PhRMA
RESEARCH • PROGRESS • HOPE
950 F STREET, NW, SUITE 300 • WASHINGTON, DC 20004 • 202-835-3400 • PhRMA.org

August 11, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on the Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification (Docket No. FDA-2014-D-0609).

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to provide comments in response to issuance by the Food and Drug Administration (FDA) of a draft guidance document entitled "Guidance for Industry: Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification" (*hereinafter* the "draft guidance").[1] PhRMA is a voluntary, non-profit association that represents the country's leading pharmaceutical research and biotechnology companies. PhRMA members are dedicated to developing medicines that allow patients to live long, healthier, and more productive lives. In 2013 alone, PhRMA members invested an estimated $51.1 billion in the research and development of new medicines.

PhRMA and its member companies welcome FDA's draft guidance as an important step towards the successful implementation of the Drug Supply Chain Security Act (DSCSA).[2] The DSCSA creates important "track-and-trace" measures that will help protect the supply chain by detecting and preventing the sale of diverted and counterfeit drugs through legitimate supply chain channels. The law creates categories of "suspect," "high-risk of illegitimacy," "illegitimate" and "cleared" products, and when products are determined to be in one of these categories, certain requirements may be triggered under the DSCSA. The draft guidance addresses some, but not all, of the provisions of the DSCSA related to suspect and illegitimate products.[3]

---

[1] 79 Fed. Reg. 33564 (June 11, 2014).
[2] Title II of the Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013).
[3] FDA was required by FDCA § 582(h)(2) (as amended by the DSCSA) to issue this draft guidance document not later than 180 days after the date of enactment of the DSCSA. In the draft guidance, the FDA was required to "(i) identify specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; (ii) provide recommendation on how trading partners may identify such product and make a determination on whether the product is a suspect product as soon as practicable; and (iii) set forth the process by which manufacturers, repackagers, wholesale distributors, and dispensers shall terminate notifications in consultation with the Secretary regarding illegitimate product pursuant to subsections (b)(4)(B), (c)(4)(B), (d)(4)(B), and (e)(4)(B)."

PhRMA and its member companies view this draft guidance as of paramount importance to public health—improper suspect and illegitimate product determinations could cause unnecessary disruptions in the pharmaceutical supply chain, limiting medicine availability or even causing a drug shortage, which ultimately harms patient health. As the entity in the supply chain with the most knowledge about the authenticity of a product, manufacturers should play a primary role in investigating a suspect product and determining if a product is illegitimate. Therefore, PhRMA and its member companies are committed to working with FDA and other supply chain stakeholders to help FDA implement requirements of the DSCSA relating to suspect and illegitimate products in a manner that secures the integrity of the supply chain while preventing unnecessary disruptions in the availability of life saving medicines. In Section I, we discuss our comments specific to the draft guidance released by FDA. In Section II, we re-emphasize the comments we made in our earlier public letter to FDA on this issue[4] and respectfully ask that FDA address these concerns.

I. PhRMA Comments on Draft Guidance

A. FDA Should Emphasize that the Manufacturer Should Be Engaged in Determining Whether a Product is Suspect or Illegitimate

PhRMA applauds FDA on recognizing the importance of trading partners discussing "with each other any observations, questions, or concerns they have related to the status of a drug as a suspect product to aid them in determining whether the drug should be considered a suspect product."[5] Because the manufacturer is best positioned to know whether the suspicion of a trading partner is substantive and valid or is easily explained, PhRMA recommends that FDA strongly encourage consultation with the manufacturer, specifically, and not just other trading partners, before making a determination that a product is suspect, as such a determination triggers quarantine.[6] The manufacturer has the greatest knowledge about the product characteristics, including covert and overt anti-counterfeiting methods and packaging. Furthermore, downstream trading partners may not have the capacity, access to propriety anti-counterfeiting information, technical expertise or resources to conduct a proper determination without assistance. If a trading partner does not coordinate with the manufacturer, the trading partner might otherwise obtain information about the product from unauthorized and potentially inaccurate, incomplete, or outdated sources (*e.g.*, unauthorized websites that may not have the most current labeling). Thus, consultation with the manufacturer would greatly reduce the number of inaccurate reports of illegitimate product and allow manufacturers to investigate potential supply chain issues and avoid unnecessary disruptions of important, life-saving medicines.

Likewise, in the guidance FDA should emphasize the importance of coordinating with the manufacturer, as required by law, before making a determination that a product is

[4] PhRMA Comments to FDA, "Docket No. FDA-2014-N-0200: Standards for the Interoperable Exchange of Information for Tracing of Human, Finished, Prescription Drugs in Paper or Electronic Format: Establishment of a Public Docket," (April 21, 2014) (*hereinafter*, PhRMA April 21, 2014 Comments).
[5] Draft Guidance, Lines 220-222.
[6] *See* FDCA §§ 582(b)(4)(A)(i)(I), (c)(A)(i)(I), (d)(4)(A)(i.)(I) and (e)(4)(A)(i)(I).

illegitimate.[7] To prompt this coordination, and to collect information that can assist with supply chain coordination, PhRMA recommends that FDA add a box on Form 3911 that confirms whether or not the trading partner has already coordinated with the manufacturer in making its determination, and provides the manufacturer's point of contact and contact information, if available.

B. FDA Should Clarify its Statements Regarding "Heightened Vigilance" and Being "Particularly Diligent"

In Section III of this draft guidance, FDA sets out to meet the DSCSA provision requiring the Agency to "identify specific scenarios that could significantly increase a risk of a suspect product entering the pharmaceutical distribution supply chain" and "provide recommendation on how trading partners may identify such product and make a determination on whether the product is a suspect product as soon as practicable."[8] While PhRMA appreciates that FDA has provided, as required by law, examples regarding potentially problematic scenarios, we are concerned with FDA's language that "there may be situations involving trading partners where heighted vigilance would be appropriate"[9] and that "[t]rading partners should be particularly diligent when engaging in transactions that"[10] involve certain characteristics. While PhRMA and its member companies support efforts to help protect the supply chain by detecting and preventing the sale of diverted and counterfeit drugs through legitimate supply chain channels, PhRMA is concerned that these statements could be mistakenly construed as suggesting that a more stringent legal standard applies to trading partners in conducting due diligence in certain situations highlighted by the FDA in the draft guidance. FDA should clarify that this language is not indicative of a different legal standard and instead, should be interpreted as recommending that companies should consider the circumstances surrounding different transactions and adjust their monitoring practices for suspect product as appropriate.

C. FDA Should Revise its List of Scenarios that Could Significantly Increase the Risk of a Suspect Product Entering the Pharmaceutical Distribution Chain

PhRMA appreciates the thorough list of scenarios that FDA has developed for trading partners to consider as they implement the suspect and illegitimate product provisions of the DSCSA and the recommendations for trading partners on ways to expeditiously identify suspect product and determine whether the product is suspect. PhRMA is concerned, however, that some of these scenarios and recommendations do not, by themselves, increase the likelihood that a particular product is suspect or illegitimate. The suggestion of using "heightened vigilance" should be reserved for a more narrowly defined set of scenarios than those provided in Section III.A in the draft guidance, as we are concerned that broad application will lead to "over-warning," which can drown out the most problematic signals, breed complacency, or even result

[7] *See* FDCA §§ 582(c)(4)(B)(i), (d)(4)(B)(i), and (e)(4)(B)(i). Note that the statutory language is ambiguous regarding whether or not such coordination with a manufacturer has to occur *prior* to notifying the Secretary that the trading partner has determined that a product is illegitimate. *See* FDCA §§ 582(c)(4)(B)(ii), (d)(4)(B)(ii), and (e)(4)(B)(ii).
[8] *See* FDCA § 582(h)(2).
[9] Draft Guidance, Lines 124-125.
[10] *Id.* at 128-129.

in unnecessary quarantining that is capable of triggering temporary drug shortages. Likewise, we urge FDA to emphasize that trading partners must look at the totality of the circumstances when identifying a suspect product as recommended in Section III.B and not necessarily rely on any one factor alone—each factor in and of itself is unlikely to be decisive, or even suggestive, of the existence of a suspect product. More specifically, PhRMA has the following feedback on the scenarios under "Trading Partners and Product Sourcing" and "Supply, Demand, History, and Value of a Product" in Section III.A of the draft guidance:

i. Trading Partners and Product Sourcing: Supply, Demand, History, and Value of a Product

Under the DSCSA, all manufacturers, repackagers, wholesale distributors, and dispensers are required to engage in transactions with only "authorized trading partners." This verification step greatly reduces the risk of interacting with fraudulent trading partners. Therefore, PhRMA believes that the scenario "Purchasing from a source new to the trading partner"[11] alone does not significantly increase the risk of a suspect product entering the supply chain. Similarly, PhRMA does not believe that, "Purchasing from a source that the trading partner knows or has reason to believe has transacted business involving suspect products, such as a trading partner that has been involved in business where they sold or delivered suspect product"[12] significantly increase the risks to the supply chain. If a trading partner has been involved in the sale or purchase of a suspect product in the past, and the suspect product was cleared, there is little or no increased risk that the product is illegitimate. In fact, the most diligent trading partners may be the most likely to identify suspect product. FDA instead might revise this section to focus more on the risk of purchasing from a source that the trading partner knows, or has reason to believe, has a history of knowingly and repeatedly transacting in illegitimate products.

ii. *Inherent Characteristics: Supply, Demand, History, Price, and Value of a Product*

As PhRMA stated in its comments to the public docket for the "Standards for the Interoperable Exchange of Information for Tracing of Human, Finished, Prescription Drugs in Paper or Electronic Format," FDA should not rely on inherent characteristics of a product (*e.g.*, high cost of the drug, limited supply, etc.) as these do not translate into a higher likelihood that something has happened to compromise the integrity of the product as it moved through the supply chain. While it is true that these characteristics can make a product more attractive to criminal enterprises, these products are produced and transported by manufacturers in a manner taking into account these risks. Therefore, the presence of product that has one of the enumerated, inherent characteristics alone cannot be viewed as more likely to be a "suspect" or "illegitimate" product or one that has a "high risk of illegitimacy."

Additionally, the inclusion of inherent product characteristic in this draft guidance, such as high sales volume or price, are practically problematic for manufacturers who

[11] Draft Guidance, Line 133.
[12] *Id.* at 145-149.

have the additional responsibility to notify FDA and their immediate trading partners within 24 hours if a manufacturer "has reason to believe" that its trading partners may possess "a product manufactured by, or purported to be a product manufactured by, the manufacturer" and "there is a high risk that such product is an illegitimate product."[13] The statute, in defining "high risk" notably points to "high risks as determined by the Secretary in [this draft guidance]."[14] Consequently, if the FDA's factors for identifying suspect products are also interpreted as indicating products that have a high risk of illegitimacy, and taken to its logical conclusion, for some manufacturers who sell only products that meet one of the inherent characteristics identified in Section III, this could mean having to notify FDA and immediate trading partners for each and every shipment of their entire product portfolio. Thus, we believe that FDA should eliminate the suggestion that trading partners have a heightened responsibility to be particularly vigilant when engaging in transactions described in (1) – (4) below:

(1) *Product that is generally in high demand in the U.S. market*.
(2) *Product that is in higher demand because of its potential perceived relationship to a public health or other emergency (e.g., antiviral drugs).*
(3) *Product that has been previously or is currently the subject of a drug shortage.*
(4) *Product that has a high sales volume or price in the United States*.

If FDA does retain these examples in its guidance, FDA should separate factors that increase the likelihood that fraud or other criminal activity could be attempted (*e.g.*, high demand, high price, etc.) from factors that suggest the product itself is suspect or illegitimate (*e.g.*, appearance of product) and clarify that factors that increase the likelihood that fraud or other criminal activity may be attempted are insufficient alone to indicate a risk to the supply chain unless coupled with factors that suggest a product itself may be suspect or illegitimate. Furthermore, it is unclear when FDA would find that product meets the criteria above such that "heightened vigilance would be appropriate." For example, by what measure would a product be considered to be "generally in high demand" or how would a downstream trading partner, such a small, community pharmacy, make this determination? Therefore, if FDA retains these examples in its guidance, FDA should further clarify what constitutes high demand, high price, and high volume products.

D. FDA Should Revise its Recommendations on How Trading Partners Might Identify Suspect Product and Determine Whether the Product is a Suspect Product as Soon as Practicable

As required by the DSCSA, FDA provides useful recommendations on the steps a trading partner might take to identify suspect product in Section III.B of the draft guidance.[15]

[13] FDCA § 582(b)(4)(B)(ii)(II).
[14] *See* FDCA § 582(b)(4)(B)(ii)(II).
[15] PhRMA notes that FDA stated in its September 2011 "FDA Preliminary Report: Review of Counterfeit and Diversion Criminal Case Information" that the agency "expects to conduct further analysis and report as appropriate" findings from actual cases. PhRMA encourages FDA to update and further report on its findings, as well as incorporate generalizable factors it has encountered in reviewing these specific cases in this guidance document. FDA, FDA Preliminary Report: Review of Counterfeit and Diversion Criminal Case Information, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/UCM272150.pdf.

We are concerned, however, that FDA fails to acknowledge that most of the characteristics provided in the list of strategies to identify suspect product are not, by themselves, suggestive of a suspect product. For example, a damaged package with a broken seal or similar issue (mentioned in Lines 232-233 of the draft guidance) is unlikely to be indicative of suspicious activity unless other suspicious factors exist. As described above, if trading partners over-burden the system with false alarms, this may result in failure to properly identify product that is actually suspect or impact product availability by leading to unnecessary quarantining of product. Accordingly, we recommend that FDA emphasize that the product characteristics provided in Section III.B are unlikely to be suggestive of a suspect product without being accompanied by other factors that are also suggestive of a suspect product (*e.g.*, a broken seal is unlikely to be suggestive of a suspect product unless it is accompanied by additional factors that are indicative of suspicious activity).

PhRMA also notes that the presence of one of the factors provided in the list of recommendations may only be suggestive of a suspect product in certain geographic locations. For example, FDA regulations allow a foreign language to be used on the label instead of English in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English while the draft guidance lists this as one of characteristics to use to potentially identify suspect product. Therefore, we suggest that FDA provide clarifying language that the use of a foreign language rather than English may be indicative of a suspect product except in the case of a product which is offered for sale in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, consistent with 21 C.F.R. § 201.15(c).

PhRMA is also concerned that FDA's draft guidance, which recommends at Line 230 that trading partners "closely examine the package" could imply that FDA is recommending that every individual package be inspected by a trading partner, which is infeasible, particularly with respect to sealed cases. To enable trading partners to manage resources efficiently, we suggest that FDA explicitly acknowledge that trading partners may adopt a risk-based approach to inspecting and confirming container, label, and packaging information. To enhance the ability of trading partners to protect the supply chain, they must be able to balance the resources devoted to inspection of particular packages with the risk of suspicious activity.

E. FDA Should Respond to a Request for Termination of a Notification of an Illegitimate Product or a High Risk of Illegitimacy in a Shorter Timeframe

In the draft guidance, FDA states that it "intends to respond to requests for termination within 10 business days of submission"[16] of a request terminating a notification of an illegitimate product or, for a manufacturer, terminating notification of a high risk of illegitimacy. PhRMA and its member companies are concerned that allotting up to 10 business days, or possibly even a greater length of time if FDA feels additional time is necessary, for FDA to respond to a request for termination could disrupt the availability of pharmaceuticals because the product will remain in quarantine during this time. PhRMA appreciates that FDA provides the requester with an opportunity on the Form 3911 to describe exigent circumstances that require

[16] Draft Guidance, Lines 327-328.

expedited consideration of a termination request (*e.g.*, a potential drug shortage), but is concerned that 10 business days of additional quarantine may create unnecessary delays in getting medicines to patients regardless of whether "exigent circumstances" exist at the time that the request for termination is submitted. PhRMA recommends that FDA instead respond to requests for termination within three business days, which is a time frame consistent with other requirements (*e.g.*, a sponsor is required to submit to FDA a field alert report within three working days of receiving certain information).[17]

F. FDA Should Clarify How it Intends to Protect Confidential Information During the Notification Process

PhRMA and its member companies believe it is important for FDA to clarify in this guidance whether or not any portion of the notifications for illegitimate products will be made public, and if so, whether there will be any protection of confidential commercial information. While PhRMA believes that it would be helpful to physicians, patients, and supply chain trading partners if FDA maintained a public database regarding information on cases of illegitimate product that the Agency has confirmed, we also feel it is important for FDA to acknowledge the importance of protecting confidential commercial information. For example, when reporting an illegitimate product a trading partner may include confidential anti-counterfeiting technology information in the Form 3911 or may include confidential business information regarding trading partner relationships. Therefore, if FDA decides to make information about confirmed cases of illegitimate products public at some point, or discloses the notification forms, the Agency should ensure that it does so in a manner that does not release any confidential commercial information.

G. FDA Should Provide More Information On Agency's Structure for Handling Notifications

In the draft guidance section on notification of illegitimate product, FDA describes that there will be a web page where trading partners can access Form 3911, which should be used to provide information regarding the notification about an illegitimate product or a product that poses a high risk of illegitimacy. PhRMA believes it would be useful if FDA provided more information about where in FDA's organizational structure (*i.e.*, which department or divisions) the responsibilities for responding to these notifications will be located. Additionally—noting that Form 3911 references alternative notification mechanisms—PhRMA asks that this guidance clarify how this notification process interacts with other notification/alert processes at FDA, such field alert reports, current counterfeit reporting mechanisms, reporting to the Office of Criminal Investigations, and the recall process.[18] Lastly, as PhRMA believes that FDA should create a central point of contact for all interactions with FDA regarding supply chain security issues covered by the DSCSA, PhRMA recommends that the web page be expanded to include instructions on how trading partners can communicate with the Agency on other DSCSA related issues.

---

[17] *See, e.g.*, 21 CFR § 314.81.

[18] PhRMA also recommends that, when developing regulations or guidance to implement Section 715 of Food and Drug Administration Safety and Innovation (FDASIA), that FDA clarify how notification for illegitimate product per the DSCSA differs or overlaps with that required by FDASIA Section 715.

H. FDA Should Clarify How the Agency Will Avoid Possible Conflicts in the Notification Process

PhRMA asks for FDA to make the following clarifications regarding the notification process:

i. Duplicate Notification

PhRMA notes that since a manufacturer is responsible for sending FDA notification of a "high risk of illegitimacy" and a separate, much further downstream trading partner could send a notification of an illegitimate product, it is possible that FDA could receive two notifications for the same product. PhRMA believes that this is another important reason for FDA to emphasize that coordination should specifically include the manufacturer, not just immediate trading partners. Further, PhRMA suggests that FDA set forth a process to avoid such duplicate notifications and believes that the addition of a box in Form 3911 as discussed earlier in this comment letter, would help confirm whether or not the trading partner has already coordinated with the manufacturer in making its determination.[19] Additionally, we suggest that FDA consider adding a box similar to the "Manufacturer Report Number" box included on the MedWatch Form (Form FDA 3500A) on the Form 3911. This type of box would aid in tracking of duplicate notifications to FDA and would help ensure the appropriate coordination among trading partners. Indeed, in FDA's draft guidance on "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines," FDA noted that for follow up reports, use of the same unique manufacturer report number assigned to the initial report was essential "to prevent duplicate counting of reports and to ensure that the follow-up information is coupled with the correct initial report."[20]

Similarly, to reduce duplicate notifications, PhRMA also suggests that FDA clarify that a trading partner is only responsible for making a notification to FDA on a Form 3911 of an illegitimate product determination if such product is within the trading partner's actual possession or physical control—the limited exception here is that manufacturers are responsible for making a notification to FDA and all immediate trading partners when the manufacturer has determined that its trading partners might be holding product manufactured by it or counterfeit product purported to be manufactured by it for which there is a "high probability of illegitimacy." The statutory provisions requiring notification of the Secretary for illegitimate product refer only to making such notification "upon determining that a product in the possession or control of the [trading partner] is an illegitimate product.[21] Without clarification that FDA interprets the statute to mean actual possession or physical control, there could be confusion over who is responsible for submitting Form 3911 to notify FDA of an illegitimate product, leading to unnecessary or improper notification.

---

[19] *See* Section I.A. of this letter for additional discussion of the recommended box on Form 3911 that confirms whether or not the trading partner has already coordinated with the manufacturer in making its determination.
[20] FDA, "Draft Guidance: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" (Mar. 2001), at lines 686-688, *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092257.pdf.
[21] *See* FDCA §§ 582(b)(4)(B)(ii), 582(c)(4)(B)(ii), 582(d)(4)(B)(ii), and 582(e)(4)(B)(ii).

ii. Disputes Over Legitimacy of Product

As noted earlier, wholesale distributors, dispensers and repackagers are required to coordinate with the manufacturer when determining whether or not a product is illegitimate.[22] PhRMA notes that it is possible for manufacturers and other trading partners to disagree over the legitimacy of a questionable or suspect product. PhRMA ask that FDA clarify whether or not a manufacturer can file a request for termination on Form 3911 if it is not the party that made the initial notification to the Agency that a product was illegitimate. PhRMA members recommend that FDA either allow manufacturers to file a request for termination even when they are not the initial notifying party, or provide an alternative method for notifying FDA that the manufacturer does not believe the product in question is illegitimate. FDA should be the final arbiter on any resulting discrepancies regarding a product's legitimacy.

I. Additional Comments on the Form 3911

PhRMA asks for FDA to make the following clarifications regarding the Form 3911:

i. FDA Should Add "High-Risk of Illegitimacy" to the Form 3911

In the draft guidance, FDA recommends that manufacturers, when making a notification for a high risk of illegitimacy as described in section 582(b)(4)(B)(ii)(II) of the FDCA, use the Form 3911 to notify FDA. The form and instructions, as provided in the draft guidance, however, do not appear to take in account the "high risk of illegitimacy" category. For example, a company will not be able to provide a "date illegitimate product was determined by company" because the product has not yet been determined to be illegitimate. Likewise, in the "Instructions for Completion of Form 3911 – Drug Notification," FDA does not provide a classification option under item number 4 for a manufacturer to indicate it is a product for which there is a high risk of illegitimacy. PhRMA recommends that FDA revise both the form and instructions to ensure that they properly incorporate provisions for "high risk of illegitimacy" notifications.

ii. FDA Should Clarify the Instructions for the Use of the "Trade Name" Box on the Form 3911

Form 3911 includes a box for "Trade Name (*if applicable*)," and the instructions for completion of the form merely state "provide the trade name of the product." PhRMA recommends that FDA clarify in the form instructions that the Trade Name should only be listed if the product in question has a trade name itself—the blank should not be filled in with the trade name of the reference listed drug, for example, if the product is a generic product without its own trade name. If the notification of a generic drug were to list the Trade Name of the innovator version of the generic product, this could lead to confusion that the product in question is an innovator product. The potential for confusion could increase if the notification forms are publicized in any manner and lead to unintended consequences.

[22] *See id.* §§ 582(c)(4)(B)(i), (d)(4)(B)(i), and (e)(4)(B)(i).

iii. Receipt of Notice

The draft guidance does not state that FDA intends to provide a receipt of notice of form submission. Because of the potential for technological errors or other issues in submitting the Form 3911, we strongly urge FDA to clarify in the guidance that it intends to send a receipt of notice after receiving a Form 3911 submission and that the receipt will include the contact information of the individual at FDA who should be contacted in the event there are any additional follow-up questions and/or issues.

iv. Promote Consistency in Notifications

To assist FDA in promoting consistency in what is collected from the reporters, PhRMA recommends that FDA request the following information as part of its instructions for completion of Form 3911 for Item 16 "For Notification, Description of Event/Issue" for known immediate trading partners (both downstream, and upstream, if applicable): a description of what led to initial product identification as "suspect" or "illegitimate" product (e.g., package condition) and a yes/no check box[23] for the submitter to indicate whether specific analytical tests were used to determine illegitimacy.

J. FDA Should Clarify its Language in the Draft Guidance Regarding a Request for Verification from FDA

In the draft guidance at Lines 104-108, FDA states "Under section 582 of the FD&C Act, and beginning not later than January 1, 2015, trading partners must have systems in place that enable them, upon determining that a product in their possession or control is suspect or upon receiving a request for verification from FDA, to quarantine suspect product and promptly conduct an investigation, in coordination with other trading partners, as applicable, to determine whether a suspect product is illegitimate." This language, however, is different from the statutory language which reads "Upon making a determination that a product in the possession or control of the manufacturer is a suspect product, or upon receiving a request for verification from the Secretary *that has made a determination that a product within the possession or control of a manufacturer is a suspect product*, a manufacturer shall … [quarantine and investigate]" (emphasis added).[24] We believe that it is important that the Secretary can only make a verification request after having made a determination that the product is suspect. Because the draft guidance does not include the language emphasized here that is included in the statutory language, we respectfully request that FDA clarify its language in the draft guidance by adding the additional clause so the language in the guidance mirrors the statutory language.

K. FDA Should Avoid the Use of Term "Pedigree"

FDA uses the term "pedigree" in the draft guidance when discussing scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical

[23] We believe that a yes/no check box is appropriate for this factor to protect against the disclosure of proprietary/ confidential information regarding covert anti-counterfeiting technologies.
[24] FDCA § 582(b)(4)(A)(i); see also FDCA § 582(c)(4)(A)(i), (d)(4)(A)(i), and (e)(4)(A)(i).

distribution chain. The term pedigree, however, is not used in the DSCSA and could be confused with regulatory frameworks that predate and are inconsistent with the scheme set out in the statute, which uses the terms "transaction history," "transaction information," and "transaction statement." When issuing rules, guidance documents, or other materials under the DSCSA, PhRMA recommends that FDA incorporate the statutory language.

L. FDA Should Create Limited Exceptions to Reporting Where Notifications Would Not be Useful

The DSCSA, through the grant of authority to FDA in Section 582(a)(3)(A)(iii) to "establish a process by which the Secretary may determine other products or transactions that shall be exempt from the requirements" for triggering notification to FDA and trading partners of illegitimate product, gives FDA the authority and flexibility to implement the DSCSA in a manner that ensures the agency learns of products that could threaten the supply chain but is not inundated with reports of products without any such potential. PhRMA and its member companies believe that FDA should use its authority and make an exception to the reporting requirements for products that might technically fall within the scope of the defined term "illegitimate product," but such product has been handled in such a manner that the product that has been destroyed or could not reasonably be re-introduced into the supply chain. One example is a few bottles of product being stolen by a trading partner's employee or vendor, and the product was recovered and destroyed. Another common example is receiving a small sample of product from law enforcement—many of whom obtain such samples outside the legitimate supply chain, such as via a rogue online pharmacy—to test whether a product is counterfeit. Such small thefts and product sampling may occur for member companies on a regular basis, and such events do not call into question the legitimacy of other product already in the supply chain. Therefore, if FDA were to establish such an exception, the agency's limited resources could be focused on notifications of illegitimate products that merit FDA's scrutiny.

PhRMA understands that it would be challenging for FDA to create a bright line rule to govern all possible circumstances under which the exemption could potentially apply. Therefore, PhRMA suggest that FDA direct trading partners to take a risk-based approach to applying the exception, meaning that a trading partner would consider factors such as any risk of re-entry into the legitimate supply chain, the quantity of product in question, and the risk of harm to patients if re-entry were in the rare case to occur, in determining whether high risk of illegitimacy (for manufacturers) or illegitimate product notifications are required.

II. PhRMA Comments on Need for Further Clarification of Suspect and Illegitimate Product Related Provisions in the DSCSA

PhRMA appreciates that FDA primarily discusses in this draft guidance the issues for suspect and illegitimate products that it was required to address by law[25] and acknowledges that the guidance "does not address all provisions of the DSCSA related to suspect and illegitimate products." Since FDA plans on issuing additional information as it implements other provisions of the DSCSA, PhRMA and its member companies wanted to take this opportunity to

[25] *See id.* § 582(h)(2).

again emphasize some of the comments made in PhRMA's earlier submission[26] to the public docket on the "Standards for the Interoperable Exchange of Information for Tracing of Human, Finished, Prescription Drugs in Paper or Electronic Format," and make additional recommendations for FDA to consider as it implements other provisions of the DSCSA related to suspect and illegitimate products.

A. Comments Regarding Communication with the Agency

In the PhRMA April 21, 2014 Comments, PhRMA made recommendations to FDA about how FDA and trading partners communicate with one another regarding the suspect and illegitimate product provisions of the DSCSA. In these comments, we describe how manufacturers currently investigate and communicate about suspect and illegitimate product with FDA and downstream trading partners. PhRMA and its member companies appreciate the flexibility that FDA adopted in this draft guidance by allowing trading partners to continue to use existing systems and processes for terminating notifications to trading partners. Along those same lines, PhRMA and its member companies respectfully request that FDA clarify that trading partners may also use their own systems and processes for the original notification of trading partners.

PhRMA believes there are additional issues regarding communication with the Agency that would fit well into this draft guidance. For example, the DSCSA requires that starting on January 1, 2015, trading partners notify the Secretary, if applicable, of a determination that a suspect product is not an illegitimate product.[27] PhRMA suggests that it would be appropriate, and a simple revision, for FDA to describe in this draft guidance how trading partners may notify the Agency when a suspect product is "cleared" after an investigation.

B. Comments Regarding Clarification of Key Terminology

In the PhRMA April 21, 2014 Comments, we also highlight areas of concern regarding the suspect and illegitimate product provisions of the DSCSA as well as provide suggestions on how FDA can implement this portion of a law in a manner that does not cause unnecessary disruption to the supply of life saving medicines. Of particular importance is FDA providing greater clarity, and illustrative examples, around the terms "suspect product," "illegitimate product," and "high risk of illegitimacy" as common understanding of those terms among trading partners will lessen confusion and prevent unnecessary quarantines that could disrupt the supply of life saving medicines. While all entities can interpret the definitions in an acceptable manner, if each trading partner in the supply chain is interpreting the definitions differently, there could be confusion, especially as trading partners must coordinate. Particularly, we are concerned that if these terms are applied in an overly broad manner by some trading partners there will be unnecessary disruptions in the supply chain, which might lead to drug shortages and other unintended consequences that harm patient health. Also important is clarifying when a product may exhibit certain issues (*e.g.*, a ripped label), but does not rise to the level of a suspect product, and therefore quarantine should not be triggered. Given the

[26] *See supra* note 4, PhRMA April 21, 2014 Comments.
[27] *See e.g.*, FDCA § 582(b)(4)(A).

importance of these clarifications for orderly compliance with the DSCSA's suspect and illegitimate product provisions by January 1, 2015, and their necessity for a trading partner to accurately complete Form 3911[28], PhRMA suggests FDA make these clarifications in this guidance when finalized. Key portions of our suggestions provided in the PhRMA April 21, 2014 Comments are reiterated below for ease of reference:

i. Clarification of the Terms "Suspect Product" and "Illegitimate Product" is Needed

PhRMA asks that FDA limit the scope of the definition of both "suspect product"[29] and "illegitimate product" [30] terms by acknowledging that these definitions apply only to product that has left the control and/or physical custody of the manufacturer that manufactured the product. This limitation is appropriate and necessary to limit overlap with quality issues with products, as such issues are already addressed by current good manufacturing practice (cGMP) requirements and related Standard Operating Procedures (SOPs).

Additionally, PhRMA and its member companies are concerned with the lack of clarity regarding clauses (C), "potentially the subject of a fraudulent transaction," and (D), "appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans," in the definition of both suspect and illegitimate product. We recommend that "fraudulent transaction" be defined as "a transaction that involves the introduction into or transportation through interstate commerce of counterfeit, diverted, intentionally adulterated, or intentionally distributed expired drugs." FDA used language similar to this in a 2011 presentation discussing the Agency's goals for a track and trace system.[31] Alternatively, FDA should provide examples that do not rise to the level of a "fraudulent transaction."

Likewise, FDA should clarify what "appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans" entails and provide an example of when a product fits this description. FDA needs to clarify that this category does not encompass quality issues that may have arisen in the manufacturing process, which are already covered by cGMP requirements and recall processes. We recommend that this phrase be limited by language that is consistent with language already used in FDA regulations. For example, the device regulations at 21 C.F.R. § 810.2 define "serious adverse health consequences" as "any significant adverse experience including those that may be either life-threatening or involve permanent or long-term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible."

---

[28] *See, e.g.*, Form 3911 Instructions, Item 4 – Classification of Notification (requiring selection of the appropriate description of the illegitimate product classification, with such classifications closely tracking the statutory definition of illegitimate product).

[29] FDCA §581(21).

[30] FDCA §581(8).

[31] FDA Track and Trace Public Workshop. Determination of System Attributes for Tracking and Tracing of Prescription Drugs. (Feb. 15-16, 2011) *available at* http://www.fda.gov/downloads/Drugs/NewsEvents/UCM245540.pdf.

ii. FDA Should Clarify the Meaning of the Evidentiary Standards "Reason to Believe" and "Credible Evidence."

The DSCSA uses the evidentiary standard "reason to believe" for the term suspect product and "credible evidence" for the term illegitimate product. Given the variation in experience that trading partners have working with FDA-focused laws and regulations, PhRMA asks that FDA assist with trading partners' understanding of these evidentiary standards by clarifying their meaning. As a starting matter, FDA should make sure any standard set for both suspect product and illegitimate product is high enough to prevent unnecessary quarantines and dispositions and allows entities to focus on the highest risk situations. In fleshing out the difference between the terms, FDA should note that these terms are used in Fourth Amendment jurisprudence with "reason to believe" generally understood to impose a lower evidentiary burden than "credible evidence," with the latter term meaning that one has drawn a definitive, although not absolute, conclusion.[32] The "reason to believe standard" is often equated with the "reasonable suspicion" standard, which requires the person who holds an opinion to have more than "a hunch" and "be able to point to specific and articulable facts which, taken together with rational inferences from those facts, reasonably warrant" the opinion held.[33] PhRMA also suggests that FDA provide examples of the difference between the two standards.

iii. FDA Should Clarify the Term "High Risk of Illegitimacy"

The DSCSA requires that manufacturers notify FDA and all immediate trading partners when the manufacturer has determined that its trading partners might be holding product manufactured by it or counterfeit product purported to be manufactured by it for which there is a "high risk of illegitimacy."[34] PhRMA and its member companies feel it would be helpful for FDA to elaborate on the meaning of the term "high risk of illegitimacy" in this draft guidance and, more specifically, provide examples of situations that may cause a product to be at a high risk of illegitimacy. PhRMA suggests that FDA consider elaborating that "high-risk" accounts for both the likelihood that a product has become illegitimate and the severity of consequences if a patient accessed the product in question.

Some examples of when a trading partner might be holding a product for which there is a "high risk of illegitimacy"—that FDA could consider for a non-exhaustive list of examples in its guidance—include: (1) when the manufacturer learns that the product had been on a vehicle that was the victim of cargo theft after the product left the manufacturer's control; and (2) notification of a manufacturer by law enforcement agencies and other authorities that there is reason to believe illegitimate versions of the their brand of product are circulating in the U.S. supply chain, and law enforcement has provided some specificity with regards to a particular shipment or lot number. We recommend that FDA consider an approach that is similar to the one used in its August 1997 Guidance for Industry titled "Postmarketing Adverse

[32] *See Walker v. Collins*, 59 F. 70, 74 (8th Cir. 1893) *rev'd on other grounds*, 167 U.S. 57 (1897) (describing "evidence which is sufficient to produce a belief that the thing is true; in other words it is credible evidence"); *Alliance for Natural Health U.S. v. Sebelius*, 786 F. Supp. 2d 1, 14 (D.D.C. 2011) (requiring the weighing of evidence under the "credible evidence" standard to determine whether the evidence supporting a qualified health claim is "'qualitatively weaker' than evidence against the claim" (internal quotation omitted)).
[33] *See Terry v. Ohio*, 392 U.S. 1 (1968).
[34] FDCA §582(b)(4)(B)(ii)(II).

Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report." In the guidance, FDA noted that "[b]efore considering any clinical incident for submission to FDA in an expedited or periodic safety report, applicants, manufacturers, and licensed manufacturers should have knowledge of [four specific data elements]."[35] For example, FDA could recommend that, before considering there to be a "high risk of illegitimacy," a manufacturer should have knowledge of: (1) an identifiable drug product lot or shipment; (2) an identifiable reporter; and (3) identifiable risk factors that provide a reasonable suspicion of illegitimacy.

III. Conclusion

PhRMA thanks FDA for issuing this draft guidance, which takes an important step toward protecting the integrity of the drug supply chain. PhRMA stands ready to work with FDA and other supply chain stakeholders to implement the DSCSA.

Respectfully submitted,

Sarah A. Spurgeon
Assistant General Counsel

[35] FDA, "Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report" (August 1997), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf.