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

Re: Supplement to Novo Nordisk, Inc. Citizen Petition on Semaglutide and the 503B Bulks List, Docket No. FDA-2024-P-4937

Novo Nordisk Inc. ("NNI") submits this supplement to the citizen petition we previously submitted to the Food and Drug Administration ("FDA" or the "Agency"), dated October 21, 2024 ("Petition"),[1] requesting that FDA take action to exclude semaglutide from the list of bulk drug substances that may be used by outsourcing facilities in compounding (the "503B Bulks List").[2] This supplement responds to the Outsourcing Facilities Association ("OFA") comments on the Petition dated October 24, 2024[3] ("2024 OFA Comment") and February 13, 2025[4] ("2025 OFA Comment") (together, "the OFA Comments"). The OFA Comments assert that the Petition is procedurally improper and request that FDA deny the Petition on the merits. NNI firmly disagrees with the assertions in the OFA Comments and submits that the Petition was properly filed and the requested actions are necessary to protect the public health. This supplement also opposes and addresses arguments raised in the nomination of semaglutide to the 503B Bulks List submitted by BPI Labs, LLC, on March 10, 2025 ("BPI Nomination")[5] and supplements our opposition to OFA's nomination of semaglutide to the 503B Bulks List.[6] For the reasons discussed below, and in the Petition, NNI respectfully reiterates our requests in the Petition.

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[1] Covington & Burling LLP on behalf of Novo Nordisk Inc., Citizen Petition (Oct. 21, 2024), Docket No. FDA-2024-P-4937-0001 (hereinafter Petition).

[2] Specifically, the Petition requests that FDA (1) publish a notice in the Federal Register excluding semaglutide from the 503B Bulks List; (2) rescind in its entirety the *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*" (Jan. 2025) guidance document (hereinafter *503B Interim Policy*); and (3) to the extent the *503B Interim Policy* is not rescinded, exclude semaglutide from Category 1 of the *503B Interim Policy*. The *503B Interim Policy* was revised in January 2025 following the submission of the Petition, but NNI's requested actions in the Petition remain the same.

[3] Comment from Outsourcing Facilities Association (Oct. 24, 2024), Docket No. FDA-2024-P-4937-0003.

[4] Comment from Outsourcing Facilities Association (Feb. 13, 2025), Docket No. FDA-2024-P-4937-0004 (hereinafter 2025 OFA Comment).

[5] Nomination from BPI Labs, LLC (March 10, 2025), Docket No. FDA-2015-N-3469-0411 (hereinafter BPI Nomination).

[6] Comment from Covington Burling LLP on Behalf of Novo Nordisk Inc. (Oct. 21, 2024), Docket No. FDA-2015-N-3469-0402.

I. The Petition Was Properly Filed and FDA Must Review and Respond on the Merits

The OFA Comments raised several purported concerns with the procedural posture of the Petition, none of which have merit. Specifically, OFA objects to the Petition as being duplicative of OFA's nomination of semaglutide to the 503B Bulks List ("OFA Nomination") in a separate docket.[7] NNI disagrees that the OFA Nomination precludes the proper filing of the Petition or FDA reaching a decision on the merits of the Petition. NNI also disagrees with OFA's assertion that the Petition fails to include information required by 21 C.F.R. § 10.30(b)(3)(B). Finally, contrary to OFA's claims, adding the additional administrative step of requesting NNI submit an economic impact statement is not necessary for FDA to review the Petition as such information is not relevant to the statutory standard for inclusion in the 503B Bulks List. Indeed, FDA's citizen petition regulation states that a "petition that appears to meet the requirements of [21 C.F.R. § 10.30(b)(3)] . . . will be filed by the Dockets Management Staff, stamped with the date of the filing, and assigned a unique docket number."[8] FDA's assignment of a unique docket number for the Petition indicates that the Petition meets the procedural requirements of 21 C.F.R. § 10.30(b)(3).

A. The Petition Is Properly Filed Notwithstanding FDA's Separate Docket for Nominations to the 503B Bulks List

The 2025 OFA Comment incorrectly asserts that the Petition is procedurally improper based on the Agency's ongoing process to develop the 503B Bulks List. Specifically, the 2025 OFA Comment asserts that the Petition is duplicative of the OFA Nomination, requests actions different from FDA's process for the OFA Nomination, would turn the OFA Nomination into a citizen petition, and would skew FDA's consideration of the OFA Nomination. All of these assertions fundamentally mischaracterize the citizen petition process. As described below, the filing of the Petition is proper, and FDA must review and respond to the Petition on its merits, notwithstanding the separate OFA Nomination.

NNI acknowledges that the Petition addresses a similar question as the OFA Nomination, namely, whether semaglutide should be included in the 503B Bulks List. But the Petition is not duplicative of the OFA Nomination, as the Petition requests that FDA take a different action than the OFA Nomination and also requests that FDA take additional actions related to FDA's interim policy on outsourcing facilities compounding using bulk drug substances.[9] Further, FDA cannot deny a citizen petition merely because it requests the Agency take an action that raises a question similar to one raised by another stakeholder in a different regulatory submission or because FDA has opened a separate docket to allow for stakeholder submissions addressing a similar regulatory question. Indeed, as the 2025 OFA Comment states, FDA recognized that citizen petitions may request actions that the Agency is considering

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[7] Nomination from Outsourcing Facilities Association (June 28, 2024), Docket No. FDA-2015-N-3469-0388 (hereinafter OFA Nomination).

[8] 21 C.F.R. § 10.30(c).

[9] *503B Interim Policy*, *supra* note 2.

under separate processes.[10] Nonetheless, FDA's regulations do not prohibit citizen petitions that request actions that implicate or relate to other ongoing regulatory processes, such as an ongoing Federal Register notice process, or that request actions that may be in opposition to actions requested by a different stakeholder through other regulatory submissions to the Agency. Thus, the OFA Nomination in no way precludes the proper filing of, or FDA deciding on the merits of, the Petition.

OFA's assertion that the Petition somehow changes the regulatory status of the OFA Nomination, and will somehow skew or interfere with the Agency's regulatory decision-making on the OFA Nomination, is unfounded. FDA retains discretion to act both on the Petition and the OFA Nomination in a process and timeframe that allows for appropriate Agency deliberation. Filing a citizen petition does not inherently impact the timing or substance of FDA's decision regarding OFA's requested action in the OFA Nomination.[11] Indeed, the Petition requests that FDA follow the same regulatory process that FDA would follow in responding to the OFA Nomination, *i.e.*, publication in the Federal Register of a determination as to whether to include or exclude semaglutide from the 503B Bulks List. For these reasons, NNI disagrees with OFA's claim that FDA's review of the Petition would set a "bad precedent."

Further, in the 2025 OFA Comment, OFA argues that the Petition's request that FDA publish a notice in the Federal Register to exclude semaglutide from the 503B Bulks List "is not how the FDA has committed to developing the 503B Bulks List."[12] Contrary to that assertion, and as the 2025 OFA Comment itself states elsewhere in the submission, FDA has announced that it plans to publish in the Federal Register the Agency's determination on whether to include a bulk drug substance in the 503B Bulks List or the Agency's determination of no clinical need and the resulting decision to exclude the substance from the list.[13] Thus, the action requested in the Petition is entirely consistent with FDA's stated process. The only conceivable departure from FDA's established process the 2025 OFA Comment identifies is that the Petition could theoretically impact the Agency's plan to review nominations to the 503B Bulks List on a rolling basis by impacting the timing of the Agency's determination on whether to include or exclude semaglutide from the 503B Bulks List. But, as discussed above, FDA retains discretion on when

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[10] Administrative Practices and Procedures, Notice of Proposed Rule Making, 40 Fed. Reg. 40682, 40686 (Sept. 3, 1975).

[11] Indeed, as the 2025 OFA Comment itself and the Agency have recognized, Agency deliberations in related ongoing regulatory processes can have the impact of slowing rather than speeding the Agency's action on a citizen petition. *Id.*

[12] 2025 OFA Comment, *supra* note 4, at 4.

[13] FDA, *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry* at 7 (Mar. 2019), https://www.fda.gov/media/121315/download (hereinafter *503B Bulk Drug Substance Evaluation Guidance*). The OFA Comment also alleges that "affirmative exclusion from the 503B Bulks List is not a request that falls within the scope of section 503B." 2025 OFA Comment, *supra* note 4, at 4. While section 503B(a)(2) of the FDCA requires the bulk drug substance to appear on a list identifying substances for which there is a clinical need established by FDA, and provides a process for FDA to establish that list via Federal Register notices, nowhere does section 503B preclude FDA from including in the Federal Register notices information on substances that the Agency has considered and determined there is not a clinical need. Therefore, FDA's established process for reviewing nominations to the 503B Bulks List and publishing Federal Register notices identifying substances that will be both included and not included in the 503B Bulks List, and the actions requested in the Petition, are entirely consistent with the statute.

to act on the Petition, as well as the OFA Nomination, consistent with the Agency's need for appropriate deliberation, the public health considerations associated with various substances under consideration, and the Agency's plan to review nominations to the 503B Bulks List on a rolling basis.

B. The Petition Included All Information Necessary to be Complete and Meet the Requirements in 21 C.F.R. § 10.30

There is no merit to OFA's assertion that the Petition fails to meet the requirement of 21 C.F.R. § 10.30(b)(3)(B) to include representative "unfavorable" information because the Petition does not (1) discuss adverse events associated with semaglutide products marketed pursuant to an approved New Drug Application ("NDA"); or (2) acknowledge that 503B facilities might do a better job of compounding than 503A facilities.

The 2025 OFA Comment suggests that without such adverse event information, FDA is deprived the ability to weigh whether "semaglutide" drugs made in compounding facilities present increased risks over NNI's FDA-approved semaglutide medicines. But this assertion fundamentally misrepresents the information relevant to the Petition's requested action to exclude semaglutide from the 503B Bulks List. Adverse events reported about an FDA-approved drug medicine are not pertinent to the statutory standard of whether there is "a clinical need" for an outsourcing facility to compound the drug[14] or the factors FDA intends to evaluate in determining whether this standard is met. Under FDA guidance, FDA will first evaluate whether (i) an attribute of the FDA-approved drug product that makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and if the compounded drug is intended to address that attribute, and (ii) there is a basis to conclude that the drug must be compounded from a bulk drug substance.[15] If so, FDA will review the following factors: (a) the physical and chemical characterization of the substance; (b) any safety issues raised by the use of the substance in compounding; (c) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and (d) current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.[16] While safety concerns associated with compounded "semaglutide" products are highly relevant to this evaluation, as discussed in detail in the Petition, none of the factors to be considered by FDA include the postmarket adverse event profile of FDA-approved drug products.[17]

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[14] FDCA § 503B(a)(2), 21 U.S.C. § 353b(a)(2).

[15] *503B Bulk Drug Substance Evaluation Guidance*, *supra* note 13, at 11.

[16] *Id.* at 11–12.

[17] Moreover, there are significant differences between the pharmacovigilance requirements for compounders as compared to the requirements for approved drug manufacturers. Manufacturers like NNI already must report every known adverse event associated with their drug products to FDA. In contrast, FDA does not require state-licensed pharmacies to submit **any** adverse event reports to FDA, so FDA understands that it is "likely that adverse events from compounded versions of [GLP-1] drugs are underreported." FDA, *FDA's Concerns with Unapproved GLP-1*
(continued…)

NNI also disagrees with OFA's concern that the Petition excludes "unfavorable" information as the Petition does not discuss OFA's assertion that 503B outsourcing facilities "might do a better job compounding" semaglutide than 503A compounders because 503B facilities are required to comply with good manufacturing practice.[18] As above, neither the statute nor FDA's guidance includes such a consideration as a factor in determining whether there is a clinical need for compounded "semaglutide" products such that semaglutide should be included in the 503B Bulks List. In fact, as *is* relevant to FDA's evaluation, and as discussed in detail in the Petition, there is significant evidence that compounded "semaglutide" products produced by 503B outsourcing facilities present serious quality and patient safety concerns, including a recall of more than 13,000 vials of compounded "semaglutide" from an outsourcing facility due to a lack of sterility assurance, [19] as well as compounders' wide use of synthetic semaglutide when the FDA-approved semaglutide medicines contain semaglutide produced by recombinant DNA technology in yeast.[20]

In addition, NNI has testing results from an outsourcing facility that supplies compounded "semaglutide" products in partnership with a large telehealth platform owned by a publicly traded company. According to LC-MS data, this sample contained an unknown impurity (0.11%) and a synthesis-related, peptide-related impurity with an in-chain deletion of amino acid threonine (0.08%). The published *in silico* analysis predicts that the deletion of a threonine in either the eleventh position (Thr11) or thirteenth position (Thr13) poses immunogenicity risks to patients.[21] Even in small quantities, clinically unqualified peptide-related impurities detected in compounded "semaglutide" products can negatively impact the safety and efficacy of the drug product, including the immunogenicity potential of the product.

Drugs Used for Weight Loss (last updated Mar. 17, 2025), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss. Even though FDA "strongly recommends that outsourcing facilities report all serious adverse drug experiences associated with their compounded prescription drug products" because "reporting all serious adverse events, whether expected or unexpected, would provide important information about potential product quality issues or public health risks associated with drug products compounded by outsourcing facilities," **no** outsourcing facility has been the sender of any adverse events related to compounded "semaglutide" in FAERS. FDA, *FDA Adverse Events Reporting System (FAERS) Public Dashboard*, https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis(hereinafter *FAERS Public Dashboard*). Therefore, comparing reported adverse events for FDA-approved semaglutide products and for compounded "semaglutide" products is an "apples-to-oranges" comparison.

[18] 2025 OFA Comment, *supra* note 4, at 6. While outsourcing facilities are subject to CGMP when compounding, outsourcing facilities are afforded discretion with respect to certain CGMP requirements and recommendations applicable to drug manufacturers, including requirements related to release testing, stability testing, and maintaining reserve samples. *See* FDA, *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act: Draft Guidance for Industry* (Jan. 2020), https://www.fda.gov/media/88905/download.

[19] *See* FDA, Enforcement Report – Week of September 11, 2024, https://www.pharmacompass.com/pdf/news/enforcement-report-week-of-september-11-2024-67667.pdf.

[20] *See* Novo Nordisk Inc., Citizen Petition and Attachments (Nov. 13, 2024), Docket Nos. FDA-2024-P-5378-0001, FDA-2024-P-5378-0003, FDA-2024-P-5378-0004.

[21] Morten Hach et al., *Impact of Manufacturing Process and Compounding on Properties and Quality of Follow-on GLP-1 Polypeptide Drugs,* 41 PHARM. RES. 1991 (2024), https://link.springer.com/article/10.1007/s11095-024-03771-6.

The neutralizing antibodies created by the immune response to these impurities can lead to anaphylaxis, injection site reactions, type-III hypersensitivity responses, and immune complex deposition.[22] Long term, these antibodies can decrease semaglutide's effectiveness at improving glycemic control, reducing the risk of end-stage kidney disease and major adverse cardiovascular events, and weight management. These antibodies can also cross-react with endogenous glucagon-like peptide 1 ("GLP-1") and adversely impact or eliminate this essential incretin's role in the body.[23]

C. An Economic Impact Statement Is Not Necessary for FDA to Decide on the Merits of the Petition

The 2025 OFA Comment speciously suggests that NNI's submission of the Petition is anticompetitive and motivated purely by protecting NNI's economic interests and should be denied, and both OFA Comments assert that FDA cannot decide on the Petition without an Economic Impact Statement concerning the costs associated with excluding semaglutide from the 503B Bulks List. NNI disagrees with these allegations.

As detailed at length in the Petition and below, as well as in NNI's DDC Petition, NNI has significant concerns about the safety of compounded "semaglutide" products and the potential harm to the public health, particularly when there is no clinical need to compound. FDA must likewise focus on its public health remit in determining whether "there is a clinical need" for a drug compounded from a bulk drug substance and whether the bulk drug substance should be included on the 503B Bulks List. Because economic considerations are not one of the criteria set forth in the statute or by FDA guidance in making this public health-driven determination, FDA should reject OFA's request for an economic impact statement under 21 C.F.R. § 10.30(b)(3) for the Petition.

FDA itself has described the importance of focusing on the criteria of clinical need when considering nominations to the 503B Bulks List.[24] FDA's guidance states that "Section 503B limits the bulk drug substances that outsourcing facilities can use in compounding to those . . . that appear on a list developed by FDA of bulk drug substances for which there is a clinical need."[25] This limitation "help[s] ensure that outsourcing facilities do not grow into conventional manufacturing operations making unapproved new drug products without complying with critical requirements."[26] The Agency states that "FDA's review provides an important safeguard to help ensure that outsourcing facilities do not use bulk drug substances to compound drug

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[22] FDA, *Immunogenicity Assessment for Therapeutic Protein Products: Guidance for Industry* 33 (Aug. 2014), https://www.fda.gov/media/85017/download.

[23] Novo Nordisk Nomination of Semaglutide to the 503A and 503B DDC Lists, Docket No. FDA-2017-N-2562-0029, at 2 (Oct. 22, 2024), https://www.regulations.gov/document/FDA-2017-N-2562-0029.

[24] FDA also explicitly adds that "FDA does not interpret considerations of cost to be within the meaning of 'clinical need.'" *503B Bulk Drug Substance Evaluation Guidance*, *supra* note 13, at 9.

[25] *Id.* at 4.

[26] *Id.* at 5.

products when there is no clinical need to do so."[27] Moreover, FDA points to the potential public health harms of evaluating nominations to the 503B Bulks Lists based on economic incentives. FDA states that "allowing outsourcing facilities to compound a drug product from a bulk drug substance that is a component of an FDA-approved drug product because of, for instance, economic incentives, when the approved drug product, or a drug product compounded from the approved drug product, would be medically appropriate for the patient, would reduce the incentive for applicants to seek FDA approval of drugs product."[28] As FDA explains, compounded drugs pose a higher risk to patients than FDA-approved medicines.[29] A decision to include a bulk drug substance on the 503B Bulks List based on economic factors could add to safety risks for patients.

The statutory limitation on the 503B Bulks List to substances for which there is a clinical need serves an important public health function.[30] The public health benefits include (i) limiting patient exposure to compounded products that have not been established to be safe and effective and (ii) preserving incentives to invest in FDA approval of safe and effective drug products.[31] Indeed, Congress enacted section 503B in response to the serious fungal meningitis outbreak in 2012 and included safeguards to prevent clinically unnecessary compounding from bulk drug substances, including FDA's creation of the 503B Bulks List. As described in the Petition, semaglutide does not meet the standard and criteria set forth by Congress and FDA for inclusion on the 503B Bulks List because it is not a bulk drug substance for which a "clinical need" to compound exists. There are no attributes of FDA-approved semaglutide medicines that make them medically unsuitable to treat certain patients for the nominated conditions and, therefore, there is no justification for compounding semaglutide. The four factors in FDA's guidance also heavily weigh against a finding that there is a "clinical need" for outsourcing facilities to compound semaglutide.

In addition, OFA misconstrues the requirements in 21 C.F.R. § 10.30(b)(3), claiming that NNI does not fulfill the Statement of Grounds requirement because the Petition did not include an economic impact statement. OFA argues that FDA should therefore regard the Petition as incomplete. Contrary to OFA's claim, an economic impact statement is not a required element of the Statement of Grounds.

The Statement of Grounds section requires that a petitioner state the "factual and legal grounds on which the petitioner relies" including all "relevant information," as well as known "representative information" that is unfavorable to the petitioner's position.[32] NNI included a Statement of Grounds section that states NNI's factual and legal grounds for the Petition. NNI does not rely on economic information in its citizen petition and thus did not include such

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[27] *Id.*

[28] *Id.* at 5–6.

[29] *Id.* at 3.

[30] *See id.* at 6.

[31] *Id.*

[32] 21 C.F.R. § 10.30(b)(3).

information in its Statement of Grounds. As we note above, doing so would be outside the contours of section 503B and FDA guidance stating that the Agency must create the 503B Bulks List based on whether "there is a clinical need" for a drug compounded from a bulk drug substance. OFA implies that economic information would be unfavorable to NNI's petition and thus NNI must include such information in the Statement of Grounds. However, the requirement that a petitioner disclose "representative information" in this instance is cabined to the "factual and legal grounds" relied on by the petitioner. Because NNI does not rely on economic information as its factual and legal grounds for its citizen petition opposing the nomination of semaglutide to the 503B Bulks List, NNI is not required to include any additional information in the Statement of Grounds. In addition, requiring a petitioner to include an economic impact statement in the Statement of Grounds would defeat the purpose of a petitioner submitting an economic impact statement "only when requested by the Commissioner following review of the petition."[33] The Petition thus meets the requirements of 21 C.F.R. § 10.30(b)(3) and is complete.

II. OFA Failed to Provide Additional Information to Demonstrate That Semaglutide Meets the Clinical Need Standard to Overcome the Deficiencies in its Nomination.

As a threshold matter, the 2025 OFA Comment does not provide any additional information to show that semaglutide meets the clinical need standard and overcome the deficiencies in its Nomination. While OFA attempts to pick at various statements and datapoints in the Petition, the fact remains that the OFA Nomination did not show that semaglutide met the standard and criteria set forth by Congress and the FDA for inclusion on the 503B Bulks List. The assertion that patients may want "personalized" compounded versions of semaglutide at varying strengths, different routes of administration, without certain inactive ingredients, and co-actives does not mean there is a "clinical need." Semaglutide is not a bulk drug substance for which a "clinical need" to compound exists and the 2025 OFA Comment does not provide any additional support for the claim that it can meet this standard. There are no attributes of FDA-approved semaglutide medicines that make them medically unsuitable to treat certain patients for the nominated conditions, particularly because these medicines have been shown to be safe and effective in a variety of strengths (0.25, 0.5, 1, 1.7, and 2.4 mg), different routes of administration (injectable and oral), and with and without certain inactive ingredients (such as propylene glycol). OFA's comment did not provide any additional information on why such FDA-approved medicines are unsuitable. Furthermore, the physical and chemical characterization, safety issues, available evidence of over-or-under effectiveness, and current and historical use of compounded "semaglutide" weigh against a finding of clinical need.

OFA wrongly asserts that the "clinical need" standard is "straightforward: the ingredient is needed in clinical treatment." However, FDA has issued Guidance with a different interpretation of this statutorily mandated requirement.[34] Under the Guidance, the phrase

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[33] *Id.*

[34] *See Athenex Inc. v. Azar*, 397 F. Supp. 3d 56, 73 (D.D.C. 2019) (holding that FDA's method of determining whether there is a "clinical need" for a bulk drug substance gives effect to the unambiguously expressed intent of Congress).

"bulk drug substances for which there is a clinical need" in Section 503B(a)(2)(A) of the FDCA is interpreted to mean that the 503B Bulks List can "include a bulk drug substance if: (1) there is a clinical need for an outsourcing facility to compound a drug product, and (2) the drug product must be compounded using the bulk drug substance."[35] The Guidance describes the factors that FDA considers when determining whether the clinical need standard has been met and sets forth a two-part test. First, when considering bulk drug substances that are components of FDA-approved drug products, FDA evaluates whether (a) there is a basis to conclude that an attribute of the approved drug makes it medically unsuitable for certain patients, and the compounded drug is intended to address that attribute, and (b) there is a basis to conclude that the drug product must be compounded from a bulk drug substance.[36] If the FDA determines that the nomination does not meet the Parts 1(a) and 1(b) of the test, the Agency will not include the nominated bulk drug substance on the 503B Bulks List.[37] Part 2 of the analysis takes into consideration four factors: (a) the physical and chemical characterization of the substance; (b) any safety issues raised by the use of the substance in compounding; (c) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance; and (d) current and historical use of the substance in compounded drug products.[38]

NNI argued in the Petition that the OFA Nomination failed to provide specific reasons to establish a clinical need to compound semaglutide. Nothing in the 2025 OFA Comment addresses this failure. Instead the 2025 OFA Comment continues to make broad and general statements on the purported need for compounded "semaglutide" without specific patient data, such as "compounded versions provide flexibility in dosage and formulation, addressing specific patient sensitivities and enhancing adherence to treatment"[39] and "some patients require doses unavailable in commercial semaglutide products, emphasizing the clinical need for compounded alternatives."[40]

Even when OFA provides a citation in the 2025 OFA Comment in an attempt to substantiate its claim, the citation does not adequately support the claim. OFA states that it is important to "tailor[] compounded medications to remove inactive ingredients for patients with sensitivities and adapt[] dosage forms to improve compliance and safety for those with unique requirements."[41] To substantiate this claim, OFA cites one study for its claim that a formulation without propylene glycol is needed, which related to injection site discomfort. OFA claims that a study showed that "95% of patients preferred the formulation without propylene glycol."[42] This is an inaccurate statement and the study did not find this. The study compared a formulation of semaglutide with phenol as a preservative and propylene glycol as an isotonicity agent in a

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[35] *503B Bulk Drug Substance Evaluation Guidance*, *supra* note 13, at 9.

[36] *Id.* at 11–14.

[37] *Id.* at 11.

[38] *Id.* at 11–12.

[39] 2025 OFA Comment, *supra* note 4, at 10.

[40] *Id.* at 9.

[41] *Id.* at 13.

[42] *Id.* at 14 (citing OFA Nomination, *supra* note 7)).

multidose pen injector ("semaglutide MPI") with two modified formulations without phenol and with either a higher concentration of propylene glycol ("semaglutide C") or sodium chloride in lieu of propylene glycol ("semaglutide D"). The study did find that "95% [of subjects] found semaglutide MPI less painful than semaglutide C." But this does not support OFA's statement that subjects preferred a propylene glycol-free formulation, as both the semaglutide MPI and semaglutide C formulations contained propylene glycol.[43] On the contrary, the mean visual analogue scale pain score for injection-site pain intensity was *higher* for the propylene glycol-free semaglutide D formulation than for the MPI formulation with propylene glycol.[44] Therefore, contrary to OFA's assertion, the study does not suggest any meaningful patient preference for propylene glycol-free formulations of semaglutide. Regardless, a "preference" for one of two formulations studied does not equate to a showing that an attribute of an FDA-approved medicine is medically unsuitable, the compounded drug is intended to address that attribute, or there is a basis to conclude that the drug must be compounded from a bulk drug substance to serve a clinical need.

OFA asserts generally that "[p]atients who benefit from customized formulations or alternative dosing forms may not have access to these options with commercially available drugs."[45] OFA cites a general study on dysphagia in older adults as evidence that compounded buccal or sublingual products are needed. The study is not specific to RYBELSUS® tablets nor is it even specific to swallowing medication. The primary purpose of the study appears to be identifying specific types of dysphagia for treatment.[46] Based on this study, there is no evidence of a patient population needing compounded "semaglutide" because they cannot swallow. Further, as discussed in the Petition, RYBELSUS® tablets are well below the FDA's recommendation that tablets should not exceed 22 mm and FDA-approved injectable semaglutide formulations are available for any patients who cannot swallow pills.[47] There is no evidence that buccal or sublingual formulations would have efficacy. [48] Moreover, there is no evidence that a prescriber would need to have this form of compounded "semaglutide" on hand as part of an office stock to meet that need if it had existed.[49] Without such evidence, OFA is basically saying all the bulk drug substances used in oral medicines should be on the 503B Bulks List because some unquantified number of patients might have trouble swallowing it, which

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[43] Søren Snitker et al., *Comparison of the Injection-site Experience of Semaglutide in a Single-dose and a Multidose Pen-injector*, 24 DIABETES OBESITY & METABOLISM 1643–1646 (2022), https://pmc.ncbi.nlm.nih.gov/articles/PMC9545130/.

[44] The study found "[t]he injection-site experience with semaglutide D was almost indistinguishable from semaglutide MPI, with >80% of injections with either product associated with no or very mild injection-site pain."

[45] 2025 OFA Comment, *supra* note 4.

[46] Shanojan Thiyagalingam et al., *Dysphagia in Older Adults*, 96 MAYO CLINIC PROCEEDINGS 488–497 (2021), https://www.mayoclinicproceedings.org/article/S0025-6196(20)30902-2/fulltext.

[47] Petition, *supra* note 1, at 12–13.

[48] A successful sublingual or buccal delivery mechanism for semaglutide has not been demonstrated. As discussed in the Petition, there are serious safety and efficacy concerns associated with the use of semaglutide in a sublingual or buccal dosage form. *See* DDC Petition, *supra* note 20, at 30–31.

[49] *503B Bulk Drug Substance Evaluation Guidance* at 17, n. 26, *supra* note 13, (providing as an example treating patients who present with infections in emergency situations for when an office is stock may be needed).

would be an untenable result given the statutory standard, purpose of outsourcing facilities, and the 503B Bulks List.

OFA also states generally that "[t]here is insufficient evidence that FDA-approved products can fully meet the needs of hyper-responders, who may experience adverse effects at standard doses."[50] The 2025 OFA Comment cites to a *New York Times* article, *The Allure of 'Microdosing' Ozempic*, as evidence that lower strength compounded options are needed to avoid adverse reactions.[51] While the article quotes a telehealth company saying there is "well-documented" evidence of "some patients [that] experience side effects," and therefore patients may benefit from microdosing, no concrete data is provided. NNI is not aware of evidence that microdosing is a safe and effective way to address side effects. NNI conducted clinical trials to identify the minimal effective doses with acceptable safety profiles. Based on the safety and effectiveness information from those trials, the FDA-approved labeling includes carefully calibrated dosage and administration instructions involving titrations from an initiation dose to a maintenance dose. A patient who is experiencing known side effects of FDA-approved medicines (*e.g.*, nausea) can either down-titrate to one of the many lower doses of the FDA-approved medicines or remain on a lower dose of the FDA-approved medicines for a longer period of time. Furthermore, the article merely provides anecdotes of those who have allegedly benefited from microdosing. Even then, Dr. Andrew Kraftson, a clinical associate professor in the division of metabolism, endocrinology and diabetes at Michigan Medicine, is quoted as saying that "[i]t's also possible that the benefits some microdosers claim to have seen are the result of the placebo effect."[52] This *New York Times* article cannot be the basis to show that there is a clinical need for strengths lower than those provided by FDA-approved medicines.

OFA attempts to clarify in the 2025 OFA Comment that its Nomination is not arguing that the addition of semaglutide to the 503B Bulks List is warranted because of "convenience" but rather "addressing patient-specific needs" such as "sensitivities" to inactive ingredients. However, OFA fails to provide concrete data supporting the position that patients' sensitivities to any particular inactive ingredients in FDA-approved semaglutide medicines render those drugs medically unsuitable for certain patients.[53] Specifically, with respect to patients who might have propylene glycol sensitivities, OFA never explains why a compounded drug to address that attribute is required. Notably, there are FDA-approved medications that do not contain propylene glycol. As discussed in the Petition, neither RYBELSUS®, an oral tablet, nor WEGOVY®, a subcutaneous injection, contains propylene glycol. OFA's position appears to be that patient sensitivities to propylene glycol mean that FDA-approved semaglutide medicines containing propylene glycol are medically unsuitable for some patients. Yet, OFA does not explain why the propylene glycol-free FDA-approved semaglutide medicines could not be used to address the patient need in question.

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[50] 2025 OFA Comment, *supra* note 4, at 13.

[51] *Id.*

[52] Dani Blum, *The Allure of 'Microdosing' Ozempic*, N. Y. TIMES, Dec. 5, 2024, https://www.nytimes.com/2024/12/05/well/ozempic-microdose-weight-loss.html.

[53] 2025 OFA Comment, *supra* note 4, at 13.

OFA asserts that NNI in its Petition "misquotes" a study that OFA cited related to buccal or sublingual films and tablets.[54] NNI did not misquote the study. In the Petition, NNI argued that the study did "not discuss a single successful sublingual or buccal delivery mechanism for semaglutide; it merely suggests the possibility of such a groundbreaking peptide" and only refers to the potential of future studies on GLP-1 RAs in these drug forms. OFA concedes, however, that the study was a theoretical discussion on buccal or sublingual films and tablets of GLP 1-RAs rather than empirical evidence that there is a clinical need for such products.[55] Such data do not exist at present.

FDA is clear that the burden is on the nominator to provide at least basic explanations for why an approved drug product is not suitable for a particular patient population, supporting information with a good-faith estimate of the patient population with the specific medical condition, citations to relevant literature regarding the incidence of the condition, and more. OFA through its Nomination and Comment provides none. Without such explanations and support, FDA cannot find a clinical need to include semaglutide on the 503B Bulks List.

III. The Statements and Data Cited in the Petition Were Substantiated and Reliable.

The Petition and the foregoing responses to OFA's comments provide sufficient bases for FDA to exclude semaglutide from the 503B Bulks List and grant NNI's Petition. Nonetheless, NNI offers the following responses to additional erroneous or misplaced claims OFA raised in the Comment.

A. NNI appropriately cites adverse event data in FAERS associated with compounded "semaglutide."

OFA contends that NNI did not provide "concrete data" on "hundreds of serious adverse events" associated with unapproved compounded "semaglutide." NNI did provide such data. In the Petition, NNI cited reports from the FDA Adverse Event Reporting System ("FAERS") which included 542 cases of adverse events associated with compounded "semaglutide" since 2018. Each of those cases are documented. They included individuals with hematuria (blood in urine) and myalgia (muscle pain or discomfort), adverse events not present on the labels for NNI's FDA-approved medicines. They also included adverse events associated with combinations of semaglutide with other ingredients for which there are no clinical studies. For example, FAERS includes a report of a patient suffering from liver injury, hospitalization, and death after taking compounded semaglutide and oxidized nicotinamide adenine dinucleotide ("NAD+") or nadide.[56] As an update to the Petition, as of December 31, 2024, FAERS has reported 695 cases of adverse events associated with compounded "semaglutide" since 2018.[57] Of those cases, 506

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[54] *Id.*

[55] *Id.* at 13–14 ("OFA emphasizes that the article does mention positive research outcomes for buccal or sublingual delivery in diabetes-related peptides, **indicating promise in this area of study**.") (emphasis added).

[56] FDA, *FAERS Public Dashboard, supra* note 17, Case ID 22756298.

[57] FDA, *FAERS Public Dashboard*, *supra* note 17.

were classified as "serious" adverse events, 159 involved hospitalization, and 13 included deaths. This is **triple** the number of adverse events for **all** compounded drugs in 2022.[58]

OFA asserts that the adverse events are not based on "clear and verifiable data," despite FDA itself having expressed concerns about the safety of compounded "semaglutide," including adverse events reported to FDA about compounded "semaglutide."[59] FDA has generally stated that compounded "semaglutide" "can be risky for patients, as unapproved versions do not undergo FDA's review for safety, effectiveness and quality before they are marketed."[60] FDA made multiple statements confirming such adverse events associated with compounded "semaglutide": "FDA received multiple reports of adverse events, some requiring hospitalization, that may be related to dosing errors associated with compounded injectable semaglutide products" and "the agency has received adverse event reports that may be related to patients prescribed compounded semaglutide…products in doses beyond what is in the FDA-approved drug label."[61] NNI also cited in the Petition to a publication with specific information on the consequences of dosing errors.[62] This *Journal of the American Pharmacists Association* publication discusses administration errors where patients accidentally self-administered doses of compounded "semaglutide" up to 10 times greater than the intended amount.[63]

Finally, OFA argues that safety concerns based on reported adverse events associated with compounded combinations of "semaglutide" and other ingredients such as pyridoxine are speculative and lack specific data. The FAERS data included in the Petition and updated numbers above include adverse events related to several combinations such as "semaglutide" with cyanocobalamin, methylcobalamin, pyridoxine, and as mentioned above, NAD+. In addition, OFA appears to imply that "[n]one of the semaglutide reports . . . for products containing more than one active ingredient" are attributable to outsourcing facilities because outsourcing facilities purportedly do not compound "semaglutide" with other ingredients.[64] OFA attempts to back this claim by citing to the time period of January – June 2024 in FDA's Outsourcing Facility Product Report database showing only "semaglutide," without co-active ingredients, being compounded. While within the specific time period of January – June 2024

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[58] FDA, *Mitigating Risks of Compounded Drugs Through Surveillance* (last updated Sept. 9, 2023), https://www.fda.gov/drugs/human-drug-compounding/mitigating-risks-compounded-drugs-through-surveillance.

[59] 2025 OFA Comment, *supra* note 4, at 7.

[60] FDA, *FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss* (last updated Mar. 17, 2025), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss.

[61] *Id. See also FDA, FDA Alerts Health Care Providers, Compounders and Patients of Dosing Errors Associated With Compounded Injectable Semaglutide Products* (last updated July 26, 2024), https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded (hereinafter *FDA Alerts Health Care Providers*).

[62] Petition, *supra* note 1, 28–29.

[63] *See* Joseph E. Lambson et al., *Administration Errors of Compounded Semaglutide Reported to a Poison Control Center—Case Series,* 63 J. AM. PHARMACISTS ASS'N 1643 (2023), https://www.japha.org/article/S1544-3191(23)00231-5/abstract.

[64] 2025 OFA Comment, *supra* note 4, at 8.

outsourcing facilities did not report to FDA that "semaglutide" was compounded with another active ingredient, outsourcing facilities have reported compounding such combinations in other periods. For example, outsourcing facilities reported in January – June 2023 compounding "semaglutide" with mannitol and, most recently in July – December 2024, "semaglutide" with cyanocobalamin.[65] Moreover, in OFA's Nomination, OFA stated that "semaglutide" will be "combined with Pyridoxine or an antiemetic medication."[66] Outsourcing facilities and OFA, and not NNI, have indicated that outsourcing facilities have compounded and intend to compound "semaglutide" with other active ingredients. As discussed in the Petition, there is no FDA-approved fixed-dose combination semaglutide medicine, and the safety and effectiveness of compounding semaglutide with other ingredients have not been established.[67]

B. NNI's safety concerns with compounded "semaglutide" apply to 503A pharmacies and 503B outsourcing facilities.

Both 503A pharmacies and 503B outsourcing facilities expose patients to risks because drugs produced in both types of facilities are exempt from new drug approval requirements (Section 505 of the FDCA) and are not required to bear labels with adequate directions for use (Section 502(f)(1) of the FDCA). Patients who receive drugs from both 503A pharmacies and 503B outsourcing facilities are not protected by the extensive safety evaluations and safeguards that are part and parcel of the review and approval of new drugs by FDA. Moreover, both 503A pharmacies and 503B outsourcing facilities widely offer compounded drugs containing chemically synthesized versions of "semaglutide" rather than semaglutide produced via recombinant-DNA technology, which is used in the FDA-approved medicines. As emphasized in the Petition, the synthetic "semaglutide" drug substances have differences in physical and chemical stability and contain peptide-related impurities, which may be associated with immunogenicity concerns, that are not present in the recombinantly produced semaglutide. This presents considerable safety risks for both compounded "semaglutide" from pharmacies and outsourcing facilities.

OFA claims specifically that any safety concerns with compounded "semaglutide" are related to 503A pharmacies and not 503B outsourcing facilities. OFA makes this claim because 503B outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA and 503A pharmacies do not. While we agree that unlike 503A compounded drugs, drugs compounded by outsourcing facilities must comply with CGMP, as well as meet all the conditions of section 503B and other conditions of the Federal Food, Drug, and Cosmetic Act applicable to them, these legal requirements do not save 503B compounded drugs from posing safety risks to patients. Because 503B compounded drugs do not comply with premarket approval, adequate directions for use in labeling, and track-and-trace requirements, they are inherently riskier than FDA-approved medicines. In addition, it is clear that 503B outsourcing facilities do not always meet applicable requirements and those compliance failures pose

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[65] *See* FDA, *Outsourcing Facility Product Report,* Reporting Years 2023-1 and 2024-2, https://dps.fda.gov/outsourcingfacility (last visited Apr. 12, 2025).

[66] OFA Nomination, *supra* note 7, at 8–9.

[67] Petition, *supra* note 1, at 19–21. *See FDA Alerts Health Care Providers*, *supra* note 61 ("The safety and effectiveness of combining semaglutide with other ingredients has not been established.").

additional risks. For example, an outsourcing facility that compounds "semaglutide" received a warning letter from FDA recently, in part, for compounding using a bulk drug substance from a manufacturer that was not an FDA registered establishment under section 510 of the FDCA.[68] In addition, as noted above, the same outsourcing facility recalled more than 13,000 vials of compounded "semaglutide" due to lack of sterility assurance at the facility in which the compounded "semaglutide" had been produced. Such recalls may be challenging for outsourcing facilities to execute effectively due to the fact that they do not track and trace their products through the supply chain. Moreover, many outsourcing facilities are engaging in prohibited wholesaling and facilitating prohibited resales of 503B compounded drugs.[69]

Furthermore, although outsourcing facilities are required to comply with CGMP requirements, they are permitted to depart from CGMP requirements that are applied to conventional manufacturers in certain key areas.[70] In addition, the requirement that outsourcing facilities comply with CGMP does not ensure that outsourcing facilities have appropriate quality specifications for their compounded drug products or meet them. OFA states that outsourcing facilities "can conduct the same testing as NNI under ICH or USP standards to ensure the impurity requirements established by FDA are met."[71] It is unclear what ICH or USP standards OFA is referring to and how they relate to outsourcing facilities' compliance with CGMP or assurance that compounded "semaglutide" drugs meet the same specifications as FDA-approved semaglutide medicines. As discussed in the Petition, FDA reviewed NNI's specifications as part of the premarket approval process, and NNI conducts a complex array of physicochemical and analytical testing to ensure the proper safety and efficacy of the product.[72]

Moreover, compliance with drug CGMP requirements is not sufficient to ensure the safety or quality of the delivery device constituent parts of compounded "semaglutide" products. Outsourcing facilities are using unapproved and uncleared autoinjector pens in their compounded "semaglutide" products, and we are not aware of these facilities complying with device Quality System Regulation ("QSR") or device labeling requirements, which increases the risk of dosing errors. Compliance with FDA's medical 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. As compared to drug CGMPs, the QSR includes unique requirements such as for

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[68] Letter from F. Gail Bormel, FDA, to Mark L'Hommedieu, ProRx , LLC (Mar. 4, 2025), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/prorx-llc-696742-12202024.

[69] Comment from Novo Nordisk Inc., Docket No. FDA-2-23-D-0939 (Feb. 4, 2025).

[70] *See supra* note 18 (explaining that outsourcing facilities are afforded some discretion with respect to certain CGMP requirements and recommendations applicable to drug manufacturers, including requirements related to release testing, stability testing, and maintaining reserve samples). *See GMP for Outsourcing Facilities Guidance*, *supra* note 18.

[71] 2025 OFA Comment, *supra* note 4, at 10.

[72] Petition, *supra* note 1, at 23–24.

design controls, corrective and preventative actions, and purchasing controls,[73] 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 required FDA clearance or approval of the delivery device, and compliance with the device quality and labeling requirements, FDA and patients lack reasonable assurance that the delivery device is safe and effective for the particular use with the compounded drug. In comparison, FDA-approved medicines that use delivery devices (*e.g.*, autoinjectors) require highly specific instructions for use that are validated through appropriate usability testing to assure that the delivery devices can be safely and effectively used for drug delivery.[74] OFA criticizes NNI's FDA-approved medicines as being "fixed-dose pens and non-divisible tablets," but these features are safety precautions to help ensure patients get FDA-approved doses and avoid dosing errors.[75] NNI's injectable semaglutide medicines come in a single-patient-use pen injector, which has been reviewed by FDA for use specifically with semaglutide, and proven to prevent degradation from exposure to air, agitation, temperature changes, certain surfaces, light, and other sources of physical stress, which is required for complex peptide medications such as semaglutide. The single-patient-use pen injector, which comes in various doses, also accurately dispenses the correct dose and comes with detailed instructions to reduce the risk that patients will accidentally overdose.

Finally, FDA statements regarding safety concerns with compounded "semaglutide" did not state that these concerns only applied to compounded products from 503A pharmacies. The statements applied to all compounded "semaglutide." In fact, FDA sent a letter to OFA, who represents 503B outsourcing facilities, warning that prescribers have started patients on doses of compounded "semaglutide" that were "approximately two to four times higher than the recommended starting doses" of FDA-approved semaglutide medicines which have led to serious adverse events reported to FDA.[76] If FDA did not think these concerns applied to 503B outsourcing facilities, FDA would not have directed a letter to OFA.

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[73] 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).

[74] *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, A*pplication 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.

[75] 2025 OFA Comment, *supra* note 4, at 10.

[76] *See* Letter from Shannon Glueck, Branch Chief, Compounding Branch 4, FDA, to Humayun J. Chaudhry, President and Chief Executive Officer, Federation of State Medical Boards at 23-24 (Jul. 16, 2024), https://www.albme.gov/uploads/pdfs/BOPSemaglutide.DeclaratoryRuling_.pdf.

C. OFA's responses to issues were misleading.

OFA asserts that NNI's statement relating to adverse event reporting—specifically, "compounding pharmacies do not conduct surveillance, evaluation, or reporting of adverse events to the FDA, which means the number of reported adverse events associated with compounded 'semaglutide' in FAERS likely reflects a small portion of the actual number of adverse events patients are experiencing after taking compounded 'semaglutide'"—is misleading because outsourcing facilities are required to submit adverse event reports to FDA.[77] As an initial matter, that statement is not misleading because it was referring to 503A compounding pharmacies not outsourcing facilities. Nevertheless, to date, no outsourcing facility has been the sender of any adverse events related to compounded "semaglutide" in FAERS.[78] While FDA "strongly recommends that outsourcing facilities report all serious adverse drug experiences associated with their compounded prescription drug products" because "reporting all serious adverse events, whether expected or unexpected, would provide important information about potential product quality issues or public health risks associated with drug products compounded by outsourcing facilities," there is no record that an outsourcing facility has been the reporter of any adverse events to date.[79] OFA states that "FAERS data for 503B products may therefore be more comprehensive than the petition suggests."[80] However, given that OFA itself claims that outsourcing facilities have provided compounded "semaglutide" to over 2 million patients,[81] it is improbable at best that there has not been a single adverse event that is both serious and unexpected, and thus must be reported to FDA outsourcing facilities.

Adverse events related to compounded products from outsourcing facilities may be underreported for an additional reason related to their business arrangements. Outsourcing facilities often partner with telehealth companies to distribute compounded products. Patients who receive compounded products from these telehealth companies may only be aware of the companies they received the products from, and therefore only report adverse events to these companies. These telehealth companies may not be reporting adverse events they receive to the outsourcing facilities or to FDA. In 2018, FDA inspected BioTe Medical, a company that marketed compounded hormone pellets made by two outsourcing facilities.[82] During an inspection, FDA investigators uncovered about 4,202 adverse events collected by BioTe Medical over five years that had never been reported to FDA.[83] The adverse events suggested that the compounded hormone pellets were possibly associated with endometrial cancer, prostate

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[77] 2025 OFA Comment, *supra* note 4, at 14.

[78] FAERS Public Dashboard, *supra* note 17.

[79] *Id.*

[80] 2025 OFA Comment, *supra* note 4, at 14.

[81] Comment from Outsourcing Facilities Association (Nov. 15, 2024), Docket No. FDA-2015-N-0030-10338.

[82] *See* FDA, *Statement on Improving Adverse Event Reporting of Compounded Drugs to Protect Patients* (last updated Sep. 9, 2019), https://www.fda.gov/news-events/press-announcements/statement-improving-adverse-event-reporting-compounded-drugs-protect-patients.

[83] *Id.*

cancer, strokes, heart attacks, deep vein thrombosis, cellulitis and pellet extrusion.[84] While BioTe Medical had an online portal to collect adverse event data from its customers, it never reported that information to FDA or provided the information to the outsourcing facilities that produced the drugs, so the outsourcing facilities did not, in turn, report the events to FDA.[85] If telehealth companies are receiving, but not reporting these adverse events to an outsourcing facility or FDA, neither the outsourcing facility nor the Agency would be able to fully assess the risks of these drugs.

The 2025 OFA Comment suggests that the outsourcing facilities use of synthetic semaglutide and the use of vials for their compounded drugs is acceptable based on FDA's approval of non-semaglutide peptide products using chemically synthesized peptides in vials.[86] OFA is wrong. First, OFA cannot rely on a non-semaglutide product to support outsourcing facilities' compounding of semaglutide products because each peptide bulk drug substance is unique.[87] Second, outsourcing facilities cannot point to an FDA-approved semaglutide drug product that contains chemically synthesized semaglutide to justify their compounding of synthetic semaglutide products because there is none.[88] Third and relatedly, there is no FDA-approved semaglutide drug product in a vial for outsourcing facilities to reference either. Finally, the outsourcing facilities do not have the type of robust data and information that would be needed to rely on FDA-approved drug products made from recombinantly produced semaglutide to support their use of synthetic semaglutide in their compounded drugs.[89] For these reasons, OFA's reliance on approvals of non-semaglutide peptide products using chemically synthesized peptides in vials to bolster their compounding of synthetic semaglutide in vials is unavailing.

OFA criticizes NNI's citation of estimates on the number of prescriptions of compounded GLP-1 RAs as potentially exaggerating the number of compounded GLP-1 RAs that come from outsourcing facilities.[90] However, OFA's own "conservative[]" estimates put the number of compounded "semaglutide" prescriptions at 80 million in a 12 month span and 2 million patients served with compounded "semaglutide" by outsourcing facilities.[91]

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[84] *Id.*

[85] *Id.*

[86] 2025 OFA Comment, *supra* note 4, at 15.

[87] Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations, 79 Fed. Reg. 37750 (July 2, 2014).

[88] *See* RYBELSUS®, Full Prescribing Information (Dec. 2024), https://www.novo-pi.com/rybelsus.pdf; OZEMPIC®, Full Prescribing Information (Jan. 2025), https://www.novo-pi.com/ozempic.pdf; WEGOVY® (Nov. 2024), Full Prescribing Information, https://www.novo-pi.com/wegovy.pdf .

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

[90] 2025 OFA Comment, *supra* note 4, at 18.

[91] *See supra* note 81.

IV. NNI Opposes BPI Labs Nomination of Semaglutide to the 503B Bulks List

BPI Labs has nominated semaglutide as a bulk drug substance for inclusion on the 503B Bulks List. The BPI Nomination does not show that semaglutide is a bulk drug substance for which a "clinical need" to compound exists. The BPI Nomination is similar to the OFA Nomination and Comment in that BPI Labs makes general statements on the clinical need of compounded "semaglutide" without providing specific patient population data. Statements such as "compounded products are necessary when mass-produced drugs do not meet a patient's specific needs"[92] and "[t]he concern of availability for this medication has been widely publicized and with the introduction of new users, it is imperitive [sic] for compounders to provide an alternative source of the necessary medication"[93] do not provide evidence that an attribute of the FDA-approved medicines makes them medically unsuitable. Furthermore, the BPI Nomination fails to show why those needs could not be satisfied by FDA-approved medicines and must instead be compounded from a bulk drug substance. Because BPI Labs makes the same assertions as OFA in its nomination, NNI incorporates its analyses in the Petition and this Supplement to address BPI Labs' claims related to the need for different dosage strength, different dosage forms (including oral and sublingual), microdosing, and the safety concerns with compounded "semaglutide" and the unapproved devices used to administer such products.

BPI Labs' nomination did make one assertion that OFA did not make. BPI Labs claims it is necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product on the grounds that "[o]ral dosages, other than commercially avaialble strenghts [sic], are required" to address a specific patient need. BPI states that, "according to published data, up to 10% or the current population deals with Trypanophobia (fear of needles) and up to 33% in children."[94] BPI Labs did not provide a citation for any publication with such data. Regardless, FDA-approved RYBELSUS® is available as oral tablets.

NNI wishes to emphasize a point by addressing a statement made by BPI Labs, which is similar to the statements made by OFA. The BPI Nomination states that "[t]here is evidence that higher doses than are currently commercially available show a superior effect as compared to the commercially available doses for oral formulations and potentially injectable formulations as evidenced by the FDA-approved sponsor's own clinical trials."[95] NNI reiterates that such reasoning undermines the investigational new drug ("IND") process and the entire drug-approval framework created by Congress to protect patients. FDA should not permit BPI Labs to use compounding as a means to circumvent the IND process and expose patients to compounded versions of investigational products at higher strengths, all while claiming that the strengths of FDA-approved medicines are medically unsuitable for some patients.

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[92] BPI Nomination, *supra* note 6, at Line 14.

[93] *Id.*

[94] *Id.* at Line 16.

[95] *Id.* at Line 24.

V. Conclusion

Therefore, for the reasons stated in the Petition and above, NNI respectfully requests that FDA publish a notice in the *Federal Register* excluding semaglutide from the 503B Bulks List; rescind in its entirety the *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*; and exclude semaglutide from Category 1 of the 503B Interim Policy.

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