ, and GSTML--that could be predictive of genetically increased risk of carcinogenesis in marijuana users.

3. **Prospective epidemiological studies of populations with HIV seropositivity or at high risk for HIV infection.**[8] Because HIV/AIDS patients constitute the largest group that reports smoking marijuana for medical purposes and they are particularly vulnerable to immunosuppressive effects, there is a pressing need for a better understanding of the relative risk posed by and the rewards of smoking marijuana. Such studies should include history of marijuana use in the analysis of potential risk factors for seroconversion and acquisition of opportunistic infections or progression to AIDS. The studies could be carried out in the context of any federally approved clinical trials of medical marijuana in immuno-compromised patients and should provide a follow-up period long enough to capture potential adverse events.

4. **Regularized recording of marijuana use by patients**. Although marijuana is the most commonly used illicit drug, medical providers often do not question patients about marijuana use and rarely document its use.[102] Among 452 Kaiser Permanente patients who reported daily or almost daily marijuana use, physicians recorded marijuana use in only 3% of their medical records (S. Sidney, IOM workshop).

5. **Additional cellular, animal, and human studies to investigate the effects of THC and marijuana on immune function.** The effects studied should include effects on proinflammatory versus immunosuppressive cytokines and on the function of leukocytes that present antigen to T cells.

The question that needs to be addressed is whether THC or marijuana is a risk factor for HIV infection, for progression to more severe stages of AIDS, or for opportunistic infection among HIV-positive patients. Studies are needed to determine the effects of marijuana use on the function of alveolar macrophages. It would be important to compare the HIV infectivity and replication of alveolar macrophages harvested from habitual marijuana users with those harvested from nonusers or infrequent marijuana users. Cell culture studies could be used to compare the susceptibility of HIV-infected alveolar macrophages to additional infection with opportunistic pathogens. Similarly, further studies on cell cultures of peripheral blood mononuclear cells could be used to assess the effects of exposure to THC on HIV infectivity and replication.

Cardiovascular System

Marijuana smoke and oral THC can cause tachycardia (rapid heart beat) in humans, 20—100% above baseline.[57,85] The increase in heart rate is greatest in the first 10—20 minutes after smoking and decreases sharply and steadily; depending on whether smoked marijuana or oral THC is used, this can last three or five hours, respectively.[68,95] In some cases, blood pressure increases while a person is in a reclining position but decreases inordinately on standing, resulting in postural hypotension (decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness). In contrast with acute administration of THC, chronic oral ingestion of THC reduces heart rate in humans.[13]

In animals, THC decreases heart rate and blood pressure.[57,156] However, most of the animal studies have been conducted in anesthetized animals, and anesthesia causes hypertension. Thus, those studies should be interpreted as reports on the effects of cannabinoids in hypertensive subjects. The results of the animal and human studies are consistent with the conclusion that cannabinoids are hypotensive at high doses in animals, as well as humans.[156]

Tolerance can appear after a few days of frequent daily administration (two or three doses per day) of oral THC or marijuana extract, with heart rate decreasing, reclining blood pressure falling, and postural hypotension disappearing.[73] Thus, the intensity of the effects depends on frequency of use, dose, and even body position.

The cardiovascular changes have not posed a health problem for healthy, young users of marijuana or THC. However, such changes in heart rate and blood pressure could present a serious problem for older patients, especially those with coronary arterial or cerebrovascular disease. Cardiovascular diseases are the leading causes of death in the United States (coronary heart disease is first; stroke is third), so any effect of marijuana use on cardiovascular disease could have a substantial impact on public health (S. Sidney, IOM workshop). The magnitude of the impact remains to be determined as chronic marijuana users from the late 1960s enter the age when coronary arterial and cerebrovascular diseases become common. Smoking marijuana is also known to decrease maximal exercise performance. That, with the increased heart rate, could theoretically induce angina (S. Sidney, IOM workshop), so, this raises the possibility that patients with symptomatic coronary artery disease should be advised not to smoke marijuana, and THC might be contraindicated in patients with restricted cardiovascular function.

Reproductive System

Animal Studies. Marijuana and THC can inhibit many reproductive functions on a short-term basis. In both male and female animals, THC injections suppress reproductive hormones and behavior.[107,159] Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum luteinizing hormone (LH).[70] (LH is the pituitary hormone that stimulates release of the gonadal hormones, testosterone and estrogen.) Embryo implantation also appears to be inhibited by THC. But it does not necessarily follow that marijuana use will interfere with human reproduction. With few exceptions, the animal studies are based on acute treatments (single injections) or short-term treatments (THC injections given over a series of days). The results are generally observed for only several hours or in females sometimes for only one ovulatory cycle.

Acute treatments with cannabinoids--including THC, CBD, cannabinol, and anandamide--can decrease the fertilizing capacity of sea urchin sperm.[135-137] The sea urchin is only a distant relative of humans, but the cellular processes that regulate fertilization are similar enough that one can expect a similar effect in humans. However, the effect of cannabinoids on the capacity of sperm to fertilize eggs is reversible and is observed at concentrations of 6—100 μM,[136,137] which are higher than those likely to be experienced by marijuana smokers. The presence of cannabinoid receptors in sperm

suggests the possibility of a natural role for anandamide in modulating sperm function during fertilization. However, it remains to be determined whether smoked marijuana or oral THC taken in prescribed doses has a clinically significant effect on the fertilizing capacity of human sperm.

Exposure to THC *in utero* can result in long-term changes. Many *in utero* effects interfere with embryo implantation (see review by Wenger and co-workers[159]). Exposure to THC shortly before or after birth can result in impaired reproductive behavior in mice when they reach adulthood: females are slower to show sexual receptivity, and males are slower to mount.[107]

Although THC can act directly on endocrine tissues, such as the testes and ovaries, it appears to affect reproductive physiology through its actions on the brain, somewhere other than the pituitary. Some of the effects of THC are exerted through its action on stress hormones, such as cortisol.[70]

Human Studies. The few human studies are consistent with the acute animal studies: THC inhibits reproductive functions. However, studies of men and women who use marijuana regularly have yielded conflicting results and show either depression of reproductive hormones, no effect, or only a short-term effect. Overall, the results of human studies are consistent with the hypothesis that THC inhibits LH on a short-term basis but not in long-term marijuana users. In other words, long-term users develop tolerance to the inhibitory effect of THC on LH. The results in men and women are similar, with the added consideration of the menstrual cycle in women; the acute effects of THC appear to vary with cycle stage. THC appears to have little effect during the follicular phase (the phase after menses and before ovulation) and to inhibit the LH pulse during the luteal phase (the phase after ovulation and before menses).[103] In brief, although there are no data on fertility itself, marijuana or THC would probably decrease human fertility--at least in the short term--for both men and women. And it is reasonable to predict that THC can interfere with early pregnancy, particularly with implantation of the embryo. Like tobacco smoke, marijuana smoke is highly likely to be harmful to fetal development and should be avoided by pregnant women and those who might become pregnant in the near future. Nevertheless, although fertility and fetal development are important concerns for many, they are unlikely to be of much concern to people with seriously debilitating or life-threatening diseases. The well-documented inhibition of reproductive functions by THC is thus not a serious concern for evaluating the short-term medical use of marijuana or specific cannabinoids.

The results of studies of the relationship between prenatal marijuana exposure and birth outcome have been inconsistent (reviewed in 1995 by Cornelius and co-workers[30]). Except for adolescent mothers, there is little evidence that gestation is shorter in mothers who smoke marijuana.[30] Several studies of women who smoked marijuana regularly during pregnancy show that they tend to give birth to lower weight babies.[46,65] Mothers who smoke tobacco also give birth to lower weight babies, and the relative contributions of smoking and THC are not known from these studies.

Babies born to mothers who smoked marijuana during pregnancy weighed an average of 3.4 ounces less than babies born to a control group of mothers who did not smoke marijuana; there was no statistically significant difference in either gestational age or frequency of congenital abnormalities.[164] Those results were based on women whose urine tests indicated recent marijuana exposure. However, when the analysis was based only on self-reports of marijuana use (without verification by urine tests), there was no difference in weight between babies born to women who reported themselves as marijuana smokers and those born to women who reported that they did not smoke marijuana. That raises an important concern about the methods used to measure the effects of marijuana smoking in any study, perhaps even more so in studies on the effects of marijuana during pregnancy, when subjects might be less likely to admit to smoking marijuana. (The study was conducted in the last trimester of pregnancy, and there was no information about the extent of marijuana use earlier in pregnancy.)

For most of these studies, much of the harm associated with marijuana use is consistent with that associated with tobacco use, and smoking is an important factor, so the contribution of cannabinoids cannot be confirmed. However, Jamaican women who use marijuana rarely smoke it; but instead prepare it as tea.[37] In a study of neonates born to Jamaican women who did or did not ingest marijuana during pregnancy, there was no difference in neurobehavioral assessments made at three days after birth and at one month.[38] A limitation of the study is that there was no direct measure of marijuana use. Estimates of marijuana use were based on self-reports, which might be more accurate in Jamaica than in the United States because less social stigma is associated with marijuana use in Jamaica but still are less reliable than direct measures.

Newborns of mothers who smoke either marijuana or tobacco have statistically significantly higher mutation rates than those of nonsmokers.[4,5]

Since 1978, the Ottawa Prenatal Prospective Study has measured the cognitive functions of children born to mothers who smoked marijuana during pregnancy.[47] Children of mothers who smoked either moderately (one to six marijuana cigarettes per week) or heavily (more than six marijuana cigarettes per week) have been studied from the age of four days to 9—12 years. It is important to keep in mind that studies like this provide important data about the risks associated with marijuana use during pregnancy, but they do not establish the *causes* of any such association.

The children in the different marijuana exposure groups showed no lasting differences in global measures of intelligence, such as language development, reading scores, and visual or perceptual tests. Moderate cognitive deficits were detectable among these children when they were four days old and again at four years, but the deficits were no longer apparent at five years.

Prenatal marijuana exposure was not, however, without lasting effect. At ages 5—6 years and 9—12 years, children in the same study who were prenatally exposed to tobacco smoke scored lower on tests of language skills and cognitive functioning.[48] In another study,[49,50] 9 to 12 year olds who were exposed to marijuana prenatally scored

lower than control subjects on tasks associated with "executive function," a term used by psychologists to describe a person's ability to plan, anticipate, and suppress behaviors that are incompatible with a current goal.[50] It was reflected in how the mothers described their children. Mothers of the marijuana-exposed children were more likely to describe their offspring as hyperactive or impulsive than were mothers of control children. The alteration in executive function was not seen in children born to tobacco smokers. The underlying causes might be the marijuana exposure or might be more closely related to the reasons underlying the mothers' use of marijuana during pregnancy.

Mice born to dams injected with the endogenous cannabinoid, anan-damide, during the last trimester of pregnancy also showed delayed effects. No effect of anandamide treatment during pregnancy was detected until the mice were adults (40 days old), at which time they showed behavioral changes that are common to the effects of other psychotropic drugs or prenatal stress.[45] As with the children born to mothers who smoked marijuana, it is not known what aspect of the treatment caused the effect. The dams might have found the dose (20 mg/kg of body weight) of anandamide aversive, in which case the effect could have resulted from generalized stress, as opposed to a cannabinoid-specific effect. Either is possible. Despite the uncertainty as to the underlying causes of the effects of prenatal exposure to cannabinoid drugs, it is prudent to advise against smoking marijuana during pregnancy.

SUMMARY AND CONCLUSIONS

This chapter summarizes the harmful effects of marijuana on individual users and, to a lesser extent, on society. The harmful effects on individuals were considered from the perspective of possible medical use of marijuana and can be divided into acute and chronic effects. The vast majority of evidence on harmful effects of marijuana is based on *smoked* marijuana, and, except for the psychoactive effects that can be reasonably attributed to THC, it is not possible to distinguish the drug effects from the effects of inhaling smoke from burning plant material.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance; it is inadvisable for anyone under the influence of marijuana to operate any equipment that might put the user or others in danger (such as driving or operating complex equipment). Most people can be expected to show impaired performance of complex tasks, and a minority experience dysphoria. People with or at risk of psychiatric disorders (including substance dependence) are particularly vulnerable to developing marijuana dependence, and marijuana use would be generally contraindicated for them. The short-term immuno-suppressive effects are not well established; if they exist at all, they are probably not great enough to preclude a legitimate medical use. The acute side effects of marijuana use are within the risks tolerated for many medications.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking and the effects of THC. Marijuana smoke is like tobacco smoke in that it is associated with increased risk of cancer, lung damage,

and poor pregnancy outcome. Smoked marijuana is unlikely to be a safe medication for any chronic medical condition. The second category is that associated with dependence on the psychoactive effects of THC. Despite past skepticism, it has been established that, although it is not common, a vulnerable subpopulation of marijuana users can develop dependence. Adolescents, particularly those with conduct disorders, and people with psychiatric disorders, or problems with substance abuse appear to be at greater risk for marijuana dependence than the general population.

As a cannabinoid drug delivery system, marijuana cigarettes are not ideal in that they deliver a variable mixture of cannabinoids and a variety of other biologically active substances, not all of which are desirable or even known. Unknown substances include possible contaminants, such as fungi or bacteria.

Finally, there is the broad social concern that sanctioning the medical use of marijuana might lead to an increase in its use among the general population. No convincing data support that concern. The existing data are consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as the use of other medications that have abuse potential, but we acknowledge a lack of data that directly address the question. Even if there were evidence that the medical use of marijuana would decrease the perception that it can be a harmful substance, this is beyond the scope of laws regulating the approval of therapeutic drugs. Those laws concern scientific data related to the safety and efficacy of drugs for individual use; they do not address perceptions or beliefs of the general population.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harm associated with smoking, the adverse effects of marijuana use are within the range tolerated for other medications. Thus, the safety issues associated with marijuana do not preclude some medical uses. But the question remains: Is it effective? That question is covered here in two chapters: chapter 2 summarizes what has been learned about the biological activity of cannabinoids in the past 15 years through research in the basic sciences, and chapter 4 reviews clinical data on the effectiveness of marijuana and cannabinoids for the treatment of various medical conditions.

Three factors influence the safety of marijuana or cannabinoid drugs for medical use: the delivery system, the use of plant material, and the side effects of cannabinoid drugs. (1) Smoking marijuana is clearly harmful, especially in people with chronic conditions, and is not an ideal drug delivery system. (2) Plants are of uncertain composition, which renders their effects equally uncertain, so they constitute an undesirable medication. (3) The side effects of cannabinoid drugs are within the acceptable risks associated with approved medications. Indeed, some of the side effects, such as anxiety reduction and sedation, might be desirable for some patients. As with many medications, there are people for whom they would probably be contraindicated.

> **Conclusion:** Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this

question is beyond the issues normally considered for medical uses of drugs, and it should not be a factor in the evaluation of the therapeutic potential of marijuana or cannabinoids.

Conclusion: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.

Conclusion: Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

Recommendation: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

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Notes

[1] Although Arizona also passed a medical marijuana referendum, it was embedded in a broader referendum concerning prison sentencing. Hence, the debate in Arizona did not focus on medical marijuana the way it did in California, and changes in Arizona youths' attitudes likely reflect factors peripheral to medical marijuana.

[2] Cell lines are created by removing cells from an organism and then treating them so they are "immortalized," meaning they will continue to divide and multiply indefinitely in culture. Cellular processes can then be studied in isolation from their original source.

[3] *Candida albicans* is a yeast infection that is particularly prevalent among people whose immune systems are suppressed, such as in AIDS patients.

[4] COPD is a slow progressive obstruction of the airways, loss of their elasticity, and loss of lung volume, characterized by chronic shortness of breath, chronic bronchitis, and reduced oxygenation of blood.

[5] Ciliated cells have hair-like projections that function to transport mucus toward the mouth by rapid wave-like motion.

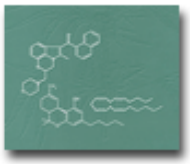
[6] In 1993 the diagnosis of AIDS was expanded to include anyone with a CD4 count of less than 200. Prior to 1993 this alone would have been insufficient for a diagnosis of AIDS.

[7] Some of the genes involved in the development of lung cancer include those that encode for Ki-67 (a nuclear proliferation protein responsible for cell division), the p53 tumor suppressor (a protein that normally suppresses cell growth), and epidermal growth factor receptor (EGFR) (a receptor found on a variety of cell types, especially epithelial cells, that promotes cellular growth and proliferation when bound to epidermal growth factor).

[8] A *prospective study* is one in which a group of subjects is identified and then studied over the course of time. Such a study allows an experimenter to balance different factors that may contribute to the study outcome. For example, age, family history, and smoking are risk factors for lung cancer. In a prospective study, these factors can be balanced to measure how much smoking increases the risk of lung cancer. A *retrospective study* is one in which people with a particular disease are identified and their histories are studied. Such studies are easier and less expensive to conduct, but they generally lack the explanatory power of prospective studies.

4

The Medical Value of Marijuana and Related Substances



During the course of drug development, a typical compound is found to have some medical benefit and then extensive tests are undertaken to determine its safety and proper dosage for medical use. In contrast, marijuana has been widely used in the United States for decades.[162] In 1996, 68.6 million people--32% of the U.S. population over 12 years old--had tried marijuana or hashish at least once; 5% were current users.[162]

The data on the adverse effects of marijuana are more extensive than the data on its effectiveness. Clinical studies of marijuana are difficult to conduct: researchers interested in clinical studies of marijuana face a series of barriers, research funds are limited, and there is a daunting thicket of regulations to be negotiated at the federal level (those of the Food and Drug Administration, FDA, and the Drug Enforcement Agency, DEA) and state levels (see chapter 5). Consequently, the rapid growth in basic research on cannabinoids contrasts with the paucity of substantial clinical studies on medical uses.

This chapter is devoted to an analysis of the therapeutic value of marijuana and cannabinoids for specific symptoms associated with various conditions. The risks associated with the medical use of marijuana are discussed in chapter 3. It should be noted that THC, the primary active ingredient in marijuana, is an FDA-approved drug referred to as dronabinol and marketed as Marinol. Marijuana is advocated primarily for relief from the symptoms of disease rather than as a cure.

For the most part, the logical categories for the medical use of marijuana are not based on particular diseases but on symptoms--such as nausea, appetite loss, or chronic pain--each of which can be caused by various diseases or even by treatments for diseases. This chapter is therefore organized by symptoms rather than by diseases. There are eight sections. The first section explains clinical trials, the following five deal with specific symptoms and conditions, and the last two summarize the medical benefits of marijuana and cannabinoids. The five sections on symptoms and conditions are as follows: pain, nausea and vomiting, wasting syndrome and appetite stimulation, neurological symptoms (including muscle spasticity), and glaucoma.

The Institute of Medicine (IOM) study team received reports of more than 30 different medical uses of marijuana, more than could be carefully reviewed in a report of this length; even more uses are reported elsewhere.[62,63] For most of the infrequently mentioned medical uses of marijuana there are only a few anecdotal reports. This report reviews only the most prominent symptoms that are reportedly relieved by marijuana. However, many of those diseases not reviewed here share common symptoms, such as

pain, nausea and vomiting, and muscle spasms, which might be relieved by cannabinoid drugs.

STANDARDS FOR EVALUATING CLINICAL TRIALS

Before evaluating individual clinical trials concerning the efficacy and safety of medical uses of marijuana and cannabinoids, it is useful to review the general qualities of clinical trials. Clinical trials involve groups of individuals in which different treatments are compared among different groups. Such trials measure the efficacy of a medication and are required by the FDA for approval of any new drug or new use of a drug (discussed further in chapter 5).

The degree of assurance that the outcome of a clinical trial is due to the treatment being tested depends on how well the trial is designed. Three important factors to consider in evaluating the design of a clinical trial are sample selection, subjective effects, and effects that are independent of the treatment. For *sample selection* it is important to ensure that patients are allocated to different treatment groups in such a way that the groups are not biased toward a particular treatment outcome. For example, the health status, gender, and ages of different treatment groups should be equivalent. *Subjective effects* must be controlled because they influence experimental results in two important ways. First, a patient's expectation that a treatment will be effective can influence the degree of its effect (for example, in the control of nausea). Second, the investigator's expectation can influence his or her interpretation of the treatment effect (for example, when assessing the level of pain experienced by a patient). For these reasons, double blinding, in which neither the subject nor the person who assesses the drug's effect is aware of the subject's treatment group, is particularly important in cannabinoid drug studies. Another important control for subjective effects includes the use of placebo drugs, which are inert substances, or the use of comparison drugs that have effects similar to the experimental drug. Finally, the quality of the experimental design depends on controlling for factors that are unrelated to the test drug but that might nonetheless influence the treatment outcome. S*equencing effects* are one example of such factors. For example, patients might react differently to the same medication depending on whether the medication was administered after an effective or an ineffective treatment. Likewise, a patient whose symptoms are initially mild might react differently to a drug than would a patient whose symptoms are initially severe. Because psychological effects are associated with cannabinoid drugs, it is important to consider how such side effects might influence the therapeutic value of the treatment. Conditions such as pain and nausea are especially susceptible to subjective influences. For example, depending on the person, THC can reduce or increase anxiety; it is important to determine to what extent this "side effect" contributes to the therapeutic effect.

While double-blind, randomized, controlled clinical trials offer the highest degree of assurance of drug efficacy, such trials are not always feasible. Vulnerable populations, such as children, older patients, and women of child-bearing age, are often excluded from experimental drug trials for safety reasons. Nonetheless, such patients are part of everyday clinical practice. The challenge of integrating the ideal of standardized and

rigorous processes for treatment evaluation with everyday clinical practice has encouraged interest in single-patient trials.[67] Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions.[66,105,159] They are particularly valuable when physicians or patients are uncertain about the efficacy of treatment for symptomatic diseases. Controls can be incorporated even in this kind of trial. Such trials can be double blinded and can involve cross-over designs in which the patient is treated with alternating treatments, such as placebo-drug-placebo or one drug followed by another drug. As with any other clinical trial, a single-patient trial should be designed to permit objective comparison between treatments.

ANALGESIA

Pain is the most common symptom for which patients seek medical assistance.[5] Pain associated with structural or psychophysiological disorders can arise from somatic, visceral, or neural structures. *Somatic pain* results from activation of receptors outside the brain and is transmitted to the brain via peripheral nerves. *Visceral pain* results from activation of specific pain receptors in the intestine (visceral nociceptive receptors); it is characterized as a deep aching or cramping sensation, but its source is often experienced at sites remote from the site of receptor activation, a phenomenon known as referred pain. *Neuropathic pain* results from injury to peripheral receptors, nerves, or the central nervous system; it is typically burning, the skin feels abnormally unpleasant when gently touched (dysesthesia), and it often occurs in an area of sensory loss, as in the case of postherpetic neuralgia (shingles).

All of the currently available analgesic (pain-relieving) drugs have limited efficacy for some types of pain. Some are limited by dose-related side effects and some by the development of tolerance or dependence. A cannabinoid, or other analgesic, could potentially be useful under any of the following circumstances:

- There is a medical condition for which it is more effective than any currently available medication.
- It has a broad clinical spectrum of efficacy and a unique side effect profile.
- It has synergistic interactions with other analgesics.
- It exhibits "side effects" that are considered useful in some clinical situations.
- Its efficacy is enhanced in patients who have developed tolerance to opioids.

There have not been extensive clinical studies of the analgesic potency of cannabinoids, but the available data from animal studies indicate that cannabinoids could be useful analgesics. In general, cannabinoids seem to be mild to moderate analgesics. Opiates, such as morphine and codeine, are the most widely used drugs for the treatment of acute pain, but they are not consistently effective in chronic pain; they often induce nausea and sedation, and tolerance occurs in some patients. Recent research has made it clear that CB_1 receptor agonists act on pathways that partially overlap with those activated by opioids but through pharmacologically distinct mechanisms (see chapter 2).

Therefore, they would probably have a different side effect profile and perhaps additive or synergistic analgesic efficacy.

In light of the evidence that cannabinoids can reduce pain in animals, it is important to re-evaluate the evidence of analgesic efficacy in humans and to ask what clinical evidence is needed to decide whether cannabinoids have any use in the treatment of pain.

Clinical Studies of Cannabinoids

There have been three kinds of studies of the effects of cannabinoids on pain in human volunteers: studies of experimentally induced acute pain, studies of postsurgical acute pain, and studies of chronic pain. Overall, there have been very few studies--only one since 1981--and they have been inconclusive.

Experimentally Induced Acute Pain

Early studies of cannabinoids on volunteers did not demonstrate consistent analgesia when experimental pain models were used. In fact, three early volunteer studies of THC and experimental pain caused by a variety of pain modalities--electrical stimulation, tourniquet pain, and thermal pain--resulted in an *increase* in pain sensitivity (hyperalgesia).[22,84,108]

Other studies also failed to show an analgesic effect of THC, but they were not well designed. Raft and co-workers found no evidence of THC effect on pain thresholds and pain tolerance following electrical stimulation and noxious pressure.[150] But their study suffers from two major methodological problems. First, they measured only the extremes of pain sensation--*threshold* (the lowest intensity at which a particular stimulus is perceived as painful) and *tolerance* (the maximum intensity of pain that a subject can withstand). However, most pain is experienced in an intermediate range, where effects on pain suppression are most detectable. Modern methods of pain assessment in humans typically use ratings of the intensity of the sensation of pain; those methods are superior to assessing the effects of a drug on the extremes of pain.[192] Second, Raft and co-workers did not include a positive control; that is, they did not demonstrate the adequacy of their method by showing that an established analgesic, such as an opiate or narcotic, was effective under their study conditions.

Clark and co-workers[22] tested the effect of smoked marijuana on thermal pain in volunteers and failed to observe an analgesic effect. However, because of the study design, the results are inconclusive. First, there was no positive control to demonstrate the adequacy of their methods; second, the study subjects were habitual marijuana users. During the study, they were hospitalized and allowed free access to marijuana cigarettes for a period of four weeks, consuming an average of four to 17 marijuana cigarettes per day. Pain was tested "approximately every one to two weeks." Thus, it is quite likely that the subjects were tolerant to THC at the time of testing.

Surgical Acute Pain

Raft and co-workers[150] found no analgesic effect of THC on surgical pain induced by tooth extraction. However, that study suffered from several serious limitations: the tooth extraction included treatment with the local anesthetic lidocaine, the pain during the procedure was assessed 24 hours later, and there was no positive control. Levonantradol (a synthetic THC analogue) was tested in 56 patients who had moderate to severe postoperative or trauma pain.[89] They were given intramuscular injections of levonantrodol or placebo 24 hours after surgery. To control for previous drug exposure, patients with a history of drug abuse or addiction and those who received an analgesic, antiinflammatory, tranquilizer, sedative, or anesthetic agent within 24 hours of the test drug were excluded from the study. On average, pain relief was significantly greater in the levonantradol-treated patients than in the placebo-treated patients. Because the authors did not report the number or percentage of people who responded, it is not clear whether the average represents consistent pain relief in all levonantradol-treated patients or whether some people experienced great relief and a few experienced none.

Chronic Pain

The most encouraging clinical data on the effects of cannabinoids on chronic pain are from three studies of cancer pain. Cancer pain can be due to inflammation, mechanical invasion of bone or other pain-sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. In one study, Noyes and co-workers found that oral doses of THC in the range of 5—20 mg produced analgesia in patients with cancer pain.[139,140] The first experiment was a double-blind, placebo-controlled study of 10 subjects and measured both pain intensity and pain relief.[140] Each subject received all drug treatments: placebo and 5, 10, 15, and 20 mg of THC in pill form; each pill was identical in appearance and given on successive days. The 15- and 20-mg doses of THC produced significant analgesia. There were no reports of nausea or vomiting. In fact, at least half the patients reported increased appetite. With a 20-mg dose of THC, patients were heavily sedated and exhibited "depersonalization," characterized by a state of dreamy immobility, a sense of unreality, and disconnected thoughts. Five of 36 patients exhibited adverse reactions (extreme anxiety) and were eliminated from the study. Only one patient experienced this effect at the 10-mg dose of THC. The mean age of the patients was 51 years, and they were probably not experienced marijuana smokers. A limitation of this study is that there were no positive controls--that is, other analgesics that could provide a better measure of the degree of analgesia produced by THC.

In a later larger single-dose study, the same investigators reported that the analgesic effect of 10 mg of THC was equivalent to that of 60 mg of codeine; the effect of 20 mg of THC was equivalent to that of 120 mg of codeine.[139] (Note that codeine is a relatively weak analgesic.) The side effect profiles were similar, though THC was more sedating than codeine. In a separate publication the same authors published data indicating that patients had improved mood, a sense of well-being, and less anxiety.[139]

The results of the studies mentioned above on cancer pain are consistent with the results of using a nitrogen analogue of THC. Two trials were reported: one compared this analogue with codeine in 30 patients, and a second compared it with placebo or

secobarbital, a short-acting barbiturate.[175] For mild, moderate, and severe pain, the THC analogue was equivalent to 50 mg of codeine and superior to placebo and to 50 mg of secobarbital.

Case Reports and Surveys

The few case reports of clinical analgesia trials of cannabinoids are not convincing.[85,120] There are, however, anecdotal surveys that raise the possibility of a role for cannabinoids in some patients who have chronic pain with prominent spasticity. A recent survey of over 100 patients with multiple sclerosis reported that a large number obtained relief from spasticity and limb pain (discussed further under the section on multiple sclerosis).[28] Several said that it relieved their phantom pain and headache.[41]

Migraine Headaches

There is clearly a need for improved migraine medications. Sumatriptan (Imitrex) is the best available medication for migraine headaches, but it fails to abolish migraine symptoms in about 30% of migraine patients.[118,147] Marijuana has been proposed numerous times as a treatment for migraine headaches, but there are almost no clinical data on the use of marijuana or cannabinoids for migraine. Our search of the literature since 1975 yielded only one scientific publication on the subject. It presents three cases of cessation of daily marijuana smoking followed by migraine attacks--not convincing evidence that marijuana relieves migraine headaches.[43] The same result could have been found if migraine headaches were a consequence of marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider all logical possibilities. Various people have claimed that marijuana relieves their migraine headaches, but at this stage there are no conclusive clinical data or published surveys about the effect of cannabinoids on migraine.

However, a possible link between cannabinoids and migraine is suggested by the abundance of cannabinoid receptors in the periaqueductal gray (PAG) region of the brain. The PAG region is part of the neural system that suppresses pain and is thought to be involved in the generation of migraine headaches.[52] The link or lack thereof between cannabinoids and migraine might be elucidated by examining the effects of cannabinoids on the PAG region.[110] Recent results indicating that both cannabinoid receptor subtypes are involved in controlling peripheral pain[15] suggest that the link is possible. Further research is warranted.

Conclusions: Analgesia

A key question to address is whether there is any receptor selectivity for the analgesic efficacy of cannabinoids. Are the unwanted side effects (amnesia and sedation) caused by the same receptors in the same brain regions as those producing the analgesia? If the answer is *yes*, enhancing efficacy will not solve the problem of sedation. Similarly, are the pleasant side effects due to an action at the same receptor? Can the feelings of well-

being and appetite stimulation be separated by molecular design? Recent results indicating that both cannabinoid receptor subtypes are independently involved in controlling peripheral pain[15] (discussed in chapter 2) strongly suggest that this is possible and that further research is warranted.

Further research into the basic circuitry underlying cannabinoid analgesia should be valuable. The variety of neural pathways that underlie the control of pain suggests that a synergistic analgesia "cocktail" would be effective. For example, Lichtman and Martin have shown the involvement of an $\alpha 2$ adrenoreceptor in cannabinoid analgesia.[111] Perhaps a combination of a CB_1 agonist and an $\alpha 2$ agonist (such as clonidine) would provide enhanced analgesia with less severe side effects.

Clinical studies should be directed at pain patients for whom there is a demonstrated need for improved management and where the particular side effect profile of cannabinoids promises a clear benefit over current approaches. The following patient groups should be targeted for clinical studies of cannabinoids in the treatment of pain:

- Chemotherapy patients, especially those being treated for the mucositis, nausea, and anorexia.
- Postoperative pain patients (using cannabinoids as an opioid adjunct to determine whether nausea and vomiting from opioids are reduced).
- Patients with spinal cord injury, peripheral neuropathic pain, or central poststroke pain.
- Patients with chronic pain and insomnia.
- AIDS patients with cachexia, AIDS neuropathy, or any significant pain problem.

In any patient group an essential question to be addressed is whether the analgesic efficacy of opioids can be augmented. The strategy would be to find the ceiling analgesic effect with an opioid (as determined by pain intensity and tolerability of side effects) and then add a cannabinoid to determine whether additional pain relief can be obtained. That would begin the investigation of potential drug combinations. As with any clinical study on analgesic drugs, it will be important to investigate the development of tolerance and physical dependence; these are not themselves reasons to exclude the use of cannabinoids as analgesics, but such information is essential to the management of many drugs that are associated with tolerance or physical dependence.

A secondary question would be whether THC is the only or the best component of marijuana for analgesia. How does the analgesic effect of the plant extract compare with that of THC alone? If there is a difference, it will be important to identify the combinations of cannabinoids that are the most effective analgesics.

In conclusion, the available evidence from animal and human studies indicates that cannabinoids can have a substantial analgesic effect. One exception is the lack of analgesic effect in studies on experimentally induced acute pain, but because of limitations in the design of those studies they were inconclusive. Further clinical work is warranted to establish the magnitude of the effect in different clinical conditions and to

determine whether the effect is sustained. Although the usefulness of cannabinoids appears to be limited by side effects, notably sedation, other effects such as anxiolysis, appetite stimulation, and perhaps antinausea and antispasticity effects should be studied in randomized, controlled clinical trials. These very "special" effects might warrant development of cannabinoid drugs for particular clinical populations.

NAUSEA AND VOMITING

Nausea and vomiting (emesis) occur under a variety of conditions, such as acute viral illness, cancer, radiation exposure, cancer chemotherapy, postoperative recovery, pregnancy, motion, and poisoning. Both are produced by excitation of one or a combination of triggers in the gastrointestinal tract, brain stem, and higher brain centers (Figure 4.1, Emesis-stimulating pathways).[127] There are numerous cannabinoid receptors in the nucleus of the solitary tract, a brain center that is important in the control of emesis.[79,80] Although the same mechanisms appear to be involved in triggering both nausea and vomiting, either can occur without the other. Much more is known about the neural mechanisms that produce vomiting than about those that produce nausea, in large part because vomiting is a complex behavior involving coordinated changes in the gastrointestinal tract, respiratory muscles, and posture, whereas nausea is a sensation involving primarily higher brain centers and lacks a discrete observable action.[104,128] Most reports on the antiemetic effects of marijuana or cannabinoids are based on chemotherapy-induced emesis; they are the subject of the following section.

Chemotherapy-Induced Nausea and Vomiting

The use of effective chemotherapeutic drugs has produced cures in some malignancies and retarded the growth of others, but nausea and vomiting are frequent side effects of these drugs. Nausea ranks behind only hair loss as a concern of patients on chemotherapy, and many patients experience it as the worst side effect of chemotherapy. The side effects can be so devastating that patients abandon therapy or suffer diminished quality of life. As a result, the development of effective strategies to control the emesis induced by many chemotherapeutic agents is a major goal in the supportive care of patients with malignancies.

The mechanism by which chemotherapy induces vomiting is not completely understood. Studies suggest that emesis is caused by stimulation of receptors in the central nervous system or the gastrointestinal tract. This stimulation appears to be caused by the drug itself, a metabolite of the drug, or a neurotransmitter.[6,12,35] In contrast with an emetic like apomorphine, there is a delay between the administration of chemotherapy and the onset of emesis. This delay depends on the chemotherapeutic agent; emesis can begin anywhere from a few minutes after the administration of an agent like mustine to an hour for cisplatin.[12]

The most desirable effect of an antiemetic is to control emesis completely, which is currently the primary standard in testing new antiemetic agents (R. Gralla, IOM workshop). Patients recall the number of emetic episodes accurately, even if their

antiemetics are sedating or affect memory;[101] thus, the desired end point of complete control is also a highly reliable method of evaluation. The degree of nausea can be estimated through the use of established visual analogue scales.[1,21,55,101]

Another consideration in using antiemetic drugs is that the frequency of emesis varies from one chemotherapeutic agent to another. For example, cisplatin causes vomiting in more than 99% of patients who are not taking an antiemetic (with about 10 vomiting episodes per dose), whereas methotrexate causes emesis in less than 10% of patients.[55,82,83] Among chemotherapeutic agents, cisplatin is the most consistent emetic known and has become the benchmark for judging antiemetic efficacy. Antiemetics that are effective with cisplatin are at least as effective with other chemotherapeutic agents. Controlling for the influence of prior chemotherapy and balancing predisposing factors such as, sex, age, and prior heavy alcohol use among study groups are vital for reliability. Reliable randomization of patients and blinding techniques (easier when there are no psychoactive effects) are also necessary to evaluate the control of vomiting and nausea.

THC and Marijuana Therapy for Chemotherapy-Induced Nausea and Vomiting

Cannabinoids are mildly effective in preventing emesis in some patients who are receiving cancer chemotherapy. Several cannabinoids have been tested as antiemetics, including THC (both Δ^9-THC and Δ^8-THC) and the synthetic cannabinoids nabilone and levonantradol. Smoked marijuana has also been examined.

Antiemetic Properties of THC

The quality and usefulness of antiemetic studies depend on adherence to the methodological considerations outlined above. Many of the reported clinical experiences with cannabinoids are not based on definitive experimental methods. In studies that compared THC with a placebo, THC was usually found to possess antiemetic properties. However, the chemotherapeutic drug varied in most trials, and some studies included small numbers of patients. In one study THC was found to be superior to a placebo in patients receiving methotrexate, an agent that is not a strong emetic.[18] When the same investigators studied THC in a small number of patients who were receiving a chemotherapeutic drug that is more likely to cause emesis than anthracycline, the antiemetic effect was poor.[19]

Other trials were designed to compare THC with that of Compazine (prochlorperazine).[143,160] In the 1980s, prochlorperazine was one of the more effective antiemetics available, but it was not completely satisfactory, and the search for better agents continued. THC and prochlorperazine given orally showed similar degrees of efficacy, but the studies often used various chemotherapeutic agents. Even when administered in combination, THC and prochlorperazine failed to stop vomiting in two-thirds of patients.[50]

In a carefully controlled double-blind study comparing THC with the antiemetic drug metoclopramide, in which no patient had previously received chemotherapy and in which anticipatory emesis was therefore not a factor, all patients received the same dose of cisplatin and were randomly assigned to the THC group or the metoclopramide group. Complete control of emesis occurred in 47% of those treated with metoclopramide and 13% of those treated with THC.[58] Major control (two or fewer episodes) occurred in 73% of the patients given metoclopramide compared to 27% of those given THC. There were many flaws in experimental methods, but those results suggest that THC has some, but not great, efficacy in reducing chemotherapy-induced emesis.[18,19,50,161] The studies also indicate that the degree of efficacy is not high. In 1985, the FDA approved THC in the form of dronabinol for this treatment (discussed in chapter 5).

The THC metabolite, 11-OH-THC, is more psychoactive than THC but is a weaker antiemetic.[121] Thus, it might be possible to design antiemetic cannabinoids without the psychological effects associated with marijuana or THC. Δ^8-THC is less psychoactive than THC[151] but was found to completely block both acute and delayed chemotherapy-induced emesis in a study of eight children, ages 3—13 years.[2] Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given Δ^8-THC as oil drops on the tongue or in a bite of bread (18 mg/m^2 body surface area). The children received a total of 480 treatments. The only side effects reported were slight irritability in two of the youngest children (3.5 and 4 years old). Based on the prediction that the THC-induced anxiety effects would be less in children than in adults, the authors used doses that were higher than those recommended for adults (5—10 mg/m^2 body surface area).

Antiemetic Properties of Synthetic THC Analogues

Nabilone (Cesamet) and levonantradol were tested in various settings; the results were similar to those with THC. Efficacy was observed in several trials, but no advantage emerged for these agents.[176,185] As in the THC trials, nabilone and levonantradol reduced emesis but not as well as other available agents in moderately to highly emetogenic settings. Neither is commercially available in the United States.

Antiemetic Properties of Marijuana

Among the efforts to study marijuana was a preliminary study conducted in New York state on 56 cancer patients who were unresponsive to conventional antiemetic agents.[188] The patients were asked to rate the effectiveness of marijuana compared with results during prior chemotherapy cycles. In this survey, 34% of patients rated marijuana as moderately or highly effective. The authors concluded that marijuana had antiemetic efficacy, but its relative value was difficult to determine because no control group was used and the patients varied with respect to previous experiences, such as marijuana use and THC therapy.

A Canadian oncology group conducted a double-blind, cross-over, placebo-controlled study comparing smoked marijuana with THC in pill form in 20 patients who were

receiving various chemotherapeutic drugs.[107] The degree of emetic control was similar: only 25% of patients achieved complete control of emesis; 35% of the patients indicated a slight preference for the THC pills over marijuana, 20% preferred marijuana, and 45% expressed no preference. [107]

Neither study showed a clear advantage for smoked marijuana over oral THC, but neither reported data on the time course of antiemetic control, possible advantages of self-titration with the smoked marijuana, or the degree to which patients were able to swallow the pills. Patients with severe vomiting would have been unlikely to be able to swallow or keep the pills down long enough for them to take effect. The onset of drug effect is much faster with inhaled or injected THC than it is for oral delivery.[87,112,141] Although many marijuana users have claimed that smoked marijuana is a more effective antiemetic than oral THC, no controlled studies have yet been published that analyze this in sufficient detail to estimate the extent to which this is the case.

Side Effects Associated with THC and Marijuana in Antiemetic Therapy

Frequent side effects associated with THC or marijuana are dizziness, dry mouth, hypotension, moderate sedation, and euphoria or dysphoria.[18,19,50,107,143,160,176,185] To patients, dry mouth and sedation are the least troubling side effects. Perhaps the most troubling side effects are orthostatic hypotension and dizziness, which could increase the patient's distress.

There is disagreement as to whether the psychoactive effects of THC correlate with its antiemetic activity. In the prospective double-blind trial comparing THC with metoclopramide, the authors reported no relationship between the occurrence of complete antiemetic control and euphoria or dysphoria.[58] Other investigators believe that the occurrence of euphoria or dysphoria is often associated with improved antiemetic control.[160] Nevertheless, there is a consensus among investigators that dysphoric effects are more common among patients who have had no prior experience with cannabinoids. An important and unexpected problem encountered in the New York state open trial with marijuana was the inability of nearly one-fourth of the patients to tolerate the administration of marijuana by smoking.[188] The intolerance could have been due to inexperience with smoking marijuana and is an important consideration.

Therapy for Chemotherapy-Induced Nausea and Vomiting

Present Therapy

New classes of antiemetics that have emerged over the past 10 years have dramatically reduced the nausea and vomiting associated with cancer chemotherapy and transformed the acceptance of cisplatin by cancer patients. The new antiemetics--including selective serotonin type 3 receptor antagonists, substituted benzamides, corticosteroids, butyrophenones, and phenothiazines--have few side effects when given over a short term and are convenient in various clinical settings.

The most effective commonly used antiemetics are serotonin receptor antagonists (ondansetron and granisetron) with or without corticosteroids.[37,56,88,145,155] In a combination trial of dexamethasone (a corticosteroid) and a serotonin antagonist, complete control of acute cisplatin-induced emesis was observed in about 75% of patients. If the chemotherapy was only moderately emetogenic, up to 90% of the patients who received the combination achieved complete control of emesis. Side effects of those antiemetic agents include headache, constipation, and alterations in liver function, but they are generally well tolerated by most patients.[13]

Other commonly used antiemetics are phenothiazines--prochlorperazine (Compazine) and haloperidol--and metoclopramide. Metoclopramide is somewhat less effective than the serotonin antagonists and has more side effects, including acute dystonic reactions, drowsiness, diarrhea, and depression.[13,37] Side effects associated with phenothiazines are severe or acute dystonic reactions, hypotension, blurred vision, drowsiness, dry mouth, urinary retention, allergic reactions, and occasional jaundice.[13]

The cost of effective antiemetic regimens can vary markedly, depending on the agent, dose, schedule, and route of administration. Overall, oral regimens cost less than intravenous regimens because of lower pharmacy and administration costs, as well as lower acquisition costs in many countries. Regimens with a cost to the pharmacy as low as about $30 to $35 per treatment session have been shown to be effective;[57] these costs are for treatment of acute emesis and delayed emesis with generic agents where available.

Although it is generally not well known by the public, major progress in controlling chemotherapy-induced acute nausea and vomiting has been made since the 1970s. Patients receiving the most difficult to control emetic agents now have no more than about a 20—30% likelihood of experiencing acute emesis,[155] whereas in the 1970s the likelihood was nearly 100% despite antiemetics.[55,86] As has been seen, most antiemetic studies with cannabinoids had methodological difficulties and are inconclusive. The evidence from the well-conducted trials indicate that cannabinoids reduce emesis in about one-fourth of patients receiving cancer chemotherapy. Cannabinoids are not as effective as several other classes of agents, such as substituted benzamides, serotonin receptor antagonists, and corticosteroids. The side effects associated with cannabinoid use are generally tolerable. Like cannabinoids, smoked marijuana, was apparently effective, but the efficacy was no greater than that of available antiemetic agents now considered to be marginally satisfactory. At present, the most effective antiemetic regimens are combinations of oral serotonin receptor antagonists with dexamethasone in single-dose regimens given before chemotherapy. Neither multiple-dose regimens nor intravenous antiemetics provide better control, and both add unnecessary costs.[59,81]

Future Therapy

Advances in therapy for chemotherapy-induced nausea and vomiting will require discovery of agents that work through mechanisms different from those of existing antiemetics, including the serotonin antagonists. Among the proposed new pathways, neurokinin-1 (NK-1) receptor antagonists appear to be the most promising. Neurokinin

receptors are found in brain and intestine and are thought to be involved in motor activity, mood, pain and reinforcement. They might well be involved in mediating intestinal sensations, including nausea. In animal models, agents that block the NK-1 receptor prevent cisplatin-induced emesis. At the time of this writing, clinical trials with NK-1 receptor antagonists were under way (phase II or small phase III comparison studies). Preliminary results indicated that these agents have useful activity in both acute and delayed chemotherapy-induced emesis (that is, beginning or persisting 24 or more hours after chemotherapy) and are safe to administer orally.[102,135]

It is theoretically possible, considering that the mechanism of cannabinoid action appears to differ from that of the serotonin receptor antagonists and of corticosteroids, that THC added to more effective regimens might enhance control of emesis. Such combinations should aim to be as convenient as possible and have few additional side effects. The critical issue is not whether marijuana or cannabinoid drugs might be superior to the new drugs, but whether some group of patients might obtain added or better relief from marijuana or cannabinoid drugs.

Even with the best antiemetic drugs, the control of nausea and vomiting that begins or persists 24 hours after chemotherapy remains imperfect. The pathophysiology of delayed emesis appears different from that of acute emesis, and it is more likely to occur with a strong emetic agent, but it varies from patient to patient. Treatment to prevent this emesis requires dosing both before and after chemotherapy.[103]

Conclusions: Chemotherapy-Induced Nausea

Most chemotherapy patients are unlikely to want to use marijuana or THC as an antiemetic. In 1999, there are more effective antiemetic agents available than were available earlier. By comparison, cannabinoids are only modest antiemetics. However, because modern antiemetics probably act through different mechanisms, cannabinoids might be effective in people who respond poorly to currently used antiemetic drugs, or cannabinoids might be more effective in combination with a new drug than is either alone. For both reasons, studies of the effects of adjunctive cannabinoids on chemotherapy-induced emesis are worth pursuing for patients whose emesis is not optimally controlled with other agents.

While some people who spoke to the IOM study team described the mood-enhancing and anxiety-reducing effects of marijuana as a positive contribution to the antiemetic effects of marijuana, one-fourth of the patients in the New York state study described earlier were unable to tolerate smoked marijuana. Overall, the effects of oral THC and smoked marijuana are similar, but there are differences. For example, in the residential studies of experienced marijuana users by Haney and co-workers, subjects reported that marijuana made them feel "mellow,"[71] whereas comparable doses of oral THC did not.[70] Such differences might be due to the different routes of delivery of THC, as well as the different mixture of cannabinoids found in the marijuana plant. As of this writing, no studies had been published that weighed the relative contributions of those different factors.

The goal of antiemetic medications is to prevent nausea and vomiting. Hence, antiemetics are typically given before chemotherapy, in which case a pill is an effective from of drug delivery. However, in patients already experiencing severe nausea or vomiting, pills are generally ineffective because of the difficulty in swallowing or keeping a pill down and slow onset of the drug effect. Thus, an inhalation (but preferably not smoking) cannabinoid drug delivery system would be advantageous for treating chemotherapy-induced nausea.

Until the development of rapid-onset antiemetic drug delivery systems, there will likely remain a subpopulation of patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. It is possible that the harmful effects of smoking marijuana for a limited period of time might be outweighed by the antiemetic benefits of marijuana, at least for patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. Such patients should be evaluated on a case-by-case basis and treated under close medical supervision.

WASTING SYNDROME AND APPETITE STIMULATION

Wasting syndrome in acquired immune deficiency syndrome (AIDS) patients is defined by the Centers for Disease Control and Prevention as the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhea or fever of more than 30 days that is not attributable to other disease processes.[17] Anorexia (loss of appetite) can accelerate wasting by limiting the intake of nutrients. Wasting (cachexia) and anorexia are common end-stage features of some fatal diseases, such as AIDS, and of some types of metastatic cancers. In AIDS, weight loss of as little as 5% is associated with decreased survival, and a body weight about one-third below ideal body weight results in death.[99,158]

There are two forms of malnutrition: starvation and cachexia. Starvation, the deprivation of essential nutrients, results from famine or poverty, malabsorption, eating disorders such as anorexia nervosa, and so on. Starvation leads to metabolic adaptations that deplete body fat before losses of lean tissue. Cachexia results from tissue injury, infection, or tumor and is characterized by a disproportionate loss of lean body mass, such as skeletal muscle. The effects of starvation regardless of the cause can usually be reversed by providing food, whereas the effects of cachexia can be reversed only through control of the underlying disease and--at least for some patients--drugs that stimulate metabolism, such as growth hormone or androgenic-anabolic hormones.

Malnutrition in HIV-Infected Patients

By 1997 more than 30 million people worldwide were infected with human immunodeficiency virus (HIV), and the number is predicted to increase to almost 40 million by the year 2000.[126,186] Malnutrition is common among AIDS patients and plays an independent and important role in their prognosis.[95,100,158] Because treatment for malnutrition depends on whether it is caused by starvation or cachexia, one needs to

know the effects of HIV infection on metabolic processes. The answer depends on the clinical situation and can be either or both.[94]

The development of malnutrition in HIV infection has many facets. Malnutrition in HIV-infected patients results in a disproportionate depletion of body cell mass,[3] total body nitrogen, and skeletal muscle mass; all are consistent with cachexia.[97,194] Body composition studies show that the depletion of body cell mass precedes the progression to AIDS (falling CD4 lymphocyte counts); this suggests that malnutrition is a consequence of the inflammatory response to the underlying viral infection, rather than a general complication of AIDS.[144] In contrast, weight loss is often episodic and related to acute complications, such as febrile opportunistic infections.[113] Mechanisms underlying wasting in HIV-infected patients depend on the stage of HIV infection and on specific associated complications.

The many reasons for decreased food intake among AIDS patients include mouth, throat, or esophageal infections or ulcers (oropharyngeal and esophageal pathology); adverse effects of medications;[196] diarrhea; enteric infection; malabsorption; serious systemic infection; focal or diffuse neurological disease; HIV enteropathy; depression; fatigue; and poverty. Nutrient malabsorption is often the result of microorganism overgrowth or infection in the intestine, especially in the later stages of AIDS.[95,157]

Marijuana and THC for Malnutrition in HIV-Infected Patients

Despite their frequency of use, little has been published about the effectiveness of marijuana or cannabinoids for the treatment of malnutrition and wasting syndrome in HIV-infected patients. The only cannabinoid evaluated in controlled clinical studies is THC, or dronabinol. Short-term (six-week) and long-term (one-year) therapy with dronabinol was associated with an increase in appetite and stable weight, and in a previous short-term (five-week) clinical trial in five patients, dronabinol was shown to increase body fat by 1%.[8,9,179] In 1992, the FDA approved THC, under the trade name Marinol (dronabinol), as an appetite stimulant for the treatment of AIDS-related weight loss. Megestrol acetate (Megace) is a synthetic derivative of progesterone that can stimulate appetite and cause substantial weight gain when given in high doses (320—640 mg/day) to AIDS patients. Megestrol acetate is more effective than dronabinol in stimulating weight gain, and dronabinol has no additive effect when used in combination with megestrol acetate.[183] HIV/AIDS patients are the largest group of patients who use dronabinol. However, some reject it because of the intensity of neuropsychological effects, an inability to titrate the oral dose easily, and the delayed onset and prolonged duration of its action.[3] There is evidence that cannabinoids modulate the immune system (see chapter 2, "Cannabinoids and the Immune System"), and this could be a problem in immunologically compromised patients. No published studies have formally evaluated use of any of the other cannabinoids for appetite stimulation in wasting.

Anecdotes abound that smoked marijuana is useful for the treatment of HIV-associated anorexia and weight loss.[23,62] Some people report a preference for smoked marijuana over oral THC because it gives them the ability to titrate the effects, which

depend on how much they inhale. In controlled laboratory studies of healthy adults, smoked marijuana was shown to increase body weight, appetite, and food intake.[47,119] Unfortunately, there have been no controlled studies of the effect of smoked marijuana on appetite, weight gain, and body composition in AIDS patients. At the time of this writing, Donald Abrams, of the University of California, San Francisco, was conducting the first clinical trial to test the safety of smoked marijuana in AIDS patients, and the results were not yet available.

A major concern with marijuana smoking in HIV-infected patients is that they might be more vulnerable than other marijuana users to immunosuppressive effects of marijuana or to the exposure of infectious organisms associated marijuana plant material (see chapter 3, "Marijuana Smoke").

Therapy for Wasting Syndrome in HIV-Infected Patients

Present Therapy

Generally, therapy for wasting in HIV-infected people focuses on appetite stimulation. Few therapies have proved successful in treatment of the AIDS wasting syndrome. The stimulant studied most is megestrol acetate, which has been shown to increase food intake by about 30% over baseline for reasons that remain unknown. Its effect in producing substantial weight gain is dose dependent, but most of the weight gained is in fat tissue, not lean body mass. Although the findings are still preliminary, anabolic compounds, such as testosterone or growth hormone, might be useful in preventing the loss of or in restoring lean body mass in AIDS patients.[10,44,64,170] Enteral and parenteral nutrition have also been evaluated and shown to increase weight, but again the increase is due more to body fat than to lean body mass.[96,98]

Encouraging advances in the antiviral treatment of HIV infection and developments in the prophylaxis of and therapy for opportunistic infections have recently changed the outlook for the long-term health of HIV-infected people. Death rates have been halved, and the frequency of serious complications, including malnutrition, has fallen markedly.[94,133]

Future Therapy

The primary focus of future therapies for wasting in HIV-infected patients is to increase lean body mass as well as appetite. Active systemic infections are associated with profound anorexia, which is believed to be mediated by cytokines that stimulate inflammation through their actions in and outside the brain.[132] Cytokine inhibitors, such as thalidomide, have been under investigation as potential treatments to increase lean body mass and reduce malnutrition. Even though cannabinoids do not appear to restore lean body mass, they might be useful as adjunctive therapy. For example, cannabinoids could be used as appetite stimulants, in patients with diminished appetite who are undergoing resistance exercises or anabolic therapy to increase lean body mass. They could also be beneficial for a variety of effects, such as increased appetite, while reducing

the nausea and vomiting caused by protease inhibitors and the pain and anxiety associated with AIDS.

Considering current knowledge about malnutrition in HIV infection, cannabinoids, by themselves, will probably not constitute primary therapy for this condition but might be useful in combination with other therapies, such as anabolic agents. Specifically, the proposed mechanism of action of increasing food intake would most likely be ineffective in promoting an increase in skeletal muscle mass and functional capacity--the goal in the treatment of cachexia in AIDS patients.

Malnutrition in Cancer Patients

Malnutrition compromises the quality of life of many cancer patients and contributes to the progression of their disease. About 30% of Americans will develop cancer in their lifetimes, and two-thirds of those who get cancer will die as a result of it.[5] Depending on the type of cancer, 50—80% of patients will develop cachexia and up to 50% of them will die, in part, as a result of cachexia.[11,40] The cachexia appears to result from the tumor itself, and cytokines (proteins secreted by the host during an immune response to tumor) are probably important factors in this development. Cachexia does not occur in all cancer patients, but generally occurs in the late stages of advanced cancer of the pancreas, lung, and prostate.

The only cannabinoid evaluated for treating cachexia in cancer patients is dronabinol, which has been shown to improve appetite and promote weight gain.[54] Present treatments for cancer cachexia are similar to that for cachexia in AIDS patients. These treatments are usually indicated in late stages of advanced disease and include megestrol acetate and enteral and parenteral nutrition. Megestrol acetate stimulates appetite and promotes weight gain in cancer patients, although the gain is mostly in fat mass (reviewed by Bruera 1998[14]). Both megestrol acetate and dronabinol have dose-related side effects that can be troublesome for patients: megestrol acetate can cause hyperglycemia and hypertension, and dronabinol can cause dizziness and lethargy. Cannabinoids have also been shown to modulate the immune system (see chapter 2, "Cannabinoids and the Immune System"), and this could be contraindicated in some cancer patients (both the chemotherapy and the cancer can be immunosuppressive).

Future treatments will probably depend on the development of methods that block cytokine actions and the use of selective ß2-adrenergic receptor agonists to increase muscle mass.[14,73] Treatments for cancer cachexia will also most likely need to identify individual patients' needs. Some patients might need only a cytokine inhibitor, whereas others could benefit from combined approaches, such as an appetite stimulant and ß2-adrenergic receptor agonists. In this respect, such cannabinoids as THC might prove useful as part of a combination therapy as an appetite stimulant, antiemetic, analgesic, and anxiolytic, especially for patients in late stages of the disease.

Anorexia Nervosa

Anorexia nervosa, a psychiatric disorder characterized by distorted body image and self-starvation, affects an estimated 0.6% of the U.S. population, with a greater prevalence in females than males.[5] Its mortality is high, and response to standard treatments is poor.

THC appears to be ineffective in treating this disease. In one study it caused severe dysphoric reactions in three of 11 patients.[65] One possible explanation of the dysphoria is that THC increases appetite and thus intensifies the mental conflict between hunger and food refusal.[13] Furthermore, such patients might have underlying psychiatric disorders, such as schizophrenia and depression, in which cannabinoids might be hazardous (see chapter 3, "Psychological Harms").

Current treatments include psychological techniques to overcome emotional or behavioral problems and dietary intervention to reverse the malnutrition.[195] Pharmacological treatments, such as antidepressants, have been used in addition to psychotherapy but tend to lack the desired level of efficacy.[33] Recently, alterations in a gene for one of the serotonin receptors have been identified in some patients with anorexia nervosa.[45] The possibility of a genetic component suggests a pathway for the development of new drugs to treat this disease.

Conclusions: Wasting Syndrome and Appetite Stimulation

The profile of cannabinoid drug effects suggests that they are promising for treating wasting syndrome in AIDS patients. Nausea, appetite loss, pain, and anxiety are all afflictions of wasting, and all can be mitigated by marijuana. Although some medications are more effective than marijuana for these problems, they are not equally effective in all patients. A rapid-onset (that is, acting within minutes) delivery system should be developed and tested in such patients. Smoking marijuana is not recommended. The long-term harm caused by smoking marijuana makes it a poor drug delivery system, particularly for patients with chronic illnesses.

Terminal cancer patients pose different issues. For those patients the medical harm associated with smoking is of little consequence. For terminal patients suffering debilitating pain or nausea and for whom all indicated medications have failed to provide relief, the medical benefits of smoked marijuana might outweigh the harm.

NEUROLOGICAL DISORDERS

Neurological disorders affect the brain, spinal cord, or peripheral nerves and muscles in the body. Marijuana has been proposed most often as a source of relief for three general types of neurological disorders: muscle spasticity, particularly in multiple sclerosis patients and spinal cord injury victims; movement disorders, such as Parkinson's disease, Huntington's disease, and Tourette's syndrome; and epilepsy. Marijuana is not proposed as a cure for such disorders, but it might relieve some associated symptoms.

Muscle Spasticity

Spasticity is the increased resistance to passive stretch of muscles and increased deep tendon reflexes. Muscles may also contract involuntarily (flexor and extensor spasms). In some cases these contractions are debilitating and painful and require therapy to relieve the spasms and associated pain.

There are numerous anecdotal reports that marijuana can relieve the spasticity associated with multiple sclerosis or spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain--areas that might influence spasticity.[51,78,130,168]

Multiple Sclerosis

Multiple sclerosis (MS) is a condition in which multiple areas of the central nervous system (CNS) are affected. Many nerve fibers become demyelinated, some are destroyed, and scars (sclerosis) form, resulting in plaques scattered throughout the white matter of the CNS. (Myelin is the lipid covering that surrounds nerve cell fibers and facilitates the conduction of signals along nerve cells and ultimately between the brain, the spinal cord, and the rest of the body.) MS exacerbations appear to be caused by abnormal immune activity that causes inflammation and myelin destruction in the brain (primarily in the periventricular area), brain stem, or spinal cord. Demyelination slows or blocks transmission of nerve impulses and results in an array of symptoms such as fatigue, depression, spasticity, ataxia (inability to control voluntary muscular movements), vertigo, blindness, and incontinence. About 90% of MS patients eventually develop spasticity. There are an estimated 2.5 million MS patients worldwide, and spasticity is a major concern of many patients and physicians.[134] Spasticity is variably experienced as muscle stiffness, muscle spasms, flexor spasms or cramps, muscle pain or ache. The tendency for the legs to spasm at night (flexor spasms) can interfere with sleep.

Marijuana is often reported to reduce the muscle spasticity associated with MS.[62,123] In a mail survey of 112 MS patients who regularly use marijuana, patients reported that spasticity was improved and the associated pain and clonus decreased.[287] However, a double-blind placebo-controlled study of postural responses in 10 MS patients and 10 healthy volunteers indicated that marijuana smoking impaired posture and balance in both MS patients and the volunteers.[61] Nevertheless, the 10 MS patients felt that they were clinically improved. The subjective improvement, while intriguing, does not constitute unequivocal evidence that marijuana relieves spasticity. Survey data do not measure the degree of placebo effect, estimated to be as great as 30 percent in pain treatments.[122,131] Furthermore, surveys do not separate the effects of marijuana or cannabinoids on mood and anxiety from the effects on spasticity.

The effects of THC on spasticity were evaluated in a series of three clinical trials testing a total of 30 patients.[24,148,187] They were "open trials," meaning that the patients were informed before treatment that they would be receiving THC. Based on patient report or clinical exam by the investigator, spasticity was less severe after the THC treatment. However, THC was not effective in all patients and frequently caused

unpleasant side effects. Spasticity was also reported to be less severe in a single case study after nabilone treatment (Figure 4.2).[117]

In general, the abundant anecdotal reports are not well supported by the clinical data summarized in Table 4.1. But this is due more to the limitation of the studies than to negative results. There are no supporting animal data to encourage clinical research in this area, but there also are no good animal models of the spasticity of MS. Without an appropriate model, studies to determine the physiological basis for how marijuana or THC might relieve spasticity cannot be conducted. Nonetheless, the survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS. Such research would require the use of objective measures of spasticity, such as the pendulum test.[4] Since THC is mildly sedating, it is also important to distinguish this effect from antispasticity effects in any such investigations. Mild sedatives, such as Benadryl or benzodiazepines, would be useful controls for studies on the ability of cannabinoids to relieve muscle spasticity. The regular use of smoked marijuana, however, would be contraindicated in a chronic condition like MS.

Spinal Cord Injury

In 1990, there were about 15 million patients worldwide with spinal cord injury, and an estimated 10,000 new cases are reported each year in the United States alone.[134,138] About 60% of spinal cord injuries occur in people younger than 35 years old. Most will need long-term care and some lifelong care.[116]

Many spinal cord injury patients report that marijuana reduces their muscle spasms.[114] Twenty-two of 43 respondents to a 1982 survey of people with spinal cord injuries reported that marijuana reduced their spasticity.[114] One double-blind study of a paraplegic patient with painful spasms in both legs suggested that oral THC was superior to codeine in reducing muscle spasms.[72,120] Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, their nausea, and the frequency of their sleepless nights. The caveats described for surveys of spasticity relief in MS patients also apply here.

Therapy for Muscle Spasticity

Present Therapy. Present therapy for spasticity includes the various medications listed in Table 4.2. Baclofen and tizanidine, the most commonly prescribed antispasticity drugs, relieve spasticity and spasms with various degrees of success. The benefit of these agents is generally only partial. Their use is complicated by the side effects of drowsiness, dry mouth, and increased weakness.

Future Therapy. The discovery of agents that work through mechanisms different from those of existing antispasticity drugs will be an important advance in the treatment of spasticity. The aim of new treatments will be to relieve muscle spasticity and pain without substantially increasing muscle weakness in conditions that result in spasticity.

The treatment for MS itself will likely be directed at immunomodulation. Various immunomodulating agents, such as beta-interferon and glatiramer acetate, have been shown to reduce the frequency of symptomatic attacks, the progression of disability, and the rate of appearance of demyelinated lesions as detected by magnetic resonance imaging.[5]

Conclusion: Muscle Spasticity

Basic animal studies described in chapter 2 have shown that cannabinoid receptors are particularly abundant in areas of the brain that control movement and that cannabinoids affect movement and posture in animals as well as humans. The observations are consistent with the possibility that cannabinoids have antispastic effects, but they do not offer any direct evidence that cannabinoids affect spasticity, even in animals. The available clinical data are too meager to either accept or dismiss the suggestion that marijuana or cannabinoids relieve muscle spasticity. But the few positive reports of the ability of THC and related compounds to reduce spasticity, together with the prevalence of anecdotal reports of the relief provided by marijuana, suggest that carefully designed clinical trials testing the effects of cannabinoids on muscle spasticity should be considered (see chapter 1).[25,62] Such trials should be designed to assess the degree to which the anxiolytic effects of cannabinoids contribute to any observed antispastic effects.

Spasticity occurring at night can be very disruptive to sleep. Thus, a long-lasting medication would be especially useful for MS patients at bedtime--when drowsiness would be a beneficial rather than an unwanted side effect and mood-altering effects would be less of a problem. One caution is related to the effects of THC on the stages of sleep, which should be evaluated in MS patients who have sleep disturbances. If THC is proven to relieve spasticity, a pill might be the preferred route of delivery for nighttime use because of its long duration of action. Compared to the currently available therapies, the long half-life of THC might allow for a smoother drug effect throughout the day. The intensity of the symptoms resulting from spasticity, particularly in MS, can rapidly increase in an unpredictable fashion such that the patient develops an "attack" of intense muscle spasms lasting minutes to hours. An inhaled form of THC (if it were shown to be efficacious) might be appropriate for those patients.

Movement Disorders

Movement disorders are a group of neurological conditions caused by abnormalities in the basal ganglia and their subcortical connections through the thalamus with cortical motor areas. The brain dysfunctions ultimately result in abnormal skeletal muscle movements in the face, limbs, and trunk. The movement disorders most often considered for marijuana or cannabinoid therapy are dystonia, Huntington's disease, Parkinson's disease, and Tourette's syndrome. Movement disorders are often transiently exacerbated by stress and activity and improved by factors that reduce stress. This is of particular interest because for many people marijuana reduces anxiety.

Dystonia

Dystonia can be a sign of other basal ganglion disorders, such as Huntington's disease and tardive dyskinesia (irreversible development of involuntary dyskinetic movements) and can be a primary basal ganglion disorder. Primary dystonias are a heterogeneous group of chronic slowly progressive neurological disorders characterized by dystonic movements--slow sustained involuntary muscle contractions that often result in abnormal postures of limbs, trunk, and neck. Dystonias can be confined to one part of the body, such as spasmodic torticollis (neck) or Meige's syndrome (facial muscles), or can affect many parts of the body, such as dystonia musculorum deformans.[5] Dystonia can cause mild to severe disability and sometimes pain secondary to muscle aching or arthritis. Some dystonias are genetic; others are caused by drugs. The specific neuropathological changes in these diseases have not been determined.

No controlled study of marijuana in dystonic patients has been published, and the only study of cannabinoids was a preliminary open trial of cannabidiol (CBD) that suggested modest dose-related improvements in the five dystonic patients studied.[30] In mutant dystonic hamsters, however, the cannabinoid receptor agonist, WIN 55,212-2, can produce antidystonic effects.[153]

Huntington's Disease

Huntington's disease is an inherited degenerative disease that usually appears in middle age and results in atrophy or loss of neurons in the caudate nucleus, putamen, and cerebral cortex. It is characterized by arrhythmic, rapid muscular contractions (chorea), emotional disturbance, and dementia (impairment in intellectual and social ability). Animal studies suggest that cannabinoids have antichoreic activity, presumably because of stimulation of CB_1 receptors in the basal ganglia.[129,168]

On the basis of positive results in one of four Huntington's disease patients, CBD and a placebo were tested in a double-blind crossover study of 15 Huntington's disease patients who were not taking any antipsychotic drugs. Their symptoms neither improved nor worsened with CBD treatment.[27,164]

The effects of other cannabinoids on patients with Huntington's disease are largely unknown. THC and other CB_1 agonists are more likely candidates than CBD, which does not bind to the CB_1 receptor. Those receptors are densely distributed on the very neurons that perish in Huntington's disease.[152] Thus far there is little evidence to encourage clinical studies of cannabinoids in Huntington's disease.

Parkinson's Disease

Parkinson's disease, a degenerative disease, affects about 1 million Americans over the age of 50.[53] It is characterized by bradykinesia (slowness in movement), akinesia (abrupt stoppage of movement), resting tremor, muscular rigidity, and postural instability.

Theoretically, cannabinoids could be useful for treating Parkinson's disease patients because cannabinoid agonists specifically inhibit the pathways between the subthalamic nucleus and substantia nigra and probably also the pathways between the subthalamic nucleus and globus pallidus (these structures shown in Figure 2.6).[165,169] The latter effect was not directly tested but is consistent with what is known about these neural pathways. Hyperactivity of the subthalamic neurons, observed in both Parkinson's patients and animal models of Parkinson's disease, is hypothesized to be a major factor in the debilitating bradykinesia associated with the disease.[36] Furthermore, although cannabinoids oppose the actions of dopamine in intact rats, they augment dopamine activation of movement in an animal model of Parkinson's disease. This suggests the potential for adjunctive therapy with cannabinoid agonists.[165—167,169]

At the time of this writing, we could find only one published clinical trial of marijuana involving five cases of idiopathic Parkinson's disease.[48] That trial was prompted by a patient's report that smoking marijuana reduced tremor, but the investigators found no improvement in tremor after the five patients smoked marijuana--whereas all subjects benefited from the administration of standard medications for Parkinson's disease (levodopa and apomorphine).[48] Although new animal data might someday indicate a use for cannabinoids in treating Parkinson's disease, current data do not recommend clinical trials of cannabinoids in patients with Parkinson's disease.

Tourette's Syndrome

Tourette's syndrome usually begins in childhood and is characterized by motor and vocal tics (involuntary rapid repetitive movements or vocalizations). It has been suggested that the symptoms might be mediated by a reduction in the activity of limbic-basal ganglia-thalamocortical circuits (shown in Figure 2.4).[42] These circuits, while not well understood, appear to be responsible for translating a person's intentions to move into actual movements. Damage to these structures leads to either involuntary increases in movement (as in Huntington's disease) or the inability to make voluntary movements (as in Parkinson's disease). The nature of the deficit in Tourette's syndrome is unknown.

No clear link has been established between symptoms of Tourette's syndrome and cannabinoid sites or mechanism of action. Pimozide and haloperidol, two widely used treatments for Tourette's syndrome, inhibit effects mediated by the neurotransmitter dopamine, whereas cannabinoids can increase dopamine release.[154,181] The physiological relevance, if any, of these two observations has not been established.

Clinical reports consist of four case histories indicating that marijuana use can reduce tics in Tourette's patients.[75,163] In three of the four cases the investigators suggest that beneficial effects of marijuana might have been due to anxiety-reducing properties of marijuana rather than to a specific antitic effect.[163]

Therapy for Movement Disorders

Various drugs are available (Table 4.3) to treat the different movement disorders. Common side effects of many of these drugs are sedation, lethargy, school and work avoidance, social phobia, and increased risk of parkinsonism and tardive dyskinesia. With some of the medications, like those used for dystonia, efficacy is lacking in up to 50% of the patients. In addition to medications, surgical interventions, such as pallidotomy and neurosurgical transplantation of embryonic substantia nigra tissue into the patient's striatum, have been tried in Parkinson's disease patients. Surgery is generally palliative and is still considered to be in the developmental phase.

Conclusion: Movement Disorders

The abundance of CB_1 receptors in basal ganglia and reports of animal studies showing the involvement of cannabinoids in the control of movement suggest that cannabinoids would be useful in treating movement disorders in humans. Marijuana or CB_1 receptor agonists might provide symptomatic relief of chorea, dystonia, some aspects of parkinsonism, and tics. However, clinical evidence is largely anecdotal; there have been no well-controlled studies of adequate numbers of patients. Furthermore, nonspecific effects might confound interpretation of results of studies. For example, the anxiolytic effects of cannabinoids might make patients feel that their condition is improved, despite the absence of measurable change in their condition.

Compared to the abundance of anecdotal reports concerning the beneficial effects of marijuana on muscle spasticity, there are relatively few claims that marijuana is useful for treating movement disorders. This might reflect a lack of effect or a lack of individuals with movement disorders who have tried marijuana. In any case, while there are a few isolated reports of individuals with movement disorders who report a benefit from marijuana, there are no published surveys indicating that a substantial percentage of patients with movement disorders find relief from marijuana. Existing studies involve too few patients from which to draw conclusions. The most promising reports involve symptomatic treatment of spasticity. If the reported neuroprotective effects of cannabinoids discussed in chapter 2 prove to be therapeutically useful, this could benefit patients with movement disorders, but without further data such a benefit is highly speculative. Since stress often transiently exacerbates movement disorders, it is reasonable to hypothesize that the anxiolytic effects of marijuana or cannabinoids might be beneficial to some patients with movement disorders. However, chronic marijuana smoking is a health risk that could increase the burden of chronic conditions, such as movement disorders.

Cannabinoids inhibit both major excitatory and inhibitory inputs to the basal ganglia. This suggests that a cannabinoid agonist could produce opposite effects on movement, depending on the type of transmission (excitatory or inhibitory) that is most active at the time of drug administration. This property could be used to design treatments in basal ganglia movement disorders, such as Parkinson's disease where either the excitatory subthalamic input becomes hyperactive or the inhibitory striatal input becomes hypoactive. The dose employed would be a major factor in the therapeutic uses of cannabinoids in movement disorders; low doses should be desirable, while higher doses

could be expected to aggravate pathological conditions. Thus, there is a clear reason to recommend pre-clinical studies; that is, animal studies to test the hypothesis that cannabinoids play an important role in movement disorders.

With the possible exception of multiple sclerosis, the evidence to recommend clinical trials of cannabinoids in movement disorders is relatively weak. Ideally, clinical studies would follow animal research that provided stronger evidence than is currently available on the potential therapeutic value of cannabinoids in the treatment of movement disorders. Unfortunately, there are no good animal models for these disorders. Thus, double-blind, placebo-controlled clinical trials of isolated cannabinoids that include controls for relevant side effects should be conducted. Such effects include anxiolytic and sedative effects, which might either mask or contribute to the potential therapeutic effects of cannabinoids.

Epilepsy

Epilepsy is a chronic seizure disorder that affects about 2 million Americans and 30 million people worldwide.[156] It is characterized by recurrent sudden attacks of altered consciousness, convulsions, or other motor activity. A seizure is the synchronized excitation of large groups of brain cells. These abnormal electrical events have a wide array of possible causes, including injury to the brain and chemical changes derived from metabolic faults of exposure to toxins.[156]

Seizures are classified as partial (focal) or generalized. Partial seizures are associated with specific sensory, motor, or psychic aberrations that reflect the function of the part of the cerebral cortex from which the seizures arise. Generalized seizures are usually the result of pathological conditions of brain sites that project to widespread regions of the brain. Such pathology can produce petit mal seizures or major grand mal convulsions.

Cannabinoids in Epilepsy

There are anecdotal and individual case reports that marijuana controls seizures in epileptics (reviewed in a 1997 British Medical Association report[13]), but there is no solid evidence. While there are no studies indicating that either marijuana or THC worsen seizures, there is no scientific basis to justify such studies.

In the only known case-controlled study that was designed to evaluate illicit drug use and the risk of first seizure, Ng and co-workers[137] concluded that marijuana is a protective factor for first-time seizures in men but not women. Men who used marijuana reportedly had fewer first-time seizures than men who did not use marijuana. That report was based on a comparison of 308 patients who had been admitted to a hospital after their first seizure with a control group of 294 patients. The control group was made up of patients who had not had seizures and were admitted for emergency surgery, such as surgery for appendicitis, intestinal obstruction, or acute cholecystitis. Compared to men who did not use marijuana, the odds ratio of first seizure for men who had used marijuana within 90 days of hospital admission was 0.36 (95% confidence interval = 0.18—0.74).

An odds ratio of less than one is consistent with the suggestion that marijuana users are less likely to have seizures. The results for women were not statistically significant. However, this was a weak study. It did not include measures of health status prior to hospital admissions for the patients' serious conditions, and differences in their health status might have influenced their drug use rather than--as suggested by the authors--that differences in their drug use influenced their health.

The potential antiepileptic activity of CBD has been investigated but is not promising. Three controlled trials were conducted in which CBD was given orally to patients who had had generalized grand mal seizures or focal seizures (Table 4.4). Two of these studies were never published, but information about one was published in a letter to the *South African Medical Journal*, and the other was presented at the 1990 Marijuana International Conference on Cannabis and Cannabinoids.[184]

Even if CBD had antiepileptic properties, these studies were likely too small to demonstrate efficacy. Proving efficacy of anticonvulsants generally requires large numbers of patients followed for months because the frequency of seizures is highly variable and the response to therapy varies depending on seizure type.[4,49]

Therapy for Epilepsy

Present Therapy. Standard pharmacotherapy for partial and generalized seizures, listed in Table 4.5, involves a variety of anticonvulsant drugs. These drugs suppress seizures completely in approximately 60% of patients who have chronic epilepsy and improve seizures in another 15% of patients. All of the anticonvulsants listed in Table 4.5 have side effects, some of the more common of which are drowsiness, mental slowing, ataxia, tremor, hair loss, increased appetite, headache, insomnia, and rash. Nevertheless, recurrent seizures are physically dangerous and emotionally devastating, and preventing them outweighs many undesirable side effects of anticonvulsant drugs.

Future Therapy. The goal of epilepsy treatment is to halt the seizures with minimal or no side effects and then to eradicate the cause. Most of the anticonvulsant research on cannabinoids was conducted before 1986. Since then, many new anticonvulsants have been introduced and cannabinoid receptors have been discovered. At present, the only biological evidence of antiepileptic properties of cannabinoids is that CB_1 receptors are abundant in the hippocampus and amygdala. Both regions are involved in partial seizures but are better known for their role in functions unrelated to seizures.[26] Basic research might reveal stronger links between cannabinoids and seizure activity, but this is not likely to be as fruitful a subject of cannabinoid research as others. Given the present state of knowledge, clinical studies of cannabinoids in epileptics are not indicated.

Alzheimer's Disease

Food refusal is a common problem in patients who suffer from Alzheimer's type dementia. The causes of anorexia in demented people are not known but may be a symptom of depression. Antidepressants improve eating in some but not all patients with

severe dementia. Eleven Alzheimer's patients were treated for 12 weeks on an alternating schedule of dronabinol and placebo (six weeks of each treatment). The dronabinol treatment resulted in substantial weight gains and declines in disturbed behavior.[190] No serious side effects were observed. One patient had a seizure and was removed from the study, but the seizure was not necessarily caused by dronabinol. Recurrent seizures without any precipitating events occur in 20% of patients who have advanced dementia of Alzheimer's type.[189] Nevertheless, these results are encouraging enough to recommend further clinical research with cannabinoids.

The patients in the study discussed above were in long-term institutional care, and most were severely demented with impaired memory. Although short-term memory loss is a common side effect of THC in healthy patients, it was not a concern in this study. However, the effect of dronabinol on memory in Alzheimer's patients who are not as severely disturbed as those in the above study would be an important consideration.

GLAUCOMA

After cataracts, glaucoma is the second-leading cause of blindness in the world; almost 67 million people are expected to be affected worldwide by the year 2000[149] (for an excellent review, see Alward, 1998[2]). The most common form of glaucoma, primary open-angle glaucoma (POAG), is a slowly progressive disorder that results in loss of retinal ganglion cells and degeneration of the optic nerve, causing deterioration of the visual fields and ultimately blindness. The mechanisms behind the disease are not understood, but three major risk factors are known: age, race, and high intraocular pressure (IOP). POAG is most prevalent among the elderly, with 1% affected in those over 60 years old and more than 9% in those over 80. In African Americans over 80, there is more than a 10% chance of having the disease, and older African Caribbeans (who are less racially mixed than African Americans) have a 20—25% chance of having the disease.[106]

The eye's rigid shape is normally maintained in part by IOP, which is regulated by the circulation of a clear fluid, the aqueous humor,[5] between the front of the lens and the back of the cornea. Because of impaired outflow of aqueous humor from the anterior chamber of the eye, a high IOP is a risk factor for glaucoma, but the mechanism by which it damages the optic nerve and retinal ganglion cells remains unclear.[174] The two leading possibilities are that high IOP interferes with nutrient blood flow to the region of the optic nerve or that it interferes with transport of nutrients, growth factors, and other compounds within the optic nerve axon (P. Kaufman, IOM workshop). If the interference continues, the retinal ganglion cells and optic nerve will permanently atrophy; the result is blindness.[68] Because high IOP is the only known major risk factor that can be controlled, most treatments have been designed to reduce it. However, reducing it does not always arrest or slow the progression of visual loss.[20,109]

Marijuana and Cannabinoids in Glaucoma

Marijuana and THC have been shown to reduce IOP by an average of 24% in people with normal IOP who have visual-field changes. In a number of studies of healthy adults and glaucoma patients, IOP was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC--a reduction as good as that observed with most other medications available today.[1,16,32,76,77,125,193] Similar responses have been observed when marijuana was eaten or THC was given in pill form (10—40 mg) to healthy adults or glaucoma patients.[76,91] But the effect lasts only about three to four hours. Elevated IOP is a chronic condition and must be controlled continuously.

Intravenous administration of Δ^9-THC, Δ^8-THC, or 11-OH-THC to healthy adults substantially decreased IOP, whereas cannabinol, CBD, and ß-OH-THC had little effect.[31,146] The cause for the reduction in IOP remains unknown, but the effect appears to be independent of the frequently observed drop in arterial systolic blood pressure (Keith Green, Medical College of Georgia, personal communication).

Three synthetic cannabinoids were investigated; BW29Y, BW146Y, and nabilone. They were given orally to patients who had high IOP. BW146Y and nabilone were as effective as ingesting THC or smoking marijuana but again with a very short duration of action; BW29Y was ineffective.[136,182]

Topical treatments with cannabinoids have been ineffective in reducing IOP. When Δ^9-THC was applied topically as eye drops, whether once or four times a day, there was no decrease in IOP.[60,90] Suspensions of lipophilic THC tended to be irritating to the eye.

In summary, cannabinoids and marijuana can reduce IOP when administered orally, intravenously, or by inhalation but not when administered topically. Even though a reduction in IOP by standard medications or surgery clearly slows the rate of glaucoma symptom progression, there is no direct evidence of benefits of cannabinoids or marijuana in the natural progression of glaucoma, visual acuity, or optic nerve atrophy.[92,115]

In addition to lowering IOP, marijuana reduces blood pressure and has many psychological effects. Merritt and co-workers reported hypotension, palpitations, and psychotropic effects in glaucoma patients after inhalation of marijuana.[125] Cooler and Gregg[31] also reported increased anxiety and tachycardia after intravenous infusion of THC (1.5—3 mg). All those side effects are problematic, particularly for elderly glaucoma patients who have cardiovascular or cerebrovascular disease**.** The reduction in blood pressure can be substantial and might adversely affect blood flow to the optic nerve.[124] Many people with systemic hypertension have their blood pressure reduced to manageable and acceptable levels through medication, but this does not seem to affect their IOP. In contrast, there is evidence that reduction in blood pressure to considerably below-normal levels influences IOP and ocular blood flow.[46,74,142] Hence, in the case of an eye with high IOP or an optic nerve in poor condition and susceptibility to high IOP, reduced blood flow to the optic nerve could compromise a functional retina and be a factor in the progression of glaucoma.

Because it is not known how these compounds work, it is also not known how they might interact with other drugs used to treat glaucoma. If the mechanism involves a final common pathway, the effects of cannabinoids might not be additive and might even interfere with effective drugs.

Therapy for Glaucoma

Present Therapy

Six classes of drugs are used to treat glaucoma; all reduce IOP (Table 4.6).[93] In the late 1970s, when early reports of the effects of marijuana on IOP surfaced, only cholinomimetics, epinephrine, and oral carbonic anhydrase inhibitors were available. They are not popular today because of their side effects, such as pupil constriction or dilation, brow ache, tachycardia, and diuresis; all of them have been superseded by the other classes of drugs.[93] Surgical options are also available today to lower IOP, including laser trabeculoplasty, trabeculectomy/sclerostomy, drainage implantation, and cyclodestruction of fluid-forming tissues.[173] Thus, there are now many effective options to slow the progression of glaucoma by reducing IOP.

One important factor in slowing the progression of glaucoma via medications that reduce IOP is patient compliance with dosing regimens. With respect to compliance, the ideal glaucoma drug is one that is applied at most twice a day (P. Kaufman, IOM workshop). If the dose must be repeated every three to four hours, patient compliance becomes a problem; for this reason, marijuana and the cannabinoids studied thus far would not be highly satisfactory treatments for glaucoma. Present therapies, especially combinations of approved topical drugs, can control IOP when administered once or twice a day, at a cost of about $60 per month.

Future Therapy

In all likelihood the next generation of glaucoma therapies will deal with neural protection, neural rescue, neural regeneration, or blood flow, and the optic nerve and neural retina will be treated directly rather than just by lowering IOP (P. Kaufman, IOM workshop). There is some evidence that a synthetic cannabinoid, HU-211, might have neuroprotective effects *in vitro;* this presents a potential approach that has nothing to do with IOP.[197] HU-211 is commonly referred to as a cannabinoid because its chemical structure is similar to THC; however, it does not bind to cannabinoid receptor.

It is known that cannabinoids lower IOP fairly substantially but not how. No one has tested whether the effect is receptor mediated (B. Martin, IOM workshop). To do so, one could test whether a receptor antagonist blocked the effects of THC or other cannabinoids. If the decrease were shown to be receptor mediated, it would be important to know whether it was through CB_1, which mediates central nervous system effects, or CB_2, which is not involved in CNS effects. If it were CB_2, it might be possible to reduce IOP without the CNS side effects. Finally, it is not known whether the endogenous cannabinoid system is a natural regulator of IOP.

Conclusion: Glaucoma

Although glaucoma is one of the most frequently cited medical indications for marijuana, the data do not support this indication. High intraocular pressure (IOP) is a known risk factor for glaucoma and can, indeed, be reduced by cannabinoids and marijuana. However, the effect is too and short lived and requires too high doses, and there are too many side effects to recommend lifelong use in the treatment of glaucoma. The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma. Clinical studies on the effects of smoked marijuana are unlikely to result in improved treatment for glaucoma.

Future research might reveal a therapeutic effect of isolated cannabinoids. For example, it might be possible to design a cannabinoid drug with longer-lasting effects on IOP and with less psychoactivity than THC.

SUMMARY

Advances in cannabinoid science of the past 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients such as those with AIDS or who are undergoing chemotherapy, and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication. The data are weaker for muscle spasticity but moderately promising. The least promising categories are movement disorders, epilepsy, and glaucoma. Animal data are moderately supportive of a potential for cannabinoids in the treatment of movement disorders and might eventually yield stronger encouragement. The therapeutic effects of cannabinoids are most well established for THC, which is the primary psychoactive ingredient of marijuana. But it does not follow from this that smoking marijuana is good medicine.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons there is little future in smoked marijuana as a medically approved medication. If there is any future in cannabinoid drugs, it lies with agents of more certain, not less certain, composition. While clinical trials are the route to developing approved medications, they are also valuable for other reasons. For example, the personal medical use of smoked marijuana--regardless of whether or not it is approved--to treat certain symptoms is reason enough to advocate clinical trials to assess the degree to which the symptoms or course of diseases are affected. Trials testing the safety and efficacy of marijuana use are an important component to understanding the course of a disease, particularly diseases such as AIDS for which marijuana use is prevalent. The argument against the future of smoked marijuana for treating any condition is not that there is no reason to predict efficacy but

that there is risk. That risk could be overcome by the development of a nonsmoked rapid-onset delivery system for cannabinoid drugs.

There are two caveats to following the traditional path of drug development for cannabinoids. The first is timing. Patients who are currently suffering from debilitating conditions unrelieved by legally available drugs, and who might find relief with smoked marijuana, will find little comfort in a promise of a better drug 10 years from now. In terms of good medicine, marijuana should rarely be recommended unless all reasonable options have been eliminated. But then what? It is conceivable that the medical and scientific opinion might find itself in conflict with drug regulations. This presents a policy issue that must weigh--at least temporarily--the needs of individual patients against broader social issues. Our assessment of the scientific data on the medical value of marijuana and its constituent cannabinoids is but one component of attaining that balance.

The second caveat is a practical one. Although most scientists who study cannabinoids would agree that the scientific pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public. Cannabinoid-based drugs will become available only if there is either enough incentive for private enterprise to develop and market such drugs or sustained public investment in cannabinoid drug research and development. The perils along this pathway are discussed in chapter 5. Although marijuana is an abused drug, the logical focus of research on the therapeutic value of cannabinoid-based drugs is the treatment of specific symptoms or diseases, not substance abuse. Thus, the most logical research sponsors would be the several institutes within the National Institutes of Health or organizations whose primary expertise lies in the relevant symptoms or diseases.

> **Conclusion:** Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
>
> **Recommendation: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.**
>
> **Recommendation: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.**
>
> **Recommendation: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:**

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n*-of-1 clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions. We recommend these *n*-of-1 clinical trials using the same oversight mechanism as that proposed in the above recommendations.

OTHER REPORTS ON MARIJUANA AS MEDICINE

Since 1996, five important reports pertaining to the medical uses of marijuana have been published, each prepared by deliberative groups of medical and scientific experts (Appendix E). They were written to address different facets of the medical marijuana debate, and each offers a somewhat different perspective. With the exception of the report by the Health Council of the Netherlands, each concluded that marijuana can be moderately effective in treating a variety of symptoms. They also agree that current scientific understanding is rudimentary; indeed, the sentiment most often stated is that more research is needed. And these reports record the same problem with herbal medications as noted here: the uncertain composition of plant material makes for an uncertain, and hence often undesirable, medicine.

The 1996 report by the Health Council of the Netherlands concluded that there is insufficient evidence to justify the medical use of marijuana *or* THC, despite the fact that the latter is an approved medication in the United States and Britain. However, that committee addressed only whether there was sufficient evidence to warrant the prescription of marijuana or cannabinoids, not whether the data are sufficient to justify clinical trials. Conclusions of the Health Council of the Netherlands contrast with that country's tolerance of marijuana use. The health council's report noted that marijuana use by patients in the terminal stages of illness is tolerated in hospitals. It also said that the council did "not wish to judge patients who consume marihuana (in whatever form) because it makes them feel better. . . ."

In contrast, the American Medical Association House of Delegates, National Institutes of Health (NIH), and the British Medical Association recommend clinical trials of smoked marijuana for a variety of symptoms. The NIH report, however, was alone in recommending clinical studies of marijuana for the treatment of glaucoma--and even then there was disagreement among the panel members (William T. Beaver, chair, NIH Ad Hoc Expert Panel on the Medical Use of Marijuana, personal communication, 1998).

Recent reviews that have received extensive attention from those who follow the medical marijuana debate have been written by strong advocates *for* (Grinspoon and Bakalar, 1993[62]; Zimmer and Morgan, 1997[198]) or *against* (Voth and Schwartz, 1997[191]) the medical use of marijuana. Those reports represent the individual views of their authors, and they are not reviewed here but have been reviewed in major scientific journals.[7,69,178,180]

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Notes

[1] The *visual analogue scale* is a continuous line representing all possible levels of a particular sensation. It is an estimation of a patient's subjective evaluation and not a true measurement. Patients select a point anywhere on the line to demonstrate the level of sensation they are experiencing, with one end representing one extreme, such as no sensations, and the other end representing the opposite extreme, such as a maximum level of that sensation.

[2] Note that the authors of this study chose to use Δ^8-THC because it is more stable and easier to produce than Δ^9-THC; it does not follow from this particular study that marijuana, with its mixture of cannabinoids, should be a more powerful antiemetic than Δ^9-THC.

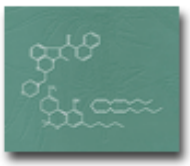
[3] Body cell mass is the fat-free cellular mass. It is composed of the cells of the muscle and organs, plus circulating hematopoietic cells and the aqueous compartment of adipocytes. It is not fat, extracellular water, or extracellular solids (such as tendons).

[4] The *pendulum test* is an objective and accurate measure of MS-induced spasticity. It is done by videotaping a patient who lies supine on a table with his or her leg extending off the edge. The leg is dropped and the resulting motion is mathematically analyzed by computer to provide a quantitative measure of spasticity.

[5] The cornea and lens must be optically clear, which means that there cannot be blood circulation in these tissues. The aqueous humor is a clear fluid that functions as alternative circulation across the rear of the cornea and to the lens, providing nutrients and removing waste from these tissues.

5

Development of Cannabinoid Drugs



Medicines today are expected to be of known composition and quality. Even in cases where marijuana can provide relief of symptoms, the crude plant mixture does not meet this modern expectation. The future of medical marijuana lies in classical pharmacological drug development, and indeed there has been a resurgence of scientific, as well as public, interest in the therapeutic applications of cannabinoids. After an initial burst of scientific activity in the 1970s, today's renewed interest has been fueled by major scientific discoveries discussed in previous chapters: the identification and cloning of endogenous cannabinoid receptors, the discovery of endogenous substances that bind to these receptors, and the emergence of synthetic cannabinoids that also bind to cannabinoid receptors. These scientific accomplishments have propelled interest in developing new drugs that can treat more effectively or more safely the constellation of symptoms for which cannabinoids might have therapeutic benefit (see chapter 4). Through the process of what is referred to as "rational drug design," scientists manipulate the chemical structures of known cannabinoids to design better therapeutic agents. Several new cannabinoids are being developed for human use, but none has reached the stage of human testing in the United States.

The purpose of this chapter is to describe the process of and analyze the prospects for development of cannabinoid drugs. It first discusses the regulatory hurdles that every new drug encounters en route to market. It then proceeds to describe the regulatory and market experiences of dronabinol (tetrahydrocannabinol, or THC, in sesame oil), the only approved cannabinoid in the United States. These sections serve as a road map to determine whether the therapeutic potential of cannabinoids is likely to be exploited commercially to meet patient needs. Finally, the chapter describes what would be needed to bring marijuana to market as a medicinal plant.

The term *cannabinoids* is used in this chapter to refer to a group of substances that are structurally related to THC--by virtue of a tricyclic chemical structure--or that bind to cannabinoid receptors, such as the natural ligand anandamide. From a chemist's point of view, this definition encompasses a variety of distinct chemical classes. But because the purpose of this chapter is to explore prospects for drug development, both chemical structure and pharmacological activity are important; therefore, the broader definition of cannabinoids is used.

FEDERAL DRUG DEVELOPMENT POLICY

Like controlled substances, cannabinoids developed for medical use encounter a gauntlet of public health regulatory controls administered by two federal agencies: the Food and Drug Administration (FDA) of the U.S. Department of Health and Human

Services (DHHS) and the Drug Enforcement Administration (DEA) of the U.S. Department of Justice. The FDA regulates human testing and the introduction of new drugs into the marketplace, whereas the DEA determines the schedule of and establishes production quotas for drugs with potential for abuse to prevent their diversion to illicit channels. The DEA also authorizes registered physicians to prescribe controlled substances. Some drugs, such as marijuana, are labeled Schedule I in the Controlled Substance Act, and this adds considerable complexity and expense to their clinical evaluation. It is important to point out that Schedule I status does not necessarily apply to all cannabinoids.

Food and Drug Administration

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the FDA approves new drugs for entry into the marketplace after their safety and efficacy are established through controlled clinical trials conducted by the drugs' sponsors.[23] FDA approval of a drug is the culmination of a long, research intensive process of drug development, which often takes well over a decade.[19,44] Drug development is performed largely by pharmaceutical companies, but some targeted drug development programs are sponsored by the National Institutes of Health (NIH) to stimulate further development and marketing by the private sector. The NIH's drug development programs--including those for AIDS, cancer, addiction, and epilepsy--have been instrumental in ushering new drugs to market in collaboration with pharmaceutical companies.[33] In fact, as noted later, most of the preclinical and clinical research on dronabinol was supported by NIH.

Drug development begins with discovery, that is, the synthesis and purification of a new compound with expected biological activity and therapeutic value. The next major step is the testing of the compound in animals to learn more about its safety and efficacy and to predict its utility for humans. Those early activities are collectively referred to as the preclinical phase. When evidence from the preclinical phase suggests a promising role in humans, the manufacturer submits an Investigational New Drug (IND) application to the FDA. The IND submission contains a plan for human clinical trials and includes the results of preclinical testing and other information.[20] Absent FDA objection, the IND becomes effective after 30 days, allowing the manufacturer to conduct clinical testing (testing in humans), which generally involves three phases (see Figure 5.1). The three stages of clinical testing are usually the most time-consuming phases of drug development, lasting five years on average.[22] The actual time depends on the complexity of the drug, availability of patients, duration of use, difficulty of measuring clinical end points, therapeutic class, and indication (the disease or condition for which the drug has purported benefits).[31]

Drug development is a long and financially risky process. For every drug that ultimately reaches clinical testing through an IND, thousands of drugs are synthesized and tested in the laboratory. And only about one in five drugs initially tested in humans successfully secures FDA approval for marketing through a new drug application (NDA).[19]

The manufacturer submits an NDA to the FDA to gain approval for marketing when clinical testing is complete. An NDA is a massive document, the largest portion of which contains the clinical data from Phase I—III testing. The other technical sections of an NDA include chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; and human pharmacokinetics and bioavailability.[23] In the case of a new cannabinoid, an abuse liability assessment would also probably be part of an NDA submission. In 1996 the median time for FDA review of an NDA, from submission to approval, was 15.1 months, a review period considerably shorter than that in 1990, when the figure was 24.3 months.[22] The shortening of approval time is an outgrowth of the Prescription Drug User Fee Act of 1992, which authorized the FDA to hire additional review staff with so-called user fees paid by industry and imposed clear deadlines for FDA action on an NDA. With respect to the cost of a single drug's development, a number of recent studies have provided a range of estimates of about $200—$300 million, depending on the method and year of calculation.[33,44]

With FDA approval of an NDA, the manufacturer is permitted to market the drug for the *approved indication*. At that point, although any physician is at liberty to prescribe the approved drug for another indication (an "off-label use"), the manufacturer cannot promote it for that indication unless the new indication is granted separate marketing approval by the FDA.[1] To obtain such approval, the manufacturer is required to compile another application to the FDA for what is known variously as an "efficacy supplement," a "supplemental application," or a "supplemental new drug application." Those terms connote that the application is supplemental to the NDA. In general, collecting new data for FDA approval of an efficacy supplement is not as intensive a process as that for an NDA; it generally requires the firm to conduct two additional Phase III studies, although under some circumstances only one additional study of the drug's efficacy is needed.[24] The preclinical studies, for example, ordinarily need not be replicated. The average cost to the manufacturer for obtaining approval for the new indication is typically about $10—$40 million.[33] The review time to obtain FDA approval for the new indication can be considerable; a recent study of supplemental indications approved by the FDA in 1989—1994 found the approval time to exceed that for the original NDA,[18] a reflection, in part, of the lower priority that the FDA accords to the review of efficacy supplements as opposed to new drugs.[23]

The manufacturer also must apply to the FDA to receive marketing approval for a new formulation of a previously approved drug. A new formulation is a new dosage form, including a new route of administration. An example of such a new formulation is an inhaled version of Marinol, which is currently approved only in capsule form. The manufacturer is required to establish bioequivalence, safety, and efficacy of the new formulation. The amount of evidence required for approval is highly variable, depending on the similarities between the new formulation and the approved formulation. New formulations are evaluated case by case by the FDA. In the case of Marinol, for example, an inhaled version is likely to require not only new studies of efficacy but also new studies of abuse liability. There appear to be no published peer-reviewed studies of the average cost and time for approval of a new formulation.

Two other FDA programs might be relevant to the potential availability of new cannabinoids. One program is authorized under the Orphan Drug Act of 1983, which provides incentives to manufacturers to develop drugs to treat "orphan diseases." An orphan disease, as defined in an amendment to the act, is one that affects 200,000 or fewer people in the United States.[2] The act's most important incentive is a period of exclusive marketing protection of seven years, during which time the FDA is prohibited from approving the same drug for the same indication.[5,6] Some of the medical conditions for which cannabinoids have been advocated--Huntington's disease, multiple sclerosis, and spinal cord injury (see chapter 4)--might meet the definition of an orphan disease and thus enable manufacturers to take advantage of the act's financial incentives to bring products to market. If a disease affects more than 200,000 people, the manufacturer sometimes subdivides the patient population into smaller units to qualify. For example, a drug for the treatment of Parkinson's disease is not likely to receive an orphan designation because its prevalence exceeds 200,000, but orphan designation has been accorded to drugs for subsets of Parkinson's patients, such as those suffering from early-morning motor dysfunction in the late stages of the disease.[25]

The other program is the Treatment-IND program, which was established by regulation in 1987 (and codified into law in 1997) to allow patients with serious and life-threatening diseases to obtain experimental medications, such as marijuana, before their general marketing.[3] Treatment INDs may be issued during Phase III studies to patients who are not enrolled in clinical trials, provided among other requirements that no comparable alternative drug is available.[22,32,33] Thus, the treatment IND program can provide a mechanism for some patients to obtain a promising new cannabinoid before its widespread commercial availability if it reached the late stages of clinical testing for a serious or life-threatening disease.

Drug Enforcement Administration

The DEA is responsible for scheduling controlled substances, that is, drugs and other agents that possess a potential for abuse. *Abuse* is generally defined as nonmedical use that leads to health and safety hazards, diversion from legitimate channels, self-administration, and other untoward results.[15,21] The legislation that gives DEA the authority to regulate drugs of abuse is the Controlled Substances Act, which was passed in 1970 and amended several times. The overall purpose of the CSA is to restrict or control the availability of drugs to prevent their abuse.

Under the CSA, the DEA places each drug that has abuse potential into one of five categories. The five categories, referred to as Schedules I—V, carry different degrees of restriction. Schedule I is the most restrictive, covering drugs that have "no accepted medical use" in the United States and that have high abuse potential. The definitions of the categories and examples of drugs in each are listed in Appendix C. Each schedule is associated with a distinct set of controls that affect manufacturers, investigators, pharmacists, practitioners, patients, and recreational users. The controls include registration with the DEA, labeling and packaging, production quotas, security, recordkeeping, and dispensing.[15] For instance, patients with a legitimate medical need for

drugs in Schedule II, the most restrictive schedule for drugs "currently with accepted medical use," can neither refill their prescriptions nor have them telephoned to a pharmacy (except in an emergency).

The scheduling of substances under the CSA is handled case by case. It may be initiated by DEA, by DHHS, or by petition from an interested party, including the drug's manufacturer or a public-interest group.[15] The final decision for scheduling rests with the DEA, but for this purpose the secretary of DHHS is mandated to provide a recommendation. The secretary's recommendation[4] to DEA is based in part on results from abuse liability testing that the FDA requires of the manufacturer seeking approval of a new drug. Abuse liability testing is not a single test; it is a compilation of several *in vitro* human and animal studies, of which some of the best known are drug self-administration and drug discrimination studies.[21,34] The secretary's recommendation for scheduling is formally guided by eight legal criteria, including the drug's actual or relative potential for abuse, scientific evidence of its pharmacological effect, risk to public health, and its psychic or physiological dependence liability (21 U.S.C. § 811 (b), (c)). Once the DEA receives a scheduling recommendation, its scheduling decision, including the requirement for obtaining public comment, usually takes weeks to months.[33] In practice, the DEA usually adheres to the recommendation of the secretary.[5] Beyond the DEA, various state scheduling laws also affect the manufacture and distribution of controlled substances.[33,50]

Under the CSA, marijuana and THC[6] are in Schedule I, the most restrictive schedule. The scheduling of any other cannabinoid under this act first hinges on whether it is found *in the plant*. All cannabinoids in the plant are automatically in Schedule I because they fall under the act's definition of marijuana (21 U.S.C. § 802 (16)). In addition, under DEA's regulations, synthetic equivalents of the substances contained in the plant and "synthetic substances, derivatives, and their isomers" whose "chemical structure and pharmacological activity" are "similar" to THC also are automatically in Schedule I (21 CFR § 1308.11(d)(27). Based on the examples listed in the regulations, the word *similar* probably limits the applicability of the regulation to isomers of THC, but DEA's interpretation of its own regulations would carry significant weight in any specific situation.

Prompted by a 1995 petition from Jon Gettman, a former president of the National Organization for the Reform of Marijuana Laws (NORML), to remove marijuana and THC from Schedule I, DEA gathered information which was then submitted to DHHS for a medical and scientific recommendation and scheduling recommendation, as required by the CSA. For the reasons noted above, any changes in scheduling of marijuana and THC would also affect other plant cannabinoids. For the present, however, any cannabinoid found in the plant is automatically controlled in Schedule I.

Investigators are affected by Schedule I requirements even if their research is being conducted *in vitro* or on animals. For example, researchers studying cannabinoids found in the plant are required under the CSA to submit their research protocol to DEA, which issues a registration that is contingent on FDA's evaluation and approval of the protocol

(21 CFR § 1301.18). DEA also inspects the researcher's security arrangements. However, the regulatory implications are quite different for cannabinoids *not found in the plant*. Such cannabinoids appear to be unscheduled unless the FDA or DEA decides that they are sufficiently similar to THC to be placed automatically into Schedule I under the regulatory definition outlined above or the FDA or the manufacturer deems them to have potential for abuse, thereby triggering *de novo* the scheduling process noted above. Thus far, the cannabinoids most commonly used in preclinical research (Table 5.1) appear to be sufficiently distinct from THC that they are not currently considered controlled substances by definition (F. Sapienza, DEA, personal communication, 1998). No new cannabinoids other than THC have yet been clinically tested in the United States, so scheduling experience is limited. The unscheduled status of some cannabinoids might change as research progresses. Results of early clinical research could lead a manufacturer to proceed with or lead the FDA to require abuse liability testing. Depending on the results of such studies, DHHS might or might not recommend scheduling *de novo* to DEA, which makes the final decision case by case.

Will newly discovered cannabinoids be subject to scheduling? That is a complex question that has no simple answer. The answer depends entirely on each new cannabinoid--whether it is found in the plant, its chemical and pharmacological relationship to THC, and its potential for abuse. Novel cannabinoids with strong similarity to THC are likely to be scheduled at some point before marketing, whereas those with weak similarity might not be. The manufacturer's submission to FDA, which contains its own studies and its request for a particular schedule, can also shape the outcome. Cannabinoids found in the plant are automatically in Schedule I until the manufacturer requests and provides justification for rescheduling. The CSA does permit DEA to reschedule a substance (move it to a different schedule) and to deschedule a substance (remove it from control under the CSA) according to the scheduling criteria (see Appendix F) and the process outlined above.

The possibility of scheduling is a major determinant of whether a manufacturer proceeds with drug development.[33] In general, pharmaceutical firms perceive scheduling to be a deterrent because it limits their ability to achieve market share for the following reasons: restricted access, physician disinclination to prescribe scheduled substances, stigma, the additional expense for abuse liability studies, and expensive delays in reaching the market due to federal and state scheduling processes.[33] Empirical evidence to support that widely held perception is difficult to find, but at least one large survey of physicians found them to have moderate concerns about prescribing opioids because of actual or perceived pressure from regulatory agencies, such as DEA.[57] On the basis of a legal analysis and widespread complaints from researchers and pharmaceutical executives, the Institute of Medicine (IOM, 1995)[33] recommended changes in the CSA to eliminate the act's barriers to undertaking clinical research and development of controlled substances; this position was supported in a later report on marijuana.[40]

DEVELOPMENT AND MARKETING OF MARINOL

The following material is based on the published literature (where cited), workshops sponsored by the IOM, and an interview with Robert Dudley, senior vice president of Unimed Pharmaceuticals, Inc., the manufacturer of Marinol and the holder of the NDA. Unimed markets Marinol jointly with Roxane Laboratories, Inc.

Marinol (dronabinol) is the only cannabinoid with approval for marketing in the United States.[7] The following description covers its development, regulatory history, pharmacokinetics, adverse effects, abuse liability, and market growth. The experience with Marinol can serve as a possible bellwether for the regulatory and commercial fate of new cannabinoids being considered for development.

Development and Regulatory History

Marinol is manufactured as a capsule containing THC in sesame oil; it is taken orally. It was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA approved marketing of dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS.[45] The preclinical and clinical research on THC that culminated in the FDA's 1985 approval was supported primarily by the National Cancer Institute (NCI), whose research support goes back to the 1970s. NCI's contribution appears pivotal, considering that Unimed, the pharmaceutical company that holds the NDA, estimates its contribution to have been only about 25% of the total research effort. The FDA's review and approval of Marinol took about two years after submission of the NDA, according to Unimed. To obtain approval for Marinol's second indication (through an efficacy supplement), the FDA required two more relatively small Phase III studies. The studies lasted three years and cost $5 million to complete.

Physical Properties, Pharmacokinetics, and Adverse Events

Marinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps needed for purification. The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10—20% of an oral dose reaches the systemic circulation.[45,60] The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing.[45,56] In contrast, inhaled marijuana is rapidly absorbed. In a study comparing THC administered orally, by inhalation, and intravenously, plasma concentration peaked almost instantaneously after both inhalation and intravenous administration; most participants' peak plasma concentrations after oral administration occurred at 60 or 90 minutes. Variation in individual responses is highest for oral THC and bioavailability is lowest.[42]

Marinol's most common adverse events are associated with the central nervous system (CNS): anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality.[8,9,45,59] In two recent clinical trials, CNS adverse events occurred in about one-third of patients, but only a small percentage discontinued

the drug because of adverse effects.[8,9] Lowering the dose of dronabinol can minimize side effects, especially dysphoria (disquiet or malaise).[47]

Abuse Potential and Scheduling

On commercial introduction in 1985, Marinol was placed in Schedule II. This schedule, the second most restrictive, is reserved for medically approved substances that have "high potential for abuse" (21 U.S.C. § 812 (b) (2)). Unimed did not encounter any delays in marketing as a result of the scheduling process because the scheduling decision was made by the DEA before FDA's approval for marketing. Nor did Unimed encounter any marketing delays as a result of state scheduling laws. Unimed was not specifically asked by the FDA to perform abuse liability studies for the first approval, presumably because such studies had been conducted earlier.

Unimed later petitioned the DEA to reschedule Marinol from Schedule II to Schedule III, which is reserved for medically approved substances that have some potential for abuse (21 U.S.C. § 812 (b) (3)). To buttress its request for rescheduling, Unimed supported an analysis of Marinol's abuse liability by researchers at the Haight Ashbury Free Clinic of San Francisco, which treats many cannabis-dependent patients and people who have HIV/AIDS. The analysis found no evidence of abuse or diversion of Marinol after a literature review and surveys and interviews of medical specialists in addiction, oncology, cancer research, and treatment of HIV, and people in law enforcement. The authors attribute Marinol's low abuse potential to its slow onset of action, its dysphoric effects, and other factors.[12] On November 5, 1998, the DEA announced a proposal to reschedule Marinol to Schedule III.[17] As of this writing, no formal action on that proposal had been taken.

The rescheduling of a drug from Schedule II to Schedule III is considered important because it lifts some of the restrictions on availability. For example, Unimed expects a sales increase of about 15—20% as a result of rescheduling. In its judgment and that of many other pharmaceutical companies,[33] scheduling limits market penetration; the more restrictive the schedules, the greater the limitation. The reasons are that physicians and other providers are reluctant to prescribe Schedule II drugs; patients are deterred from seeking prescriptions because of Schedule II prohibition of refills, as opposed to other commercially available scheduled substances; additional restrictions are imposed by several states, such as quantity restrictions (for example, 30-day supply limits) and triplicate prescriptions;[50] and some Schedule II drugs are excluded from hospital formularies because of onerous security and paperwork requirements under federal and state controlled substances laws.

Market Growth and Transformation

Annual sales of Marinol are estimated at $20 million, according to Unimed. Of Marinol's patient population 80% use it for HIV, 10% for cancer chemotherapy, and about 5—10% for other reasons. The latter group is thought to consist of Alzheimer's patients drawn to the drug by a recently published clinical study indicating Marinol's

promise for the treatment of their anorexia and disturbed behavior.[58] As noted earlier, Unimed cannot promote Marinol for this unlabeled indication, but physicians are free to prescribe it for such an indication. Unimed is conducting additional research in pursuit of FDA approval of a new indication for Marinol in the treatment of Alzheimer disease.

The 1992 approval of Marinol for the treatment of anorexia in AIDS patients marked a major transformation in the composition of the patient population. Marinol's use had been restricted to oncology patients. The oncology market for Marinol gradually receded as a result of the introduction of newer medications, including such serotonin antagonists as ondansetron, which are more effective (see chapter 4, "Nausea and Vomiting) and are not scheduled. Much of the recent growth of the market for Marinol (which is about 10% per year) is attributed to its increasing use by HIV patients being treated with combination antiretroviral therapy. Marinol appears to have a dual effect, not only stimulating appetite but also combating the nausea and vomiting associated with combination therapy. Unimed is supporting a Phase II study to examine this combined effect and, with promising results, plans to seek FDA approval for this new indication.

Unimed has two forms of market protection for Marinol. In December 1992, the FDA granted Marinol seven years of exclusive marketing under the Orphan Drug Act. The market exclusivity is related to Marinol's use in anorexia associated with AIDS. Because of the designated orphan indication, the active ingredient, THC, cannot be marketed by another manufacturer for the same indication until December 1999. Other pharmaceutical manufacturers are not constrained from manufacturing and marketing THC for its *other* indication, antiemesis for cancer chemotherapy, but none appears to be interested in what is, by pharmaceutical company standards, a small market. In addition to market exclusivity, Unimed secured in June 1998 a "use patent" for dronabinol for the treatment of disturbed patients with dementia; this confers patent protection to Unimed for this use for 20 years from the date of filing of the application,[8] assuming that this indication eventually gains FDA approval.

The rate-limiting factors in the growth of the market for Marinol, according to Unimed are the lack of physician awareness of the drug's efficacy, its adverse effects, and its restricted availability as a result of placement in Schedule II. Unimed perceives only a small percentage of its market to be lost to "competition" from marijuana itself, but there are, admittedly, no reliable statistics on the number of people who have chosen to treat their symptoms with illegally obtained marijuana, despite their ability to obtain Marinol.

New Routes of Administration

It is well recognized that Marinol's oral route of administration hampers its effectiveness because of slow absorption and patients' desire for more control over dosing. A drug delivered orally is first absorbed from the stomach or small intestine and then passed through the liver, where it undergoes some metabolism before being introduced into the circulation. To overcome the deficiencies of oral administration, Unimed activated an IND in 1998 as a step toward developing new formulations for Marinol. Four new formulations--deep lung aerosol, nasal spray, nasal gel, and sublingual

preparation--are under study in Phase I clinical studies being conducted in conjunction with Roxane Laboratories. These formulations seek to deliver Marinol to the circulation more rapidly and directly. The first two fall under inhalation as a route of administration. Inhalation is considered the most promising method, owing to the rapidity of onset of its effects and potential for better titration of the dose by the patient, but it might also carry an increased potential for abuse. The abuse of a drug correlates with its rapidity of onset (G. Koob, IOM workshop). Sublingual route (under the tongue) administration also affords rapid absorption into the circulation, in this case from the oral mucosa. Other researchers are pursuing the delivery of THC through rectal suppositories, but this slower route might not be acceptable to many patients. Transdermal (skin patches) administration, which is best suited to hydrophilic drugs, is precluded by the lipophilicity of THC. Thus, the choice of routes of administration depends heavily on the physicochemical characteristics of the drug and on its safety, abuse liability, and tolerability.

Unimed expects the FDA to require it to conduct studies of the bioavailability, efficacy, and possibly abuse liability of any new formulation it seeks to market. Any formulation that expedites Marinol's onset of action, as suggested above, is thought to carry greater possibility of abuse. The cost of developing each new formulation is estimated by Unimed at $7—$10 million.

Unimed and Roxane are developing, or considering development of, five new indications for Marinol: disturbed behavior in Alzheimer's disease, nausea and vomiting in HIV patients who are receiving combination therapy, spasticity in multiple sclerosis, intractable pain, and anorexia in cancer and renal disease.

Costs of Marinol and Marijuana

During the IOM public workshops held during the course of this study, many people commented that an important advantage of using marijuana for medical purposes is that it is much less expensive than Marinol. But this comparison is deceptive. While the direct costs of marijuana are relatively low, the indirect costs can be prohibitive. Individuals who violate federal or state marijuana laws risk a variety of costs associated with engaging in criminal activity, ranging from increased vulnerability to theft and personal injury legal fees to long prison terms. In addition, when purchasing illicit drugs there is no guarantee that the product purchased is what the seller claims it is or that it is not contaminated.

The price of Marinol for its most commonly used indication, anorexia in AIDS, is estimated at $200 per month. The less common indication-- nausea and vomiting with cancer chemotherapy--is not as expensive because it is not chronic. Regardless of indication, patients' out-of-pocket expenses tend to be much less--often minimal--because of reimburse-ment through public or private health insurance. For indigent patients who are uninsured, Roxane sponsors a patient assistance program to defray the cost.

The street value of marijuana, according to the DEA's most recent figures, is about $5—$10 per bag of loose plant.[169] At the California buyers' clubs, the price is $2—$16 per gram, depending on the grade of marijuana. The cost to a patient using marijuana depends on the number of cigarettes smoked each day, their THC content, and the duration of use. Insurance does not cover the cost of marijuana. In addition, it is possible for a person to cultivate marijuana privately with little financial investment.

Thus, Marinol appears to be less expensive than marijuana for patients with health insurance or with financial assistance from Roxane. But if the full cost of Marinol is borne out of pocket by the patient, the cost comparison is not so unambiguous. In this case the daily cost in relation to marijuana varies according to the number of cigarettes smoked: If the patient smokes two or more marijuana cigarettes per day, Marinol might be less expensive than marijuana; if the patient smokes only one marijuana cigarette per day, Marinol might be more expensive than marijuana, according to an analysis submitted to the DEA by Unimed. The cost comparisons will depend on fluctuations in the retail price and street value of Marinol and marijuana, respectively, and will vary if marijuana becomes commercially available.

In summary, Marinol has been on the U.S. market since 1985. Its commercial development depended heavily on research supported by the NIH. Marinol's market has grown to $20 million in annual sales. Further market growth is expected but is still constrained by lack of awareness, adverse effects, the oral route of administration, and restrictions imposed by drug scheduling. The manufacturer is proceeding with research on new forms of delivery to overcome the problems associated with oral administration. The manufacturer also is proceeding with research on an array of new indications for Marinol.

MARKET OUTLOOK FOR CANNABINOIDS

The potential therapeutic value of cannabinoids is extremely broad. It extends well beyond antiemesis for chemotherapy and appetite stimulation for AIDS, the two indications for which the FDA has approved dronabinol (Marinol). Chapter 4 of this report assesses the possible wider therapeutic potential of marijuana and THC in neurological disorders, glaucoma, and analgesia--all conditions for which clinical research has been under way to fulfill unmet patient needs. New therapeutic uses are being explored in preclinical research. For any of these therapeutic indications, will novel cannabinoids reach the market to satisfy the medical needs of patients?

Economic Factors in Development

The outcomes of preclinical and clinical research determine whether a drug is sufficiently safe and effective to warrant FDA approval for marketing. But the decisions to launch preclinical research and to proceed to clinical trials if early results are promising are dictated largely by economic factors. A pharmaceutical company must decide whether to invest in what is universally regarded as a long and risky research path. For any given drug the question is, Will there be an adequate return on investment? The

investment in this case is the high cost of developing a drug. The expectation of high financial returns on investment is what drives drug development.[44,53]

Market analyses are undertaken to forecast whether a drug will reap a substantial return on investment. The market analysis for a cannabinoid is likely to be shaped by various factors. The average cost of developing a cannabinoid is likely to be higher than that of developing other drugs if its clinical indication is in the therapeutic categories of neuropharmaceutical or nonsteroidal antiinflammatory drug, the two therapeutic categories associated with the highest research and development costs.[19] One reason for higher costs is the need to satisfy the DEA's regulatory requirements related to drug scheduling.

On the "market return" side are multiple factors. A market analysis examines the expected returns from the possible markets for which a cannabinoid could be clinically pursued. The financial size of each market is calculated mostly on the basis of the current and projected patient prevalence (for a given clinical indication), sales data (if available), and competition from other products. The duration of use is also factored in--a drug needed for long-term use in a condition with an early age of onset is desirable from a marketing perspective. Factors that can augment or diminish market return include patentability and other forms of market protection, reimbursement climate, restrictions in access due to drug scheduling, social attitudes, adverse effect profile, and drug interactions.[33,53] New cannabinoids generally can receive product patents, giving the patent holder 20 years of protection from others seeking to manufacture or sell the same product. According to U.S. patent law, the product must be novel and "nonobvious" in relation to prior patents.[28]

Cannabinoids under Development

From publicly available sources, the IOM was able to learn of several cannabinoids being developed for human use (Table 5.2). With the exception of Marinol and marijuana, all are in the preclinical phase of testing in the United States. This list might not be comprehensive, inasmuch as other compounds could be under development, but that information is proprietary.[10] The table does not list the full complement of cannabinoids, both agonists and antagonists, being used in research as tools to understand the pharmacology of cannabinoids (for more comprehensive lists of cannabinoids, see Felder and Glass, 1998[26]; Mechoulam et al., 1998[36]; Howlett, 1995[30]; Pertwee 1997[46]). Nor does it list cannabinoids once considered for development but later discontinued. An 18-year survey of analgesics in development in 1980—1998 found that six of the nine cannabinoids under development for analgesia were discontinued or undeveloped,[49,11] but work on most of these was halted before 1988, when the first endogenous cannabinoid receptor was discovered (chapter 3).

Three points can be made on the basis of Table 5.2. First, virtually all of the listed cannabinoids are being developed by small pharmaceutical companies or by individuals. In general, that implies that their development is considered especially risky from a commercial standpoint in that small companies are often willing to assume greater

development risks than larger more established firms (W. Schmidt, personal communication, 1998). Without the benefit of sales revenues, small companies are able to fund their research through financing from venture capital, stock offerings, and relationships with established pharmaceutical companies.[43]

Second, with the exception of THC, no constituents of the marijuana plant appear to be undergoing development by pharmaceutical companies. A number of plant compounds have been tested in experimental models and humans. For example, the antiemetic properties and negligible side effects of Δ^8-THC were demonstrated in a clinical trial in children who were undergoing cancer chemotherapy,[1] but no sponsor was interested in developing Δ^8-THC for commercial purposes (R. Mechoulam, Hebrew University, personal communication, 1998). The absence of plant cannabinoids under development implies that the specter of automatic placement in Schedule I under the CSA is an important deterrent, even though rescheduling would occur before marketing.[12] The point from the earlier discussion is that automatic, as opposed to *de novo*, scheduling appears to cast a pall over development of a cannabinoid found in the plant. Another impediment is that a cannabinoid extracted from the plant is not likely to fulfill the criteria for a product patent, although other forms of market protection are possible. Marinol, for example, was accorded orphan drug status and its manufacturer obtained a use patent.

Third, cannabinoids are being developed for therapeutic applications beyond those discussed earlier in this chapter and in chapter 4. One of the most prominent new applications of cannabinoids is for "neuroprotection," the rescue of neurons from cell death associated with trauma, ischemia, and neurological diseases.[29,36] Cannabinoids are thought to be neuroprotective--through receptor-dependent[51] as well as receptor-independent pathways; both THC, which binds to CB_1 receptors, and CBD, which does not, are potent antioxidants, effective neuroprotectants because of their ability to reduce the toxic forms of oxygen (free radicals) that are formed during cellular stress.[29] The synthetic cannabinoid HU-211 (dexanabinol) is an antioxidant and an antagonist of the NMDA receptor, rather than an agonist at the cannabinoid receptor.[52] Earlier research demonstrated that HU-211 protects neurons from neurotoxicity induced by excess concentrations of the excitatory neurotransmitter glutamate. Excess release of glutamate, which acts by binding to the NMDA receptor, is associated with trauma and disease.[54] As an NMDA antagonist, HU-211 blocks the damaging action of glutamate and other endogenous neurotoxic agents.[52,55] After having been studied in the United Kingdom in Phase I clinical trials, HU-211 progressed to Phase II clinical trials in Israel for treatment of severe closed-head trauma (Knoller et al., 1998).[35]

Market Prospects

It is difficult to gauge the market prospects for new cannabinoids. There certainly appears to be scientific interest, particularly for the discovery of new cannabinoids, but whether this interest can be sustained commercially through the arduous course of drug development is an open question. Research and development experience is limited; only one cannabinoid, dronabinol, is commercially available, and most of its research and

development costs were shouldered by the federal government. Furthermore, the size of dronabinol's market (at about $20 million) is modest by pharmaceutical company standards. None of the other cannabinoids in development has reached clinical testing in the United States. Their scientific, regulatory, and commercial fates are likely to be very important in shaping future investment patterns. Experience with the drug scheduling process also is likely to be watched very carefully. If the early products are heavily regulated in the absence of strong abuse liability, future development might be deterred. For the present, what seems to be clear from the dearth of products in development and the small size of the companies sponsoring them is that cannabinoid development is seen as especially risky.

One scenario is that cannabinoids will be pursued for lucrative markets that reflect large unmet medical needs. Of the therapeutic needs for which cannabinoid receptor agonists have been tested, analgesia is by far the largest. The annual U.S. prescription and over-the-counter analgesic market in 1997 was $4.4 billion.[49] Given the long-standing need for less addictive, safer, easier to use, and more effective drugs for acute and chronic pain, it would not be surprising to see cannabinoids developed to treat some segments of the current analgesic market, if their safety and effectiveness were clearly established in clinical trials.

In addition to cannabinoid receptor agonists, two classes of cannabinoid-related drugs might prove therapeutically useful: cannabinoid antagonists and inverse agonists, compounds that bind to receptors but produce effects opposite those of agonists. Neither would be subject to the same scheduling concerns as cannabinoid agonists because they are not found in marijuana and would be highly unlikely to have any abuse potential. Another set of cannabinoid-related drugs, such as those that affect the synthesis, uptake, or inactivation of endogenous cannabinoids might, however, have abuse potential because they would influence the signal strength of endogenous cannabinoids.

The development of specific cannabinoid antagonists, like SR141716A for CB_1 receptors and SR144528 for CB_2 receptors, has provided a substantial impetus to understand cannabinoid actions. Those compounds block many of the effects of THC in animals, and their testing in humans has just begun. Cannabinoid antagonists have physiological effects on their own, in the absence of THC. They might have important therapeutic potential in a variety of clinical situations. For example, THC reduces short-term memory, so it is possible that a CB_1 antagonist like SR141716A could act as a memory-enhancing agent. Similarly, for conditions in which cannabinoids decrease immune function (presumably by binding to CB_2 receptors in immune cells), a CB_2 antagonist might be useful as an immune stimulant.

Cannabinoid inverse agonists would exert effects opposite those of THC and might thus cause appetite loss, short-term memory enhancement, nausea, or anxiety. Those effects could possibly be separated by molecular design, in which case inverse agonists might have some therapeutic value. One report has been published suggesting that the CB_1 receptor antagonist, SR141617A,[11] is an inverse agonist, and there will likely be others.

REGULATION OF AND MARKET OUTLOOK FOR MARIJUANA

Marijuana is not legally marketed in the United States.[13] No sponsor has ever sought marketing approval from the FDA for medical use of marijuana. One sponsor has an IND for a clinical safety study on HIV anorexia (D. Abrams, University of California at San Francisco, personal communication, 1998). Another has an IND pending for the treatment of migraine headaches (E. Russo, Western Montana Clinic, personal communication, 1998). Since 1970, marijuana's manufacture and distribution have been tightly restricted under the CSA, which places marijuana in Schedule I, which is reserved for drugs or other substances with "a high potential for abuse," "no currently accepted medical use," and "lack of accepted safety for use . . . under medical supervision" (21 U.S.C. § 812 (b)(1)).

Marijuana has remained in Schedule I despite persistent efforts at rescheduling since the 1970s by advocacy groups, such as NORML. Through petitions to the DEA, advocacy groups contend that marijuana does not fit the legal criteria for a Schedule I substance, owing to its purported medical uses and lack of high abuse liability.[3,4,48] Another rescheduling petition, which was filed in 1995, is being evaluated by the FDA and DEA.

Availability for Research

To use marijuana for research purposes, researchers must register with the DEA, as well as adhere to other relevant requirements of the CSA and other federal statutes, such as the FD&C act. The National Institute on Drug Abuse (NIDA), one of the institutes of NIH, is the only organization in the United States licensed by the DEA to manufacture and distribute marijuana for research purposes. NIDA performs this function under its Drug Supply Program.[14] Through this program, NIDA arranges for marijuana, to be grown and processed through contracts with two organizations: the University of Mississippi and the Research Triangle Institute. The University of Mississippi grows, harvests, and dries marijuana; and the institute processes it into cigarettes. A researcher can obtain marijuana free of charge from NIDA through an NIH-approved research grant to investigate marijuana, or through a separate protocol review.[39] Research grant approvals are handled through the conventional NIH peer review process for extramural research, a highly competitive process with a success rate in 1997 of 32% of approved NIDA grants.[41] Through the separate protocol review, in which a researcher funds research independently of an NIH grant, NIDA submits the researcher's protocol to several external reviewers who evaluate the protocol on the basis of scientific merit and relevance to the mission of NIDA and NIH.

Through those two avenues marijuana has been supplied to several research groups--most of those that apply. While there has been much discussion of NIDA's alleged failure to supply marijuana for research purposes, we are unaware of recent cases in which they failed to supply marijuana to an investigator with an NIH-approved grant for research on marijuana. Donald Abrams's difficulty in obtaining research funding and marijuana from NIDA has been much discussed,[2] but the case of a single individual should not be

presumed to be representative of the community of marijuana researchers. Failure of investigators who apply to NIH for marijuana research grants to receive funding is hardly exceptional: in 1998 less than 25% of *all* first-time investigator-initiated grant applications (known as RO1s) to the NIH were funded.[38]

To import marijuana under the CSA for research purposes, the procedures are more complex. Under DEA regulations, marijuana can be imported, provided that the researcher is registered with the DEA, has approval for marijuana research (21 CFR § 1301.11, .13, and .18), and has a DEA-approved permit for importation (21 CFR § 1312.11, .12, and .13), and that the exporter in the foreign country has appropriate authorization by the country of exportation. Importation would enable U.S. researchers to conduct research on marijuana grown by HortaPharm, a company that has developed unique strains of marijuana. However, no U.S. researcher has imported HortaPharm's marijuana because Dutch authorities have refused to issue an export permit, despite the issuance of an import permit by the DEA (D. Pate, HortaPharm, personal communication, 1998).[15]

HortaPharm, which is in the Netherlands, grows marijuana as a raw material for the manufacture of pharmaceuticals. Through selective breeding and controlled production, HortaPharm has developed marijuana strains that feature single cannabinoids, such as THC or cannabidiol. The plants contain a consistently "clean" phytochemical profile and a higher concentration of THC (16%) or other desired cannabinoids than seized marijuana. Marijuana seized in the United States in 1996 had a THC content averaging about 5%.[16] Consistency of THC content is desirable because it overcomes the natural variability due to latitude, weather, and soil conditions. Product consistency is a basic tenet of pharmacology because it enables standardized dosing for regulatory and treatment purposes.

The difficulties of conducting research on marijuana were noted in the 1997 NIH report[40] that recommended that NIH facilitate clinical research by developing a centralized mechanism to promote design, approval, and conduct of clinical trials.

Regulatory Hurdles to Market

For marijuana to be marketed legally in the United States, a sponsor with sufficient resources would be obliged to satisfy the regulatory requirements of both the FD&C act and the CSA.

Under the FD&C act, a botanical product like marijuana *theoretically* might be marketed in oral form as a dietary supplement;[16] however, as a practical matter, only a new drug approval is likely to satisfy the provisions of the CSA, which require prescribing and distribution controls on drugs of abuse that also have an "accepted medical use." (The final paragraphs of this section clarify the criteria for "accepted medical use.")

Bringing marijuana to market as a new drug is uncharted terrain. The route is fraught with uncertainty for at least three pharmacological reasons: marijuana is a botanical product, it is smoked, and it is a drug with abuse potential. In general, botanical products are inherently more difficult to bring to market than are single chemical entities because they are complex mixtures of active and inactive ingredients. Concerns arise about product consistency, potency of the active ingredients, contamination, and stability of both active and inactive ingredients over time. These are among the concerns that a sponsor would have to overcome to meet the requirements for an NDA, especially those related to safety and to chemistry, manufacturing, and control.

A handful of botanical preparations are on the market, but none received formal approval as a new drug by today's standards of safety and efficacy (FDA, Center for Drug Evaluation and Research, personal communication, 1998). The three marketed botanical preparations are older drugs that came to market years before safety and efficacy studies were required by legislative amendments in 1938 and 1962, respectively. One of the botanical preparations is the prescription product digitalis. Because it came to market before 1938, it is available today, having been "grandfathered" under the law; but it does not necessarily meet contemporary standards for safety and effectiveness.[20] Two other botanical preparations, psyllium and senna, came to market between 1938 and 1962. Drugs entering the market during that period were later required to be evaluated by the FDA in what is known as the over-the-counter drug review process,[20] through which psyllium and senna were found to be generally recognized as safe and effective and so were allowed to remain on the market as over-the-counter drugs.[17] Although no botanical preparations have been approved as new drugs, it is important to point out that a number of individual plant constituents, either extracted or synthesized *de novo*, have been approved (for example, taxol and morphine). But these drug approvals were for single constituents rather than botanical preparations themselves. The FDA is developing guidance for industry to explain how botanicals are reviewed as new drugs, but the final document might not be available before 1999.

That marijuana is smoked might pose an even greater regulatory challenge. The risks associated with smoking marijuana are described in chapter 2. The FDA would have to weigh those risks with marijuana's therapeutic benefits to arrive at a judgment about whether a sponsor's NDA for marijuana met the requirements for safety and efficacy under the FD&C act. Marijuana delivered in a novel way that avoids smoking would overcome some, but not all, of the regulatory concerns. Vaporization devices that permit inhalation of plant cannabinoids without the carcinogenic combustion products found in smoke are under development by several groups; such devices would also require regulatory review by the FDA.

The regulatory hurdles to market posed by the CSA are formidable but not insurmountable. If marijuana received market approval as a drug by the FDA, it would most likely be rescheduled under the CSA, as was the case for dronabinol. That is because a new drug approval satisfies the "accepted medical use" requirement under the CSA for manufacture and distribution in commerce.[13] But a new drug approval is not the *only* means to reschedule marijuana under the CSA.[14] For years advocates for

rescheduling have argued that marijuana does enjoy "accepted medical use," even in the absence of a new drug approval. Although advocates have been unsuccessful in rescheduling efforts, their actions prompted the DEA to specify the criteria by which it would determine whether a substance had "accepted medical use." In the DEA's 1992 denial of a rescheduling petition, it listed these elements as constituting "accepted medical use": the drug's chemistry must be known and reproducible, there must be adequate safety studies, there must be adequate and well-controlled studies proving efficacy, the drug must be accepted by qualified experts, and the scientific evidence must be widely available.[14]

Assuming that all of those criteria were satisfied, marijuana could be rescheduled--but into which schedule? The level of scheduling would be dictated primarily by a medical and scientific recommendation to the DEA made by the secretary of DHHS.[18] As noted earlier, this recommendation is determined by the five scheduling criteria listed in the CSA. However, scheduling in a category less restrictive than Schedule II might be prohibited by international treaty obligations. The Single Convention on Narcotic Drugs, a treaty ratified by the United States in 1967, restricts scheduling of the plant and its resin to at least Schedule II (the more restrictive Schedule I is another option).[13]

Market Outlook

The market outlook for the development of marijuana as a new drug, on the basis of the foregoing analysis, is not favorable, for a host of scientific, regulatory, and commercial reasons. From a scientific point of view, research is difficult because of the rigors of obtaining an adequate supply of legal, standardized marijuana for study. Further scientific hurdles are related to satisfying the exacting requirements for FDA approval of a new drug. The hurdles are even more exacting for a botanical product because of the inherent problems with, for example, purity and consistency. Finally, the health risks associated with smoking pose another barrier to FDA approval unless a new smoke-free route of administration is demonstrated to be safe. Depending on the route of administration, an additional overlay of regulatory requirements might have to be satisfied.

From a commercial point of view, uncertainties abound. The often-cited cost of new drug development, about $200—$300 million, might not apply, but there are probably additional costs needed to satisfy the FDA's requirements for a botanical product. As noted above, no botanical products have ever been approved as new drugs by the FDA under today's stringent standards for safety and efficacy. Satisfying the legal requirements of the CSA also will add substantially to the cost of development. On the positive side, so much research already has been done that some development costs will be lower. The cost of bringing dronabinol to market, for example, was reduced dramatically as a result of clinical trials supported with government funding. Nevertheless, it is impossible to estimate the cost of developing marijuana as a new drug. Estimating return on investment is similarly difficult. A full-fledged market analysis would be required for the indication being sought. Such an analysis would take into

account the market limitations resulting from drug scheduling restrictions, stigma, and patentability.

The plant does not constitute patentable subject matter under U.S. patent law because it is unaltered from what is found in nature. So-called products of nature are not generally patentable.[28] New marijuana strains, however, could be patentable in the United States under a product patent or a plant patent because they *are* altered from what is found in nature. (A product patent prohibits others from manufacturing, using, or selling each strain for 20 years; a plant patent carries somewhat less protection.) HortaPharm has not yet sought any type of patent for its marijuana strains in the United States, but it has received approval for a plant registration in Europe (David Watson, HortaPharm, personal communication, 1998).

In short, development of the marijuana plant is beset by substantial scientific, regulatory, and commercial obstacles and uncertainties. The prospects for its development as a new drug are unfavorable unless return on investment is not a driving force. It is noteworthy that no pharmaceutical firm has sought to bring it to market in the United States. The only interest in its development appears to be in England in a small pharmaceutical firm (see Boseley, 1998[10]) and in the United States among physicians without formal ties to pharmaceutical firms (D. Abrams, University of California at San Francisco, and E. Russo, Western Montana Clinic, personal communications, 1998).

CONCLUSIONS

Cannabinoids are an interesting group of compounds with potentially far-reaching therapeutic applications. There is a surge of scientific interest in their development as new drugs, but the road to market for any new drug is expensive, long, risky, and studded with scientific, regulatory, and commercial obstacles. Experience with the only approved cannabinoid, dronabinol, might not illuminate the pathway because of the government's heavy contribution to research and development, drona-binol's scheduling history, and its small market.

There appear to be only two novel cannabinoids actively being developed for human use, but they have yet to be tested in humans in the United States. Their experience is likely to be more predictive of the marketing prospects for other cannabinoids. It is too early to forecast the prospects for cannabinoids, other than to note that their development at this point is considered to be especially risky, to judge by the paucity of products in development and the small size of the pharmaceutical firms sponsoring them.

The market outlook in the United States is distinctly unfavorable for the marijuana plant and for cannabinoids found in the plant. Commercial interest in bringing them to market appears nonexistent. Cannabinoids in the plant are automatically placed in the most restrictive schedule of the Controlled Substances Act, and this is a substantial deterrent to development. Not only is the plant itself subject to the same scheduling strictures as are individual plant cannabinoids, but development of marijuana also is

encumbered by a constellation of scientific, regulatory, and commercial impediments to availability.

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Notes

[1] FDA policies for off-label use are being transformed as a result of the Food and Drug Administration Modernization Act of 1997. The FDA recently promulgated new rules to give manufacturers greater flexibility to disseminate information about off-label uses (FDA, 1998b[24a]). As of this writing, however, court decisions have left the status of the new rules somewhat unclear.

[2] The FDA can grant orphan designation to a drug intended for a condition that affects a larger population if the manufacturer's estimated expenses are unlikely to be recovered by sales in the United States (Public Law 98-551).

[3] Marijuana cigarettes were available under a special FDA-sponsored Compassionate Investigational New Drug Program for desperately ill patients until March 1992, when the program was closed to new participants.[48]

[4] The FDA and the National Institute of Drug Abuse, two agencies of DHHS, work jointly to develop the medical and scientific analysis that is forwarded to the secretary, who makes a recommendation to the administrator of the DEA (DEA, 1998[15]).

[5] Under the CSA, "the recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance" (21 U.S.C.§ 811 (b)).

[6] Technically, the CSA and the regulations use the term "tetrahydrocannabinols."

[7] The only cannabinoid licensed outside the United States is nabilone (Cesamet), which is an analogue of THC available in the United Kingdom for the management of nausea and vomiting associated with cancer chemotherapy (Pertwee, 1997).[46]

[8] A use patent--also known as a process patent--accords protection for a method of using a composition or compound. A use patent is not considered as strong as a product patent, which prohibits others from manufacturing, using, or selling the product for all uses, rather than for the specific use defined in a use patent.

[9] The DEA did not provide an estimate of the weight of marijuana per bag.

[10] Information about the existence of an IND is proprietary; it can be confirmed only by the manufacturer, not the FDA.

[11] Discontinued: levonantradol, nabitan, nantradol, and pravadoline. Undeveloped: CP-47497 and CP-55244.

[12] As a result of the FDA's approval of an NDA, the drug would be, at a minimum, rescheduled in Schedule II. Depending on abuse liability data supplied by the manufacturer and the FDA's recommendation, the drug could be moved to a less restrictive schedule or be descheduled.

[13] Under the CSA, its only legal use is in research under strictly defined conditions.

[14] This is also the program through which several patients receive marijuana under a compassionate use program monitored by the FDA. For history and information on this effort, see Randall (1993).[48]

[15] It might eventually be possible to import HortaPharm's marijuana from England, where HortaPharm is growing its marijuana strains for research use in clinical trials for multiple sclerosis (Boseley, 1998).[10] England, as the country of origin, would have to provide appropriate authorization for export of the strains to the United States. Permission to export for research purposes is part of the basis for HortaPharm's participation in this project with GW Pharmaceuticals through a special set of licenses with the British Home Office (David Pate, HortaPharm, personal communication, 1998).

[16] Inhaled products may not lawfully be marketed as dietary supplements.

[17] Over-the-counter monographs for these products have been issued as tentative final monographs (proposed rules) but have not yet been issued in final form as final rules (FDA, Center for Drug Evaluation and Research, personal communication, 1998).

[18] At present, there is no practical mechanism for generating such a recommendation outside the new drug approval process, although such a mechanism could, theoretically, be developed.[33]

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LAWRENCE G. KEANE
SENIOR VICE PRESIDENT
& GENERAL COUNSEL

June 6, 2016

Bureau of Alcohol, Tobacco, Firearms and Explosives
Attn: Carolyn King
Firearms Industry Programs Branch
99 New York Avenue, NE
Mailstop 6.N-672
Washington, DC 20226

Re: Federal Register Notice ATF 4473, Doc. No. 2016-07970, Vol. 81, No. 67, P. 20424, Published April 7, 2016.

Dear Ms. King:

The National Shooting Sports Foundation (NSSF) is the trade association for America's firearms, ammunition, hunting, and recreational shooting sports industry. On behalf of our over 13,000 members, we appreciate the opportunity to submit comments regarding the Bureau of Alcohol, Tobacco, Firearms and Explosives' (ATF) proposed revision to ATF Form 4473 (5300.9).

From hosting regularly held retailer education seminars across the country, to the annual Firearms Industry Compliance Conference, and providing members with site visits by one of NSSF's FFL Compliance Consultants, NSSF champions compliance as part and parcel of its mission to promote, protect, and preserve hunting and the shooting sports. Federal Firearms Licensees (FFLs) cannot afford to make any mistakes when their licenses are on the line each time they open their doors for business. What may be viewed as a small oversight by a customer filling out an ATF Form 4473 will not be viewed in the same light by the ATF during an inspection. Through its many efforts to ensure FFLs have all the tools in their toolkit necessary to operate within the bounds of the law, NSSF works tirelessly to promote industry compliance with all regulations.

NSSF is pleased by many of the updates reflected in the proposed Revised Form 4473. We believe the proposed revised form contains many well drafted changes that should make it easier for the firearms transferee to complete the form, such as the revisions in the area of citizenship and alien information. These comments are offered as additional clarifications to the form that will help both the FFL and the transferee complete the form accurately.

I. Block 2.

First, the size of the space provided for "County" could be increased by moving the "State" and "Zip Code" blocks two spaces to the right. While a zip code is only five numbers in length, many counties have very lengthy names and the limited space tends to leave the incorrect impression with transferees that the county name can be abbreviated.

Second, a change should be made to address those people who do not live in counties. For example, there are independent cities in Virginia, Missouri, and Maryland that are not part of a county. We suggest that a sentence be added to the instructions for Block 2, which states: "Transferees who do not reside in a county, such as in an independent city, should record 'No County' in the County block." This additional instruction will eliminate guesswork on the part of the transferee and FFL.

II. Block 12a.

The instruction to Block 12a directs the transferee that "Nationals of the United States may check U.S.A.", however "U.S.A." is not an option provided below. There is sufficient room in this block to write out "United States of America" as it appears in the selection options.

III. Blocks 14, 23, and 37.

Blocks 14, 23, and 37 contain signature dates. We recommend that "Month/Day/Year" be added to these blocks. Many transferees use the European or military way of recording dates, which is "Day/Month/Year." This can and is misread by FFLs and ATF IOIs alike. The addition of "Month/Day/Year" would allow for the consistent recording of dates.

IV. Block 21.

Additional room should be provided for the "Issuing State and Permit Type" as licensees have encountered Industry Operations Investigators who insist the full permit name, such as "Connecticut State Permit to Carry Pistols and Revolvers," be written out without abbreviations.

V. Block 24.

Rather than "Manufacturer and Importer (if any)" perhaps consider "Manufacturer and Importer (if imported)" to avoid potential confusion.

VI. Blocks 24 through 28.

NSSF recommends that the first sentence of the instructions for these blocks be changed from "These blocks must be completed with the firearm(s) information" to "These blocks must be completed with the information on the firearm(s) proposed to be transferred prior to the initiation of the NICS or State background check on the transferee."

VII. Block 30.

Consider adding "from Item 24 above" after "Line Number(s):".

VIII. Block 31.

The space provided in this block is much smaller compared to previous block 30c and the provision of additional space may be helpful.

IX. Block 33.

The business name and FFL should not be combined on the same line and the space should be larger to allow for the use of a stamp.

X. Blocks 34 through 37.

There are no instructions for completing blocks 34 through 37. At many FFLs with transactions denied or cancelled by NICS, NSSF consultants find the Forms 4473 are not signed. NSSF suggests that even though the form is fairly clear, that instructions for signing the form, including when to sign the form, be included on the revised form.

XI. Additional Comments.

Whether by oversight or intention, we wish to point attention to the fact that current Form 4473 Block 13, state of residence, is not on the revised form.

The addition of an optional line for a phone number might be beneficial as many FFLs currently request this information from their customers.

XII. Conclusion.

Again, NSSF appreciates this opportunity to comment on proposed revisions to ATF Form 4473 and we welcome any questions you might have.

Sincerely,

Lawrence G. Keane

Lawrence G. Keane

U.S. Department of Justice

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Re: Federal Register Notice, OMB Number 1140-0020, Proposed Collection of Information Relating to Revision of ATF Form 4473 (5300.9) (April 7, 2016)

Dear Messrs. Kraut and Prince:

This responds to the comments you submitted to the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) dated June 6, 2015 [sic], regarding ATF's revised collection of information on ATF Form 4473 under OMB Number 1140-0020. ATF submitted the revised information collection request to the Office of Management and Budget (OMB) for review and approval in accordance with the Paperwork Reduction Act of 1995. ATF responds as follows.

ATF's Authority to Publish ATF Form 4473 and Relevant Definitions

You first commented that ATF is not the appropriate agency for drafting, modifying or amending ATF Form 4473, or for defining or clarifying what constitutes an "unlawful user of or addicted to any controlled substance" or "fugitive from justice" because the Federal Bureau of Investigation (FBI) is the agency empowered to interpret 18 U.S.C. § 922(g).

ATF disagrees with your assertion that it is not responsible for interpreting 18 U.S.C. § 922(g), including the definitions of "unlawful user of or addicted to any controlled substance" or "fugitive from justice." While the FBI was granted the authority to establish and maintain the National Instant Criminal Background Check System (NICS), ATF is the agency responsible for interpreting the provisions of the Gun Control Act (GCA), including its statutory terms.

By way of background, the first Form 4473 was issued by ATF's predecessor agency in 1968 for use by licensed importers, manufacturers, and dealers. In 1972, ATF became an independent Bureau under the U.S. Department of the Treasury and Form 4473 was revised to reflect that change. ATF was expressly delegated the authority to perform the functions, exercise the powers, and carry out the duties of the Secretary of the Treasury in the administration and

enforcement of the GCA, among other laws. *See* 37 FR 11696-97 (June 10, 1972). In 2002, Congress passed Section 1111 of the Homeland Security Act (codified at 28 U.S.C. § 599A) which transferred ATF to the U.S. Department of Justice. Among other authorities, that Act expressly conferred on ATF the responsibility for investigating criminal and regulatory violations of the GCA, and any other function related to the investigation of violent crime delegated by the Attorney General. The Attorney General then expressly delegated to ATF the authority to "[i]nvestigate, administer, and enforce the laws related to … firearms … and perform other duties as assigned by the Attorney General, including exercising the functions and powers of the Attorney General" under the GCA. 28 C.F.R. § 0.130(a)(1). Indeed, after the Brady law was passed, ATF used its delegated authority to promulgate implementing regulations, including definitions for the various prohibited persons in section 922(g).[1]

ATF also exercised its delegated authority to issue Form 4473. The GCA at 18 U.S.C. § 923(g)(1)(A) states, in relevant part, that each licensed importer, licensed manufacturer, and licensed dealer shall maintain such records of sale or other disposition of firearms at his place of business for such period, and in such form, as the Attorney General may by regulations prescribe. Additionally, 18 U.S.C. § 926(a) authorizes the Attorney General to prescribe rules and regulations that are necessary to carry out the provisions of the GCA. Based on these authorities, ATF as the delegate of the Attorney General promulgated 27 C.F.R. § 478.124, which states, in relevant part, that a licensed importer, licensed manufacturer, or licensed dealer shall not sell or otherwise dispose of any firearm to an unlicensed person unless the licensee records the transaction on a firearms transaction record, Form 4473. ATF also promulgated 27 C.F.R. § 478.21(a) which provides the following:

> The Director is authorized to prescribe all forms required by this part. All of the information called for in each form shall be furnished as indicated by the headings on the form and the instructions on or pertaining to the form. In addition, information called for in each form shall be furnished as required by this part.

Thus, ATF's authority to promulgate rules and issue Form 4473 is well-established, and has been upheld in court.[2]

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[1] *See* 62 FR 34634 (June 27, 1997) (Definitions for Prohibited Persons); 63 FR 58271 (October 29, 1998) (Final Rule implementing Public Law 103-159 Relating to the Permanent Provisions of the Brady Act).

[2] *See, e.g., Armalite v. Lambert*, 512 F. Supp. 2d 1070, 1081 (N.D. Ohio 2007), *aff'd*, 544 F.3d 644 (6th Cir. 2008) (rejecting a challenge to ATF's authority requiring completion of certain items on ATF Form 4473, in light of 18 U.S.C. §§ 923(g)(1)(A) and 926(a)); *RSM v. Herbert*, 2006 U.S. Dist. LEXIS 97237 (D.Md 2006), *aff'd*, 466 F.3d 316 (4th Cir. 2006) (ATF has authority, pursuant to section 926, to promulgate rules necessary to carry out the provisions of Chapter 44, and is accorded great deference to its longstanding interpretations of law); and *Nat'l Rifle Ass'n v. Brady*, 914 F.2d 475, 479 (4th Cir. 1990) (ATF had authority under section 926 to promulgate and implement such regulations as are necessary to carry out the purposes of the Gun Control Act, and is entitled to deference in determining which regulations are necessary).

Adam Kraut, Counsel
Joshua Prince, Chief Counsel
Firearms Industry Consulting Group

Proposed Revision to Instructions for Question 11.d

In your comments, you question ATF's definition of "fugitive from justice" when it modified the federal regulations in 1997, and allege that ATF did not give a 90-day notice and comment period, pursuant to 18 U.S.C. § 926(b), to include this definition on the revised form. However, as you point out, ATF added the regulatory definition of "fugitive from justice" when it amended its regulations in 1997. Because the revised Form 4473 merely restates the same definition it promulgated years ago, *see* 27 C.F.R. § 478.11 (regulatory definition of "fugitive from justice"), your comment challenging that definition is beyond the scope of the current Federal Register notice. ATF is not currently amending the definition of "fugitive from justice" it promulgated in 1997, and ATF is not reconsidering that definition.

Moreover, even though the current notice does not make any changes to the regulatory definition of "fugitive from justice," or to any promulgated rules or regulations, there was, in fact, a 90-day notice and comment period – one 60-day period, followed by a current 30-day period – in accordance with the Paperwork Reduction Act of 1995, 44 U.S.C. §§ 3506(c)(2)(A), 3507(b). *See* 81 FR 20424 (April 7, 2016); 81 FR 48847 (July 26, 2016). Thus, all persons were given formal notice and had a substantial opportunity to comment on the revised Form 4473, which should address any concerns regarding transparency and participation.

Proposed Revision to Question 11.e

In its notice, ATF proposes to revise Form 4473 to include a warning that marijuana use or possession remains unlawful under Federal law regardless of whether it has been decriminalized for medicinal or recreational purposes in the State where the transferee resides. In your comment, you requested that ATF specifically find that users of state-licensed physician prescribed marijuana for medicinal purposes are not "unlawful users of or addicted to any controlled substance" pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11.

ATF cannot accept your suggestion. As ATF explained in its Open Letter to All Federal Firearms Licensees dated September 21, 2011, marijuana is expressly listed in the Controlled Substances Act (and ATF regulations) as a controlled substance. 21 U.S.C. § 812(c)(Schedule I)(c)(10); 27 C.F.R. § 478.11. Controlled substances in Schedule I are defined as having "a high potential for abuse," "no currently accepted medical use in treatment in the United States," and "a lack of accepted safety for use of the drug or other substance under medical supervision." 21 U.S.C. § 812(b)(1). There are no exceptions for medical purposes.[3]

Because marijuana cannot be prescribed by a licensed physician consistent with Federal law, anyone who currently uses it, whether for "medical" purposes or otherwise, is by definition an

[3] *See U.S. v. Oakland Cannabis Buyers' Coop.*, 532 U.S. 483, 491 (2001) ("[M]arijuana has no medical benefits worthy of an exception (outside the confines of a Government-approved research project). Whereas some other drugs can be dispensed and prescribed for medical use, see 21 U.S.C. § 829, the same is not true for marijuana.").

"unlawful user of a controlled substance".[4] Recognizing this impossibility, most, if not all of the States that permit the use of medical marijuana have carefully avoided using the word "prescribe" in their laws in favor of authorizing individuals to use medical marijuana when *advised* or *recommended* by a physician. *See, e.g.*, Cal. Health & Safety § 11362.5(b)(1)(A); Nev. Rev. St. § 453A.210; Ore. Rev. Stat. § 475B.415(2)(a). Since it cannot be prescribed, the revised form instruction properly warns marijuana users and possessors of their potential violation of section 922(g)(3), and it does not conflict with ATF regulations.[5]

Proposed Revision to the Instructions for Box 20

You commented that because Pennsylvania is a "point of contact state" for utilizing NICS all firearms background checks must go through the Pennsylvania State Police. And because silencers are not defined as "firearms" under Pennsylvania law, you allege that FFLs cannot comply with the instruction for Question 20 which requires background checks when no background check was conducted through the NFA approval process.

As a threshold matter, we do not believe that many background checks would need to be conducted on silencer transfers at a Federal firearms licensee's (FFL's) premises. This is because almost all individuals receiving silencers from FFLs will have undergone a background check during the NFA approval process. Assuming that a background check is required in a given case, we understand that Pennsylvania FFLs can arrange to conduct these particular checks directly with NICS. No change to the instruction is necessary.

Fields for Firearms Received on Behalf of Legal Entities

You request that ATF create a field that would allow licensees to record that the firearm is being disposed of to a legal entity, and include an area for the licensee or transferee/buyer to list the name and address of the legal entity. We agree that such additions may be useful, and already considered adding fields for legal entities. Unfortunately, adding those fields would require substantial revisions to the format and increase the length of the form. While we are unable to make those revisions at this time, we will revisit the possibility of adding those fields on the next version of the form. We encourage you to resubmit this comment along with any recommendations as to the format of those items.

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[4] *See also Wilson v. Holder*, 7 F.Supp.2d 1104, 1118 n.3 (D.Nev. 2014) ("Plaintiff's argument that the policy in the Open Letter violates the Second Amendment because 'more than half of the U.S. population' uses marijuana is absurd at best. The mere fact that many people engage in illegal activity does not alter the illegal nature of the activity. Furthermore, the fact that the use of marijuana may be legal under the laws in some states does not later the illegality of this use under federal law.")

[5] As to commenters' suggested alternative that ATF delay until DEA makes a determination whether marijuana should be "removed from or rescheduled under the CSA," ATF will revisit the form instructions if that occurs.

Adam Kraut, Counsel
Joshua Prince, Chief Counsel
Firearms Industry Consulting Group

Certification Statement for Transferors

Finally, you commented that the transferor's certification statement should be revised with respect to its reference to ATF's State Laws and Ordinances Publication (5300.5) because it may not include the most recent amendments of applicable State laws and published ordinances.

ATF agrees with this comment. There may be State laws and ordinances that are not included in the most recent edition of ATF's State Laws and Published Ordinances. For this reason, we have revised the certification to reference "State or local law applicable to the firearms business," rather than ATF Publication 5300.5, State Laws and Published Ordinances.

We trust the foregoing has been responsive to your comments.

Sincerely yours,

Krissy Y. Carlson
Chief, Firearms and Explosives Industry Division

U.S. Department of Justice

Bureau of Alcohol, Tobacco,
Firearms and Explosives

Firearms and Explosives Industry Division

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200000:EME

Thomas R. Beveridge, Chief Counsel
Cannabis Industry Law Group
934 E. High Street
Pottstown, PA 19464

Re: Federal Register Notice, OMB Number 1140-0020, Proposed Collection of Information Relating to Revision of ATF Form 4473 (5300.9) (April 7, 2016)

Dear Mr. Beveridge:

This responds to the comments you submitted to the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) dated June 6, 2015 [sic], regarding ATF's revised collection of information on ATF Form 4473 under OMB Number 1140-0020. ATF submitted the revised information collection request to the Office of Management and Budget (OMB) for review and approval in accordance with the Paperwork Reduction Act of 1995. ATF responds as follows.

ATF's Authority to Publish Form 4473 and Relevant Definition

You first commented that ATF is not the appropriate agency for drafting, modifying or amending ATF Form 4473, or for defining or clarifying what constitutes an "unlawful user of or addicted to any controlled substance" because the Drug Enforcement Administration (DEA) is the agency empowered to interpret that term.

ATF disagrees with your assertion that it is not the agency responsible for defining the term "unlawful user of or addicted to any controlled substance" under 18 U.S.C. § 922(g)(3). While the DEA may have been delegated authority to interpret provisions of the Controlled Substances Act (21 U.S.C., Chapter 13), ATF is the agency responsible for interpreting the provisions of the Gun Control Act (GCA), including section 922(g)(3).

By way of background, the first Form 4473 was issued by ATF's predecessor agency in 1968 for use by licensed importers, manufacturers and dealers. In 1972, ATF became an independent Bureau under the U.S. Department of the Treasury and Form 4473 was revised to reflect that change. ATF was expressly delegated the authority to perform the functions, exercise the powers, and carry out the duties of the Secretary of the Treasury in the administration and

enforcement of the GCA, among other laws. *See* 37 FR 11696-97 (June 10, 1972). In 2002, Congress passed Section 1111 of the Homeland Security Act (codified at 28 U.S.C. § 599A) which transferred ATF to the U.S. Department of Justice. Among other authorities, that Act expressly conferred on ATF the responsibility for investigating criminal and regulatory violations of the GCA, and any other function related to the investigation of violent crime delegated by the Attorney General. The Attorney General expressly delegated to ATF the authority to "[i]nvestigate, administer, and enforce the laws related to … firearms … and perform other duties as assigned by the Attorney General, including exercising the functions and powers of the Attorney General" under the GCA. 28 C.F.R. § 0.130(a)(1). Indeed, after the Brady law was passed, ATF used its delegated authority to promulgate implementing regulations, including the definitions for the various prohibited persons in section 922(g).[1]

ATF also exercised its delegated authority to issue Form 4473. The GCA at 18 U.S.C. § 923(g)(1)(A) states, in relevant part, that each licensed importer, licensed manufacturer, and licensed dealer shall maintain such records of sale or other disposition of firearms at his place of business for such period, and in such form, as the Attorney General may by regulations prescribe. Additionally, 18 U.S.C. § 926(a) authorizes the Attorney General to prescribe rules and regulations that are necessary to carry out the provisions of the GCA. Based on these authorities, ATF as the delegate of the Attorney General promulgated 27 C.F.R. § 478.124, which states, in relevant part, that a licensed importer, licensed manufacturer, or licensed dealer shall not sell or otherwise dispose of any firearm to an unlicensed person unless the licensee records the transaction on a firearms transaction record, Form 4473. ATF also promulgated 27 C.F.R. § 478.21(a) which provides the following:

> The Director is authorized to prescribe all forms required by this part. All of the information called for in each form shall be furnished as indicated by the headings on the form and the instructions on or pertaining to the form. In addition, information called for in each form shall be furnished as required by this part.

Thus, ATF's authority to promulgate rules and issue Form 4473 is well-established, and has been upheld in court.[2]

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[1] *See* 62 FR 34634 (June 27, 1997) (Definitions for Prohibited Persons); 63 FR 58271 (October 29, 1998) (Final Rule implementing Public Law 103-159 Relating to the Permanent Provisions of the Brady Act).

[2] *See, e.g., Armalite v. Lambert*, 512 F. Supp. 2d 1070, 1081 (N.D. Ohio 2007), *aff'd*, 544 F.3d 644 (6th Cir. 2008) (rejecting a challenge to ATF's authority requiring completion of certain items on ATF Form 4473, in light of 18 U.S.C. §§ 923(g)(1)(A) and 926(a)); *RSM v. Herbert*, 2006 U.S. Dist. LEXIS 97237 (D.Md. 2006), *aff'd*, 466 F.3d 316 (4th Cir. 2006) (ATF has authority, pursuant to section 926, to promulgate rules necessary to carry out the provisions of Chapter 44, and is accorded great deference to its longstanding interpretations of law); and *Nat'l Rifle Ass'n v. Brady*, 914 F.2d 475, 479 (4th Cir. 1990) (ATF had authority under section 926 to promulgate and implement such regulations as are necessary to carry out the purposes of the Gun Control Act, and is entitled to deference in determining which regulations are necessary).

Thomas R. Beveridge, Chief Counsel
Cannabis Industry Law Group

Proposed Revision to Question 11.e

In its notice, ATF proposes to revise Form 4473 to include a warning that marijuana use or possession remains unlawful under Federal law regardless of whether it has been decriminalized for medicinal or recreational purposes in the State where the transferee resides. In your comment, you requested that ATF specifically find that users of state-licensed physician prescribed marijuana for medicinal purposes are not "unlawful users of or addicted to any controlled substance," pursuant to 18 U.S.C. § 922(g)(3) and 27 C.F.R. § 478.11.

ATF cannot accept your suggestion. As ATF explained in its Open Letter to All Federal Firearms Licensees dated September 21, 2011, marijuana is expressly listed in the Controlled Substances Act (and ATF regulations) as a controlled substance. 21 U.S.C. § 812(c)(Schedule I)(c)(10); 27 C.F.R. § 478.11. Controlled substances in Schedule I are defined as having "a high potential for abuse," "no currently accepted medical use in treatment in the United States," and "a lack of accepted safety for use of the drug or other substance under medical supervision." 21 U.S.C. § 812(b)(1). There are no exceptions for medical purposes.[3]

Because marijuana cannot be prescribed by a licensed physician consistent with Federal law, anyone who currently uses it, whether for "medical" purposes or otherwise, is by definition an "unlawful user of a controlled substance".[4] Recognizing this impossibility, most, if not all of the States that permit the use of medical marijuana have carefully avoided using the word "prescribe" in their laws in favor of authorizing individuals to use medical marijuana when *advised* or *recommended* by a physician. *See, e.g.*, Cal. Health & Safety § 11362.5(b)(1)(A); Nev. Rev. St. § 453A.210; Ore. Rev. Stat. § 475B.415(2)(a). Since it cannot be prescribed, the revised Form 4473 properly warns marijuana users and possessors of their potential violation of section 922(g)(3), and the instruction does not conflict with ATF regulations.[5]

ATF's Regulatory Definition of "Unlawful User"

Finally, in your comments (p.7, note 7) you allege that ATF revised its regulatory definition of "unlawful user of or addicted to any controlled substance" by not recognizing that a patient may use state-licensed prescribed marijuana for medicinal purposes. You further asserted that ATF failed to provide 90-days public notice and comment as required to amend GCA rules, pursuant to 18 U.S.C. § 926(b).

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[3] *See U.S. v. Oakland Cannabis Buyers' Coop.*, 532 U.S. 483, 491 (2001) ("[M]arijuana has no medical benefits worthy of an exception (outside the confines of a Government-approved research project). Whereas some other drugs can be dispensed and prescribed for medical use, see 21 U.S.C. § 829, the same is not true for marijuana.").

[4] *See also Wilson v. Holder*, 7 F.Supp.2d 1104, 1118 n.3 (D.Nev. 2014) ("Plaintiff's argument that the policy in the Open Letter violates the Second Amendment because 'more than half of the U.S. population' uses marijuana is absurd at best. The mere fact that many people engage in illegal activity does not alter the illegal nature of the activity. Furthermore, the fact that the use of marijuana may be legal under the laws in some states does not later the illegality of this use under federal law.")

[5] As to commenter's suggested alternative that ATF delay until DEA makes a determination whether marijuana should be "removed from or rescheduled under the CSA," ATF will revisit the form instructions if that occurs.

Thomas R. Beveridge, Chief Counsel
Cannabis Industry Law Group

As explained previously, ATF's form instruction is fully consistent with the regulatory definition of "unlawful user." Moreover, since ATF did not create or amend a rule or regulation, 90-days public notice was not required pursuant to section 926(b). Nonetheless, even though the current notice does not make any changes to any promulgated rules or regulations, there was, in fact, a 90-day notice and comment period – one 60-day period, followed by a current 30-day period – in accordance with the Paperwork Reduction Act of 1995, 44 U.S.C. §§ 3506(c)(2)(A), 3507(b). *See* 81 FR 20424 (April 7, 2016); 81 FR 48847 (July 26, 2016). Thus, all persons were given formal notice and had a substantial opportunity to comment on the revised Form 4473, as you have, which should address any concerns regarding transparency and participation.

We trust the foregoing has been responsive to your comments.

Sincerely yours,

Krissy Y. Carlson
Chief, Firearms and Explosives Industry Division

U.S. Department of Justice

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Re: Federal Register Notice, OMB Number 1140-0020, Proposed Collection of Information Relating to Revision of ATF Form 4473 (5300.9) (April 7, 2016)

Dear Mr. Conte:

This responds to your letter on behalf of the National Rifle Association (NRA) to the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) dated May 26, 2016, commenting on ATF's revised collection of information on ATF Form 4473 under OMB Number 1140-0020. ATF submitted the revised information collection request to the Office of Management and Budget (OMB) for review and approval in accordance with the Paperwork Reduction Act of 1995.

NRA commented that it believes the portions of the form requiring that the form be completed only at the licensed premises amount to a legislative rule that may only be adopted pursuant to notice and comment rulemaking in accordance with the Administrative Procedure Act (APA), 5 U.S.C. §§ 551-559 (2012). In support of this comment, NRA cites three APA cases: *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106 (D.C. Cir. 1993); *Appalachian Power Co. v. E.P.A.*, 208 F.3d 1015 (D.C. Cir. 2000); and *Catholic Health Initiatives v. Sebelius*, 617 F.3d 490 (D.C. Cir. 2010). NRA also asserts that because ATF allows licensees to display firearms and take orders for firearms away from the licensed premises, ATF has not explained its rationale for requiring some activities to be conducted at the licensed premises while others may be conducted elsewhere. ATF responds to NRA's comments as follows.

ATF Provided Notice and Comment

ATF provided formal notice of revisions to Form 4473 in the Federal Register, and a 60-day comment period followed by a 30-day comment period in accordance with the Paperwork Reduction Act of 1995, 44 U.S.C. §§ 3506(c)(2)(A); 3507(b). *See* 81 FR 20424 (April 7, 2016); 81 FR 48847 (July 26, 2016). None of the cases cited by NRA involve a form to be approved by

OMB after a formal notice and comment period. *See Am. Mining*, 995 F.2d at 1107 (program policy letters); *Appalachian Power*, 208 F.3d at 1107 ("Periodic Monitoring Guidance"); *Catholic Health*, 617 F.3d at 491 ("Provider Reimbursement Manual"). Thus, like NRA, all persons were given formal notice and had a substantial opportunity to comment on the revised Form 4473 which satisfies the APA's goals of transparency and participation. In fact, NRA was the only commenter to express any concerns regarding these particular revisions to the form. ATF believes the lack of comments on this issue is because licensees have understood since 1968 that Form 4473 (Part I) is an over-the-counter transaction record that must be completed at the licensed premises.

ATF May Interpret the Law without Notice and Comment Rulemaking

Even if ATF's clarifying revisions are considered a "rule" under the APA, they are an interpretive rule which reflect ATF's longstanding interpretation of the Gun Control Act (GCA) and its implementing regulations. As NRA recognized in its letter, interpretive rules under the APA, 5 U.S.C. § 553(b)(3)(A), are not subject to notice and comment rulemaking. *See, e.g., McKenzie v. Bowen*, 787 F.2d 1216 (8th Cir. 1986) (rulemaking not required when Social Security Administration published a method for calculating benefit payments based on its interpretation of a statute). "Interpretive rules … are 'issued … to advise the public of the agency's construction of the statutes and rules which it administers.'" *Perez v. Mortgage Bankers Assn*, 135 S.Ct. 1199, 1201 (2015) (*quoting Shalala v. Guernsey Memorial Hospital*, 514 U. S. 87, 99 (1995)). Amending the form to incorporate instructions and a certification clarifying that the form was prepared at the licensed premises reflects ATF's longstanding interpretation of the GCA and its implementing regulations. The revisions simply confirm that firearms transactions must occur at the licensed premises (or temporary extension at a qualifying in-state gun show or event) in order to help licensees identify and prevent straw purchases, and ensure that transactions can be regulated and inspected by law enforcement at a fixed location.

More specifically, ATF Form 4473 is a "Firearm Transaction Record" that documents an attempted or completed transfer of a firearm from a licensee to an unlicensed person. From June 1969 until 2013, Form 4473 was issued in two separate parts – "over-the-counter" (Part I), and "non-over-the-counter" (Part II).[1] This distinction was made because of the GCA's express statutory limitation that firearms transactions be conducted either over-the-counter at the licensed business premises, or non-over-the-counter solely in accordance with the narrow dictates of 18 U.S.C. § 922(c) (A licensee "may sell a firearm to a person who does not appear in person at the licensee's business premises … only if" specified conditions are met).[2] However, since 2013, there is only one Form 4473 that may be used for both over-the-counter and eligible non-over-

[1] The first Form 4473 issued in December 1968 contained both over-the-counter (Item #13) and non-over-the counter certifications (Item #14).

[2] *See Abramski v. U.S.*, 134 S.Ct. 2259 (2014) ("Only a narrow class of prospective buyers may ever purchase a gun from afar ... [y]et on Abramski's view, a person could easily bypass the scheme, purchasing a gun without ever leaving his home by dispatching to a gun store a hired deliveryman.").

the-counter firearm transactions.[3]

ATF's interpretation is consistent with numerous other provisions of the GCA and implementing regulations that restrict licensees to conducting firearms business at their licensed premises. Notably, the GCA requires license applicants to: (1) have a premises from which to conduct business subject to license, 18 U.S.C. § 923(d)(1)(E) (which is extended temporarily at a qualifying in-state gun show or event in accordance with section 923(j)); (2) certify that the business to be conducted is not prohibited by State or local law in the place where the licensed premise is located, 18 U.S.C. § 923(d)(1)(F)(i); (3) *maintain*[4] records of sale or other disposition of firearms at the business premises, 18 U.S.C. § 923(g)(1)(A); (4) pay a separate fee for each place in which the applicant is to do business, 18 U.S.C. § 923(a); and (5) post the license and keep it available for inspection on the premises covered by the license, 18 U.S.C. § 923(h).[5]

Additionally, the legislative history of the GCA clearly reflects Congress' desire that firearms business be conducted only from a permanent, licensed premises. In S. Rep. No. 1866, 89th Cong., 2d Sess. 88, 89 (1966), the Senate Judiciary Committee discussed the provision in S. 3767 requiring an applicant for a firearms license to have business premises. This standard was included in Title IV of the Omnibus Crime Control and Safe Streets Act of 1968 and ultimately became existing law, 18 U.S.C. § 923(d)(1)(E). The Committee stated as follows:

> The provisions of paragraph (5) would preclude the issuance of licenses to applicants who do not have, or do not intend to have or maintain, or do not intend to have or maintain, bona fide business premises for the conduct of the business. This provision will be a definite aid in limiting licensees under the Federal Firearms Act to persons bona fidely engaged in business, and assuring that there will be an appropriate place that is subject to proper inspection where the required records will be maintained.

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[3] *See* ATF Procedure 2013-2. ATF also discontinued the low-volume Form 4473 (LV) on October 3, 2014. *See* 79 FR 45091 (Aug. 4, 2014).

[4] Contrary to NRA's comment, section 923(g)(1)(A) (and its implementing regulation, 27 C.F.R. § 478.121(c)) require licensees to "maintain" records at their licensed premises, not merely "store" them. ATF interprets "maintain" as it is commonly understood. For example, the Privacy Act of 1974 defines "maintain" to include maintenance, collection, use, or dissemination of information. 5 U.S.C. § 552a(a)(3).

[5] *See also* 27 C.F.R. §§ 478.11 ("Business premises" means "[t]he property on which the ...dealing in firearms is or will be conducted."); 478.41(b) ("A license as...a dealer in firearms shall...entitle the licensee...to engage in the business ... at the location described on the license..."); 478.50 ("A separate license must be obtained for each location at which a firearms...business or activity requiring a license under this part is conducted..."); 478.91 ("Any license issued under this part shall be kept posted and kept available for inspection on the premises covered by the license."); 478.100 ("A licensee may conduct business temporarily at a gun show or event ... if the gun show or event is located in the same State specified on the license."); Rev. Rul. 69-59 (a person holding a valid license may engage in the business covered by the license only at the specific business premises for which his license has been obtained); ATF Rul. 2016-2 (p.3, proviso #4) (and former ATF Rul. 2008-3, p.2, #3) (electronic Forms 4473 must be completed "while physically present at the seller's premises").

> The information developed at the public hearings held by the subcommittee disclosed a definite need for such a provision. It was shown that in some cases importers or dealers maintained no regular place of business which could be found, and conducted their operations through post office boxes, mail drops, answering services, etc., or from a vehicle, vessel, or aircraft which moved from place to place.

Moreover, an important purpose of the GCA was to make available to State and local law enforcement officials firearms information within their own States to assist them in their own law enforcement activities. *See* S. Rep. No. 1501, 90th Cong., 2d Sess. 25 (1968). Later, when Congress passed the Firearm Owner's Protection Act of 1986 creating the *limited* exception for dealing at in-state gun shows, 18 U.S.C. § 923(j), Congress explained:

> Section 923(j) [would] permit licensed importers, manufacturers, and dealers to conduct business at gun shows for the first time since the Gun Control Act of 1968 was enacted. Under current law, a licensee may not conduct business at any location other than the one specified on his license, i.e., his business premises. This precludes all temporary locations, such as organized gun shows.

S. Rep. 98-583, 98th Cong., 2d Sess. 19 (1984) (report on S. 914).[6]

ATF Form 4473 is Not a Firearms Order Form

As NRA points out, ATF has allowed licensees to display and take orders for firearms away from their licensed business premises in limited circumstances. However, this does not mean that *ATF Form 4473* may be used as an order form for prospective sales. Form 4473 has been issued since 1968 to determine and document the eligibility of persons to acquire firearms, prevent straw purchases, and allow the tracing of firearms to actual purchasers. It is not designed to be used as a firearms order form. ATF does not believe Congress intended records documenting firearms transactions to be completed away from the licensed premises, and returned to the licensed premises simply for storage. Doing so would make it easy for licensees to deal in firearms away from their licensed premises.[7]

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[6] *See also* 131 Cong. Rec. S9101-05 (July 9, 1985) (Statement of Sen. Hatch) (Requiring "[t]hat all interstate sales of firearms including handguns must take place over the counter face to face … allows the dealer to identify and make inquiries of the purchasers, and thus it prevents sales to felons and others prohibited from acquiring firearms. Second, all interstate sales of firearms, including handguns, have to be recorded in the dealer's records so that tracing can be readily obtained."); *id.* (Statement of Sen. Kerry) ("All dealers had to sign a form indicating a customer had produced identification showing he was not a resident of another State. This form, which also identified the firearms sold and gave the purchaser's name, address, and description was retained by the dealer and made available for inspection by the Alcohol, Tobacco and Firearms agents. All of this provided a Federal framework for the monitoring of interstate firearms sales to help State and local efforts to keep arms away from criminals, and to trace weapons when they were used to commit crimes. This Federal regulatory system was the heart an[d] soul of the 1968 Gun Control Act.").

[7] ATF disagrees with NRA's comment that it would be difficult for ATF to enforce the limitations expressed in ATF's website Q&A regarding activities at out-of-state gun shows beyond displaying and taking orders for firearms. *See, e.g., U.S. v. Bailey*, 123 F.3d 1381, 1392 (11th Cir. 1997) (affirming 922(a)(1)(A) conviction of licensee who

Perhaps more importantly, allowing the form to be maintained away from the licensed premises would make it easier for prohibited persons to straw purchase firearms. Actual purchasers could simply complete the questions at home or in the parking lot, and have a straw purchaser enter the premises merely to show her identification and receive the firearms on their behalf. Licensees would not have the opportunity to observe the actions and demeanor of the purchasers reviewing and completing Section A, and would thereby be unable to fulfill their gatekeeper role to prevent ineligible persons from receiving firearms.

Conclusion

Based on the statutory and regulatory scheme, legislative history, and sound policy, ATF is clarifying that ATF Form 4473 is to be completed at the licensed business premises for most firearm transactions. Specifically, because this version of Form 4473 will no longer state that it is an "over-the-counter" transaction record, it is important to affirm that the form is completed at the licensed business premises for over-the-counter transactions, unless the requirements under section 922(c), 27 C.F.R. § 478.96(b), and ATF Proc. 2013-2 are satisfied. In doing so, ATF has reasonably interpreted what it means to conduct business subject to license at the location specified on the license, and to maintain transaction records at the licensed business premises. Even assuming ATF's revised form constitutes a "rule" subject to the APA, ATF was not required to promulgate a new regulation through notice and comment rulemaking because it reflects ATF's interpretation of the GCA and its implementing regulations. Nonetheless, ATF did publish notice of the form in the Federal Register for anyone to comment, as NRA has done.

We trust the foregoing has been responsive to your comments.

Sincerely yours,

Krissy Y. Carlson
Chief, Firearms and Explosives Industry Division

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dealt in firearms at his home, rather than one of his two licensed premises); *U.S. v. Hern*, 926 F.2d 764 (8th Cir. 1991) (upholding the convictions of an in-State middleman dealer for conspiring with an out-of-state dealer to sell firearms at a local gun show, in violation of sections 371 and 922(b)(3), and for recording false statements about these sham transactions in his records, in violation of section 922(m)); *U.S. v. Ruisi*, 460 F.2d 153 (2nd Cir. 1972) (affirming convictions of licensed corporation's official and employee for engaging in the business at a gun show, in violation of section 922(a)(1)(A)); *Cisewski v. ATF*, 773 F. Supp. 148, 152 (E.D. Wis. 1991) (upholding revocation of licensee who sold firearms away from his licensed premises, in violation of section 922(a)(1)(A)); and *Powers v. ATF*, 505 F. Supp. 695 (N.D. Fla. 1980) (upholding denial of licensee who dealt firearms off-premises in violation of 922(a)(1)(A)). While the court in the case cited by NRA, *U.S. v. Caldwell*, 49 F.3d 251, 252 (6th Cir. 1995), found that a dealer who sells away from his licensed premises could not be considered "unlicensed" and convicted under section 922(a)(1)(A), the court expressly recognized that "...a thorough reading of the statute indicates that such conduct is improper and perhaps violative of other provisions..."