November 4, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2024-N-3762: Agency Information Collection Activities; Proposed Collection; Comment Request; Obtaining Information To Understand Challenges and Opportunities Encountered by Compounding Outsourcing Facilities

To Whom It May Concern:

Novo Nordisk Inc. ("NNI") appreciates this opportunity to submit comments in response to the Food and Drug Administration ("FDA" or "the Agency") notice of proposed information collection on the challenges and opportunities pertaining to human prescription drug compounding by outsourcing facilities.[1] Novo Nordisk is a healthcare company with a 100-year history of innovation in developing medicines to treat serious chronic diseases, like diabetes and obesity. NNI is the only company in the United States with FDA-approved medicines containing semaglutide. Semaglutide is the foundational molecule that serves as the primary ingredient for Novo Nordisk's well-known, prescription only medicines: Rybelsus® (semaglutide) tablets to improve glycemic control in adults with type 2 diabetes, Ozempic® (semaglutide) injection to improve glycemic control in adults with type 2 diabetes and to reduce the risk of major adverse cardiovascular events ("MACE") in adults with type 2 diabetes and established cardiovascular disease, and Wegovy® (semaglutide) injection to reduce the risk of MACE in adults with established cardiovascular disease and either obesity or overweight or for chronic weight management in adult and pediatric patients with obesity or adults with overweight.

In the wake of unprecedented demand for semaglutide medicines, outsourcing facilities and their partners are marketing unapproved and clinically untested compounded "semaglutide" products to patients nationwide. While there are no verified estimates of how many patients are using compounded "semaglutide," some "industry officials" have recently estimated that the number of patients on compounded "semaglutide" could be in the millions.[2] Many outsourcing

[1] 89 Fed. Reg. 72410 (Sept. 5, 2024).

[2] *See* Dani Blum, *More People Are Overdosing on Ozempic Alternatives*, NY TIMES (Aug. 6, 2024), https://www.nytimes.com/2024/08/06/well/ozempic-semaglutide-overdose-risks.html; *see also* Arthur Allen, *Why Millions Are Trying FDA-Authorized Alternatives to Big Pharma's Weight Loss Drugs*, KFF HEALTH NEWS (July 23,

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facilities are establishing relationships with telehealth platforms and ramping up manufacturing operations to distribute mass amounts of compounded "semaglutide."[3] They are engaging in these operations without adhering to the legal guardrails intended to ensure that compounding occurs only in appropriate circumstances and are engaging in these operations without the supply chain integrity and pharmacovigilance protections provided by sponsors of FDA-approved medications.

The rampant compounding of "semaglutide" is putting patients at risk. FDA's adverse event database shows that 619 adverse events, including 144 hospitalizations and 12 deaths, have been reported to the Agency following use of a compounded "semaglutide" product.[4] This is more than double the number of adverse events that FDA received for all compounded drugs in 2022.[5] Yet, the adverse events associated with compounded "semaglutide" are likely underreported, and the adverse events reported in FAERS are expected to be only a small portion of the adverse events patients are experiencing after taking compounded "semaglutide."

FDA issued a risk alert announcing that some of these reports and hospitalizations may relate to dosing errors, including several patients who mistakenly administered five to 20 times more than the intended dose of compounded "semaglutide."[6] The Agency believes the containers and packaging used by compounders, including multidose vials and prefilled syringes, the varying product concentrations, and the instructions accompanying the compounded drug, contributed to the dosing errors.[7] A publication from the Journal of the American Pharmacists Association article discussed administration errors where patients accidentally self-administered doses of compounded "semaglutide" up to 10 times greater than the intended amount.[8]

NNI urges FDA to address the present and growing risk posed by drugs compounded by outsourcing facilities, including by revising the Agency's proposed survey of outsourcing

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2024), https://kffhealthnews.org/news/article/glp1-compounding-pharmacies-wegovy-zepbound-copycat-drugs-shortages/.

[3] Gabriela Barkho, *Weight loss drugs like Ozempic are giving DTC telemedicine platforms a boost*, MODERNRETAIL (Mar. 25, 2024), https://www.modernretail.co/operations/weight-loss-drugs-like-ozempic-are-giving-dtc-telemedicine-platforms-a-boost/.

[4] *See* FDA, FAERS Database for Compounded Semaglutide, https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis (accessed Nov. 4, 2024).

[5] *See* FDA, Mitigating Risks of Compounded Drugs Through Surveillance, https://www.fda.gov/drugs/human-drug-compounding/mitigating-risks-compounded-drugs-through-surveillance (accessed Nov. 4, 2024).

[6] FDA, FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products, https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded (accessed Nov. 4, 2024).

[7] *Id.*

[8] *See* Joseph E. Lambson et al., Administration errors of compounded semaglutide reported to a poison control center—Case series, 63 J. AM. PHARM ASSOC. 1643 (2023), https://www.japha.org/article/S1544-3191(23)00231-5/abstract.

facilities. NNI agrees with the comment submitted by the Pharmaceutical Research and Manufacturers of America ("PhRMA"), including PhRMA's proposed survey questions. We write to provide additional context for PhRMA's proposed survey questions and to separately propose additional survey questions. We also would like to emphasize the importance of adding more probative questions to the Agency's survey to elucidate outsourcing facilities' compliance with federal compounding law and policy. We believe the proposed questions discussed further below will enhance the quality, utility, and clarity of the information proposed for collection in FDA's survey of outsourcing facilities.

PhRMA Proposed Survey Questions

Adverse Event Reporting Procedures

Proposed Question:

- "What are outsourcing facilities' written and implemented procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA?"[9]

As noted above, there are 619 adverse events associated with compounded "semaglutide" in FAERS, including 12 deaths. As the Agency acknowledges on its website, taking compounded "semaglutide" "can be risky for patients" and "it is likely that adverse events from compounded [semaglutide] are underreported."[10] Indeed, no outsourcing facility is identified as a "sender" of *any* adverse event associated with compounded "semaglutide" in FAERS.[11]

Unlike sponsors of FDA-approved medicines that are subject to expansive postmarketing reporting of adverse drug experiences,[12] outsourcing facilities are required to report only a limited subset of adverse events associated with use of the compounded products.[13] In addition,

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[9] Federal Food, Drug, and Cosmetic Act ("FDCA") § 503B(b)(5).

[10] FDA, FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss (accessed Nov. 4, 2024), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss.

[11] *See* FDA, FAERS Database for Compounded Semaglutide, https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis (showing that no outsourcing facilities are listed under the "sender" column when completing a search on FAERS for any products containing semaglutide as an active ingredient, with the filter of "Yes" under "Compounded Flag").

[12] 21 C.F.R. § 314.80.

[13] Outsourcing facilities are required to report only serious and unexpected adverse events. 21 C.F.R. § 310.305(c). Unlike the adverse event reporting regulation for approved drugs, the regulation governing outsourcing facilities does not require the reporting of any other adverse events, including those that are serious and expected or non-serious and unexpected. FDA appears to acknowledge this deficit in its guidance on adverse event reporting by outsourcing facilities with FDA stating that the Agency "strongly recommends" reporting of all serious adverse drug experiences

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outsourcing facilities may not have developed or implemented written procedures for the surveillance, receipt, or evaluation of adverse events, further resulting in underreporting. Furthermore, pharmacies that resell drug products compounded by outsourcing facilities are not held accountable by FDA for any pharmacovigilance obligations. As such, they likely do not have the policies and procedures in place to conduct pharmacovigilance or to ensure that adverse event reports are shared with either the outsourcing facility or FDA.

In guidance, FDA states that it may "review whether [a] outsourcing facility has developed and implemented written processes" for adverse event reporting.[14] The Agency should add a question to its proposed survey to do just that—assess outsourcing facilities' current adverse event reporting procedures—and take action to help protect patients from the risk of harm from compounded products.

Wholesaling and Resale Prohibitions and Office-Use Only Restriction

Proposed Questions:

- "How do outsourcing facilities secure compliance with the prohibitions on wholesaling and resale when they enter into commercial arrangements with other entities?"[15]
- "Do outsourcing facilities label compounded drugs as 'Not for Resale' and 'Office Use Only' when they are selling or transferring compounded drugs outside of clinical settings?"[16]
- "How do outsourcing facilities ensure that compounded drugs are not resold or used in violation of the 'Not for Resale' and 'Office Use Only' labeling requirements?"

Wholesaling and resale of 503B compounded drugs increases patient exposure to compounded drug safety and efficacy risks, undermines the drug approval process, risks the integrity of the U.S. drug supply chain, and exacerbates significant gaps in the adverse event reporting obligations for compounded drugs. These risks are amplified when outsourcing facilities partner with telehealth providers, online "facilitators," and state-licensed pharmacies to engage in the sale, marketing, and advertising of compounded products using a model that may

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associated with compounded products. Such a recommendation is not legally binding, however, and leaves the reporting of many serious adverse events to the discretion of individual outsourcing facilities. FDA, Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, at 5 (Oct. 2015), https://www.fda.gov/files/drugs/published/Adverse-Event-Reporting-for-Outsourcing-Facilities-Under-Section-503B-of-the-Federal-Food--Drug--and-Cosmetic-Act.pdf.

[14] FDA, Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, at 10 (Oct. 2015), https://www.fda.gov/files/drugs/published/Adverse-Event-Reporting-for-Outsourcing-Facilities-Under-Section-503B-of-the-Federal-Food--Drug--and-Cosmetic-Act.pdf.

[15] FDCA §§ 503B(a)(8), 301(ccc)(1).

[16] *Id.* § 503B(a)(10)(A)(IX).

constitute impermissible wholesaling and resale.[17] We encourage FDA to use its proposed survey to probe outsourcing facilities' compliance with FDA's wholesaling and resale prohibitions and office-use only restriction and take appropriate action against companies that are violating the law.

Bulk Drug Substances

Proposed Question:

- "How are outsourcing facilities establishing the validity of the certificates of analyses ("COA") accompanying bulk drug substances that will be used in compounding?"[18]

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), any bulk drug substance used in compounding must be accompanied by a valid COA.[19] This requirement is critical to ensuring that bulk drug substances used by outsourcing facilities do not lead to unsafe and ineffective compounded drugs. The importance of the valid COA requirement is particularly acute for the bulk "semaglutide" used in compounding. Unlike NNI's FDA-approved semaglutide medicines that contain recombinantly produced semaglutide, compounded "semaglutide" is produced using synthetic semaglutide unaffiliated with any approved application. Use of such a bulk drug substance can introduce peptide-related impurities and other complexities and expose patients to safety and effectiveness risks. This distinction underscores that a valid COA for synthetic semaglutide should identify, characterize, quantify, and justify peptide-related impurities.

FDA guidance describes the risk that "[d]ifferences between the peptide-related impurities in a proposed generic synthetic peptide and those in [a reference listed drug] of [recombinant DNA] origin could produce different impurity profiles, which could adversely affect the safety or effectiveness of a proposed generic synthetic peptide product, if uncontrolled."[20] The guidance recommends that applicants (1) show that for each peptide-related impurity found in both the synthetic peptide and recombinantly produced peptide, the level of each impurity is the same or lower than that found in the recombinantly produced peptide; (2) show that the generic synthetic peptide does not contain any new specified peptide-related impurity that is more than 0.5% of the drug substance; (3) characterize each new specified peptide-related impurity; and (4) justify for each new specified peptide-related impurity that is no more than 0.5% of the drug substance why the presence of such impurity would not be expected to affect the safety or effectiveness of the synthetic peptide.[21] It further recommends that each peptide-related

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[17] *See* Gabriela Barkho, *Weight loss drugs like Ozempic are giving DTC telemedicine platforms a boost*, MODERNRETAIL (Mar. 25, 2024), https://www.modernretail.co/operations/weight-loss-drugs-like-ozempic-are-giving-dtc-telemedicine-platforms-a-boost/.

[18] FDCA § 503B(a)(2)(D).

[19] *Id.*

[20] FDA, ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin: Guidance for Industry, at 7 (May 2021), https://www.fda.gov/media/107622/download.

[21] *Id.* at 2.

impurity that is 0.10 percent of the drug substance or greater be identified, while noting that depending on the potential immunogenicity risk of a particular product, applicants may need to also identify peptide-related impurities present at levels below this threshold.[22] Adhering to these scientific standards is critical to ensuring that patients do not receive unsafe and ineffective drug products made with synthetic peptides that are unaffiliated with approved applications.

In the drug shortage context, FDA has noted, "[i]t is important to patients and prescribers that compounded drugs prepared to address a shortage closely resemble the drug in shortage, and for that reason, the statute seeks to allow compounders to compound drugs that are as close as possible to the drug in shortage."[23] According to FDA's guidance, not only must the compounded drug be identical or nearly identical to the FDA-approved drug, but the quality of the bulk drug substance must also have the quality of the bulk drug substance in the FDA-approved medicines. As noted above, the bulk drug substance used by compounders of "semaglutide" is manufactured by peptide synthesis, whereas the bulk drug substance used in Novo Nordisk's FDA-approved semaglutide medicines is recombinantly produced. Synthetic peptide-based semaglutide may have a different impurity profile relative to the approved products with recombinant-based semaglutide. This difference in manufacture makes it particularly challenging to ensure that the bulk drug substances are identical or nearly identical to the bulk drug substances used in the FDA-approved semaglutide medicines. A close and exacting evaluation of the COA accompanying the bulk drug substance "semaglutide" used in compounding, as well as the underlying scientific and clinical evidence, is therefore necessary. Such an evaluation is necessary to ensure that the bulk synthetic "semaglutide" outsourcing facilities use to compound their products will not pose adverse effects on the safety or effectiveness of the compounded drugs. We recommend FDA investigate compliance with the valid certificate of analysis and quality requirements through the Agency's proposed survey.

503B Copies

Proposed Questions:

- "When outsourcing facilities are compounding versions of FDA-approved drugs that appear on FDA's drug shortage list, are they ensuring that those compounded drugs are identical or nearly identical to the FDA-approved drugs currently in shortage?"[24]

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[22] *Id.* at 10.

[23] FDA, Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, at 7 (Jan. 2018), https://www.fda.gov/media/98964/download.

[24] FDCA § 503B(a)(5), 503B(d)(2)(A).

- "How do outsourcing facilities make certain that the prescribing practitioner is arriving at their own determination that a change between a compounded drug and the comparable approved drug produces a clinical difference for an individual patient?"[25]

FDA should evaluate whether outsourcing facilities may be compounding drugs that are not identical or nearly identical to the FDA-approved drugs, as required under section 503B.[26] A review of the outsourcing facility product report searchable database provides examples of "semaglutide" drugs being compounded by outsourcing facilities that are not identical or nearly identical to the FDA-approved semaglutide medicines that appear on FDA's drug shortage list.[27] We urge the Agency to pose more probative questions about outsourcing facilities' compliance with FDA's copies provisions.

Additionally, outsourcing facilities may not be ensuring that the change between their compounded drugs and the FDA-approved medicines will make a clinical difference to a patient. FDA's guidance states that it will not question a prescriber's determination.[28] This policy position is problematic in light of reports that telehealth companies are working with a select group of physicians to prescribe compounded drugs to potentially hundreds of thousands of patients, raising serious questions about whether prescribers are making meaningful, independent and individual determinations about clinical differences.[29] The Agency should use its proposed survey to scrutinize how outsourcing facilities are obtaining meaningful prescriber determinations.

Telehealth Advertising

Proposed Question:

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[25] *Id.* § 503B(a)(5), 503B(d)(2)(B).

[26] *Id.* § 503B(a)(5), 503B(d)(2)(A).

[27] *See* FDA, Outsourcing Facility Product Report (accessed Nov. 4, 2024), https://dps.fda.gov/outsourcingfacility/searchresult?year=&type=active_ingredients&name=semaglutide (showing the compounding of dosage strengths offered by outsourcing facilities that are not marketed by the FDA-approved semaglutide medicines when completing a search for any products containing semaglutide as an active ingredient).

[28] FDA, Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, at 11 (Jan. 2018), https://www.fda.gov/media/98964/download.

[29] Katie Palmer, *How invisible medical groups are powering telehealth's GLP-1 'gold rush'*, STAT+ (Oct. 17, 2024), https://www.statnews.com/2024/10/17/telehealth-online-compounded-glp1-prescriptions-medical-groups/#:~:text=Telehealth%20companies%20have%20been%20able,cash%20grab%20surrounding%20GLP%2D1s.

- "What measures are outsourcing facilities taking to ensure that they and their partners do not engage in false and misleading advertising and promotion of compounded drugs?"[30]

Outsourcing facilities and their telehealth partners are making false and misleading statements in advertising and promotional materials for compounded products, in violation of the FDCA. For instance, Novo Nordisk is aware that an outsourcing facility claims that its "semaglutide" products are equivalent in quality to Novo Nordisk's FDA-approved semaglutide medicines. And Novo Nordisk has also seen a telehealth provider who partners with an outsourcing facility claim that their compounded "semaglutide" products can treat the same populations for which the FDA-approved semaglutide medicines have been indicated. Such statements pose risks to patient safety and the public health, particularly when they concern the safety and efficacy of the compounded product. We urge FDA to ask outsourcing facilities about the measures they take to ensure that the advertising and promotional materials of outsourcing facilities and their partners are truthful and non-misleading.

Novo Nordisk Proposed Survey Questions

NNI proposes these questions for FDA's consideration in addition to PhRMA's proposed survey questions.

503B Interim Policy

New Proposed Question:

- "How do outsourcing facilities plan to transition from using the hundreds of bulk drug substances on Category 1 to the limited number of bulk drug substances on the 503B Bulks List when FDA sunsets the 503B Interim Policy?"

FDA should solicit information on how outsourcing facilities plan to handle the sunset of the temporary 503B Interim Policy. Under Section 503B of the FDCA, a drug compounded with a bulk drug substance must appear on either the 503B Bulks List or must be identical or nearly identical to a drug product on FDA's drug shortage list.[31] At the early stage of section 503B implementation, FDA believed that an interim policy was necessary to ensure the continuity of care for some patients who have a medical need for treatment with certain compounded drugs.[32] Notably, FDA characterized the policy as *interim* because "the Agency intended for it to be

[30] FDCA § 502(a), 502(bb); FDA, Compounding and the FDA: Questions and Answers, https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (accessed Nov. 4, 2024).

[31] FDCA § 503B(a)(2)(A).

[32] FDA, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Draft Guidance for Industry, at 9 (Rev. 2, Dec. 2023), https://www.fda.gov/media/174453/download.

temporary."[33] Over a decade later, FDA has established the 503B Bulks List and included five substances and excluded 22 substances from the List.[34] Because the 503B Interim Policy is temporary, and FDA has already determined that categorization under the interim policy no longer serves the guidance's stated objective of preventing unnecessary disruption to patient treatment,[35] outsourcing facilities should be prepared for the transition to the narrower list of substances in accordance with the law on the 503B Bulks List. The Agency should use its proposed survey to evaluate how outsourcing facilities will comply with this transition.

Combination Products

New Proposed Questions:

- "Are outsourcing facilities complying with device quality system regulation requirements as described in 21 C.F.R. Part 4 when they make new single-entity combination products comprised of a compounded drug and delivery device?"

- "Are outsourcing facilities using devices that lack approval or 510(k)-clearance for use with their compounded drugs or using devices outside their cleared or approved indications for use?

- "Do outsourcing facilities supply adequate directions for use of the device constituents of their compounded drugs?"

Several outsourcing facilities are using unapproved and uncleared autoinjector pens to deliver their compounded "semaglutide" products. While sections 503A and 503B of the FDCA exempt compounded drug products from certain provisions of the FDCA, neither section 503A nor section 503B of the FDCA exempts compounders from *device* clearance or approval requirements under sections 510(k) or 515 of the FDCA, from the requirement to provide adequate directions for use for *devices* manufactured or distributed by the facility, including device constituents of a combination product, nor from the requirements of the device quality system regulation ("QSR"), 21 CFR Part 820. Compliance with these device requirements by compounders for any delivery devices, such as pen injectors, supplied with or incorporated into compounded drug products is necessary to ensure patient safety of the delivery devices and the new combination product. Delivery devices like autoinjectors often require highly specific instructions for use that must be validated through appropriate usability testing to assure that

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[33] *Id.*

[34] FDA, 503B Bulk Drug Substances List (last updated August 21, 2023), https://www.fda.gov/drugs/human-drug-compounding/503b-bulk-drug-substances-list.

[35] FDA, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Draft Guidance for Industry, at 9 (Rev. 2, Dec. 2023), https://www.fda.gov/media/174453/download.

the delivery devices can be safely and effectively used for drug delivery.[36] Without such instructions, there is a meaningful risk of use errors that present concerning patient risks. Likewise, even if outsourcing facilities comply with drug good manufacturing practices ("GMP"), this is not sufficient to ensure the quality of any delivery device constituent parts. The QSR includes unique requirements such as for design controls, corrective and preventative actions, and purchasing controls,[37] which are necessary to ensure the consistency of supplied pen injector quality and compatibility with the compounded drug, even where the facility utilizes delivery devices originally manufactured by a third-party. Without appropriate FDA clearance or approval of the delivery device, FDA and patients lack reasonable assurance that the delivery device is safe and effective for the particular use with the compounded drug. The Agency should use its proposed survey to evaluate how outsourcing facilities are complying with device-specific requirements when compounding combination drug/device products.

Thank you for the opportunity to provide comments on this notice of proposed information collection. We would be pleased to provide further input or clarification of our comments if needed.

Sincerely,

Robert B Clark

Robert B. Clark
Vice President, Regulatory Affairs
Novo Nordisk Inc.

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[36] *See, e.g.*, FDA, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff (Feb. 2016), https://www.fda.gov/files/about%20fda/published/Human-Factors-Studies-and-Related-Clinical-Study-Considerations-in-Combination-Product-Design-and-Development.pdf; FDA, Application of Human Factors Engineering Principles for Combination Products: Questions and Answers: Guidance for Industry and FDA Staff (Sept. 2023), https://www.fda.gov/media/171855/download.

[37] FDA recognized that the device QSR includes elements not adequately addressed by drug GMP when issuing regulations for GMP requirements for combination products by requiring drug-device combination product manufacturers that are in compliance with the drug GMP to, at a minimum, also comply with certain additional provisions of the device QSR, including design controls, purchasing controls, management responsibility, and corrective and preventative action. 21 C.F.R. § 4.4(b)(1).