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OFA

OUTSOURCING FACILITIES ASSOCIATION

February 13, 2025

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20825

Re: Response in Opposition to Novo Nordisk's Citizen Petition, requesting that FDA take certain actions with respect to the Outsourcing Facilities Association ("OFA") nomination of semaglutide to the list of bulk drug substances that may be used by outsourcing facilities in compounding (the "503B Bulks List"); Docket No. FDA-2024-P-4937.

I. Introduction

The Outsourcing Facilities Association (OFA) submits this response to address claims made by Novo Nordisk, Inc. ("NNI" or "Novo") in its Citizen Petition, which seeks that the FDA take certain actions with respect to the Outsourcing Facilities Association's ("OFA") nomination of semaglutide to the list of bulk drug substances that may be used by outsourcing facilities in compounding (the "503B Bulks List").[1]

OFA represents registered outsourcing facilities committed to providing high-quality compounded medications, tailored to meet unique patient needs and provider preferences. OFA opposes the requests made in this petition, which seek to restrict access to compounded versions of semaglutide and limit flexibility for healthcare providers, ultimately impacting patient care. OFA also opposes any prioritization of the petition which would necessarily result in the unjustified diversion of precious agency resources from higher priority issues.

NNI continues the long and sordid history of branded drug manufacturers using citizen petitions to maintain or gain a market advantage despite clear interest by the FDA in protecting the public

[1] On October 24, 2024, OFA submitted a comment in response to Novo's Citizen Petition, requesting that the FDA exercise its authority to request an economic impact statement from Novo under 21 CFR 10.30(b)(3). FDA-2024-P-4937-0003. The present comment is intended to supplement OFA's previous comment. Regarding its request that the FDA request an economic impact statement, OFA further states that the economic considerations are far too significant to ignore—to the point that a decision granting the Citizen Petition without addressing them would be arbitrary and capricious and subject to vacatur. It is manifestly unreasonable for an agency to have "entirely failed to consider an important aspect of the problem" before it, *Motor Vehicle Manufacturers Association v. State Farm Mutual Automobile Insurance Co*., 463 U.S. 29, 43 (1983). The costs associated with limiting or prohibiting compounding of semaglutide products are important, to say the least, and the competitive dynamics of the market for semaglutide products is undoubtedly relevant to the investments that compounding pharmacies and outsourcing facilities might make in compounding semaglutide. An agency action that fails to consider this aspect of the problem before it would be arbitrary and subject to vacatur.

health by ensuring the safety, efficacy, and security of human drugs.[2] Previously, FDA has referred some citizen petitions filed by pharmaceutical companies to the FTC for administrative review.[3]

II. Background

On July 2, 2024, OFA nominated semaglutide for inclusion on the 503B Bulks List, requested the FDA to evaluate semaglutide as a bulk drug substance and determine that there is a clinical need for outsourcing facilities to compound drug products using semaglutide under section 503B of the Federal Food, Drug, and Cosmetic Act ("FD&C Act").[4]

To date, FDA has added only five bulk drug substances to the 503B Bulks List.[5] It has also determined to not add 22 other bulk drug substances to this list.

On October 21, 2024, Novo Nordisk filed a Citizen Petition ("CP") under 21 C.F.R. 10.30, requesting that in response to OFA's Nomination the FDA take the following actions:

> 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* ("503B Interim Policy"); and
> 3) Exclude semaglutide from Category 1 of the 503B Interim Policy.

The FDA should not prioritize its review of this petition over agency decision making or over other pending citizen petitions. To the extent the FDA decides to address the merits of the petition, OFA maintains that the FDA should grant none of the requested actions in this citizen petition.

III. The Petition Should Be Dismissed or Denied Because It Is Procedurally Improper.

A. <u>The Novo Citizen Petition improperly would turn OFA's nomination into a citizen petition and skew the FDA's timing and consideration.</u>

OFA followed the FDA's requested path of nominating semaglutide through the designated docket, FDA-2015-N-3469. OFA is more than content to permit the FDA to evaluate its nomination pursuant to the administrative process the FDA has established, and on the timeline the FDA chooses, using its inherent discretion to allocate agency resources to its priorities. In effect, the Novo citizen petition would up-end OFA's nomination, and have the FDA pull OFA's

[2] Feldman, Robin; Wang, Connie (March 2017), A Citizen's Pathway Gone Astray — Delaying Competition from Generic Drugs, New England Journal of Medicine, 376 (16): 1499–1501.
[3] FDA denial of citizen petition by Par Sterile Products LLC. Docket No. FDA-2021-P-1211. December 15, 2021. ("The Agency intends to refer this matter to the Federal Trade Commission (FTC), which has the administrative tools and the expertise to investigate and address anticompetitive business practices.").
[4] *See* FDA-2015-N-3469-0388.
[5] 503B Bulk Drug Substances List, FDA. https://www.fda.gov/drugs/human-drug-compounding/503b-bulk-drug-substances-list

nomination out of sequence in order to comply with the statutory timeline associated with citizen petitions.

In its 1975 proposed rule regarding citizen petitions, the FDA noted the dangers of incorrectly prioritizing a citizen petition. It appears that even then the agency was aware of circumstances in which it was considering an issue already, only to have a citizen petition filed on the same matter. For the agency to act on the basis of the filing of the citizen petition rather than its underlying processes could result in an untimely decision or the waste of resources:

> To grant the relief sought in the petition in such instances would be premature; to deny the petition would constitute final administrative action possibly triggering the unnecessary initiation of judicial review by the petitioner. A delay in ruling on the petition would be prudent in such instances.[6]

The FDA should not accede to NNI's attempts to skew the agency's consideration of OFA's nomination of semaglutide to the 503B Bulks List. Concerns of regulatory capture abound.

The FDA should not permit Novo to transform the nature of OFA's nomination, and the FDA should not prioritize NNI's Citizen Petition.

B. <u>The Citizen Petition is duplicative of OFA's underlying nomination of semaglutide to the 503B Bulks List.</u>

The Citizen Petition is a particularly inappropriate vehicle for agency action when, as here, the matter is already under consideration by the FDA. OFA has already requested the FDA's consideration of semaglutide for the 503B Bulks List. The Citizen Petition is duplicative of that nomination. Fifty years ago, the FDA noted its scarcity of resources to deal with petitions and similar requests.[7] The FDA back then anticipated precisely the situation that NNI has tried to put the agency in:

> An apparent delay in responding to a petition might also result from the fact that the agency is in the process of taking action of the type sought in the petition, but has not reached the point of implementation.[8]

NNI's Citizen Petition asks the FDA to take a specific action with respect to OFA's nomination, notwithstanding that the FDA is already seized of the matter. OFA's nomination of semaglutide to the 503B Bulks List followed the desired process set out by the FDA. NNI's filing of a citizen petition, in lieu of or addition to a nomination, is procedurally improper, given the existence of a more specific vehicle to obtain that relief.[9]

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[6] 40 Fed. Reg. at 40,686.
[7] FDA Administrative Practices and Procedures, 40 Fed. Reg. 40,682, 40,686 (Sept. 3,1975).
[8] *Id.*
[9] *Compare* 5 U.S.C. § 703 (providing a generic cause of action to obtain review of agency actions only in the absence of the availability of a "special statutory review proceeding").

Nor can NNI claim that its Citizen Petition is distinct from OFA's Nomination on the basis that section 503B(a)(2)(A)(i) of the FD&C Act only directs the FDA to issue a Federal Register notice and seek input from the public when it proposes to *include* bulk drug substances on the 503B Bulks List, whereas NNI's requested relief is to *exclude* semaglutide from that list. As will be discussed below, affirmative exclusion from the 503B Bulks List is not a request that falls within the scope of section 503B. But, in any event, the FDA has committed to issue a Federal Register notice and seek public comment both when it its proposed course of action is to include a substance on that list *and* when it is proposing to decline a nomination and not to include the substance on the list.[10]

The Citizen Petition should be dismissed on these bases. At the least, the FDA should refuse to devote agency resources to NNI's Citizen Petition and exercise its inherent discretion to prioritize other matters, including citizen petitions that are not duplicative.

C. Novo's requested relief of excluding a drug substance from the 503B Bulks List is improper.

The requested relief is not how the FDA has committed to developing the 503B Bulks List. The FDA does not publish in the Federal Register an exclusion of a drug substance from the 503B Bulks List. Rather, it considers the substance and decides whether to include the substance at the time of its determination. The FDA initially establishing a docket in 2013 to receive nominations to the 503B Bulks List, 78 FR 72838, and reports that it received over 2,000 nominations. Because many of the nominations were not for bulk drug substances or did not include sufficient information to be evaluated by the FDA, the FDA reopened the docket in 2014, 79 FR 37747, to provide stakeholders with information the FDA needed in order to evaluate nominations for the list. It thereafter received nominations for over 2,590 substances, but the FDA determined that approximately 1,750 were not eligible for a variety of reasons, and that 650 other substances contained insufficient supporting evidence.[11]

In response, the FDA ultimately established a continuing docket, FDA-2015-N-3469, to "provide an opportunity for interested persons to submit new nominations of bulk drug substances, renominate substances with sufficient information, or submit comments on nominated substances." The FDA set out information it would require to evaluate clinical need, including:

- A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat;
- A list of FDA-approved drug products, if any, that address the same medical condition;
- If there are any FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary;
- If the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product;

[10] 88 Fed. Reg. at 56,838 n.11.
[11] 80 Fed. Reg. 65,770, 65,772 (Oct. 27, 2015).

- A bibliography of safety and efficacy data for the drug product compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature; and
- If there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.[12]

Then, in 2023, the FDA set forth its methodology for developing the 503B Bulks List. 88 Fed. Reg. 56,837 (Aug. 21, 2023). The FDA stated that it intended to publish notices for public comment of its proposed position on each substance, along with the rationale for that position. Id. at 56,838. It would then accept and consider public comments, and decide whether input from the Pharmacy Compounding Advisory Committee (PCAC) would be helpful, and possibly seek that input. Based on that input and public comment, the FDA would then reach a final determination on whether to include the bulk drug substance on the 503B Bulks List, or its determination of no clinical need and the resulting decision to not include the substance on such list.

In addition, the FDA announced that it would evaluate bulk drug substances for inclusion on the 503B Bulks List on a "rolling basis," and announce proposed and final determinations until it had dealt with all sufficiently supported nominations.

In a list last updated May 20, 2024 (which means it doesn't include OFA's July 2, 2024 nomination of semaglutide), FDA indicates that it has over 300 substances it considers under current evaluation.[13]

The Novo Citizen Petition attempts to crash through this methodical process like Kool-Aid Man through the wall, and seeks an end-run to advance its business interests. It attempts to use the citizen petition process, with the 180-day statutory deadline for response to gain priority over the vast number of other nominations.

D. Processing the duplicative Citizen Petition would set a bad precedent.

If the FDA elects to consider the Citizen Petition, it will establish for interested stakeholders that they can receive priority over other FDA matters. Not only that, but if the FDA were to do so, it would teach every stakeholder seeking to nominate a bulk drug substance to do so not within the process that the FDA set out in its 2023 notice, but to do so as a citizen petition.

And, it would teach every opponent to a nomination to file a strategic citizen petition in opposition. After all, denying the citizen petition would not result in semaglutide being added to the 503B Bulks List, because Novo's petition does not seek a decision on whether to include it on the list or not. It only asks for the exclusion of semaglutide from the 503B Bulks List. In a

[12] 80 Fed. Reg. 65,770, 65,772.
[13] Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf

heads-I-win-tails-you-lose move, Novo would have the opportunity in the future to submit public comment whenever the FDA reaches the point of proposing to include semaglutide on this list, essentially getting a free do-over.

This is yet another reason to dismiss the petition or, at a minimum, refuse to prioritize it.

IV. The Petition Should Be Dismissed or Denied Because It Fails To Satisfy Requirements for Citizen Petitions.

A. NNI's Citizen Petition does not, despite certification, include "representative information known to the petitioner which is unfavorable to the petitioner's position." 21 C.F.R. 10.30(b)(3)(B).

NNI's Citizen Petition does not fulfil the requirement to include "representative information known to the petitioner which is unfavorable to the petitioner's position." The requirement to include representative unfavorable information dates back to the original regulation for citizen petitions. The 1975 proposed rule recognized that the Commissioner "has found, in reviewing petitions submitted in the past, that adverse or unfavorable information is omitted and ignored, thus resulting in a very unbalanced and misleading presentation."[14] It recognized that without the requirement to include information on both sides of the issue, a petitioner "could present only one side of the story and thus mislead both the Food and Drug Administration and the public as to the true situation."[15] Indeed, the FDA considered the presentation of representative data on both sides of an issue to be so critical that it considered that the "failure to include such data and information would constitute a violation of the False Reports to the Government Act, 18 U.S.C. 1001."[16]

Nowhere, however, does NNI's Citizen Petition specifically include "representative information known to the petitioner which is unfavorable to the petitioner's position."[17] Two areas in particular stand out as misleading and imbalanced. First, where NNI points to adverse event reports related to compounding facilities, it deprives the FDA of the ability to weigh whether compounding facilities present increased risks over NNI's own production, because it fails to acknowledge NNI's own reporting of adverse events and why those reports are any less significant than those it attributes to compounding facilities.

Second, NNI's Citizen Petition does not separately analyze its claims regarding 503A pharmacies versus 503B compounding facilities. This failure obscures any countervailing (i.e., unfavorable) information showing that 503B facilities might do a better job compounding based, for example, on their required adherence to current good manufacturing practice (cGMP).

NNI's Citizen Petition is defective because it fails to include this required information and should be dismissed on that basis.

[14] FDA Administrative Practices and Procedures, 40 Fed. Reg. 40,682, 40,686 (Sept. 3,1975).
[15] *Id.*
[16] *Id.*
[17] 21 C.F.R. 10.30(b)(3)(B).

For all of the forgoing reasons, the FDA should not permit Novo to abuse the citizen petition process and gain an unfair allocation of agency resources to its request. The FDA should dismiss Novo's citizen petition.

V. To the Extent the FDA Decides to Consider the Merits of Novo's Citizen Petition, It Should Deny the Request.

NNI's Citizen Petition does not provide the FDA with segregated data and allegations about the ability of 503B outsourcing facilities (relevant to including semaglutide on the 503B Bulks List) to safely compound semaglutide products, but instead combines the alleged risks from 503A pharmacies. NNI presents a mish-mash of supporting allegations, combining past incidents from both 503A pharmacies and 503B outsourcing facilities. The agency has no obligation to unravel the Citizen Petition's improperly intertwined claims.

A. Unsubstantiated Safety Claims

Novo Nordisk's petition claims, "hundreds of serious adverse events have been reported in patients who have received unapproved compounded 'semaglutide,' including hospitalizations and deaths, notwithstanding the underreporting of adverse events associated with compounded drugs."[18] OFA contends that this statement is misleading, as Novo Nordisk provides no concrete data to substantiate the claim. Instead, the petition's cited footnote simply states, "Data supporting the safety of compounded 'semaglutide' is lacking,"[19] without verifying specific cases of hospitalization or death. Assertions regarding adverse events should be based on clear and verifiable data, as unsupported statements risk creating undue alarm.

The petition further asserts, "There also have been documented risks of overdoses and efficacy issues with subpotent and superpotent compounded semaglutide, which can be life-threatening to patients."[20] OFA argues that without detailed documentation or case reports, this claim remains speculative. Claims of overdosing or subpotency should be substantiated with specific evidence to accurately assess the safety of compounded medications. For example, the petition does not differentiate between 503B compounding and 503A compounding. The petition requests that the FDA take regulatory action under Section 503B. Conflating 503B and 503A together, which petitioner does, is misleading. Further, while the petitioner inappropriately discusses purported overdosing or subpotency associated from unidentified "compounders," the only pertinent information would be from 503B outsourcing facilities. The petition does not even mention the thousands of adverse events that have been reported to the Agency for petitioner's own product.

Novo Nordisk also refers to a recent FDA letter stating, "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, leading to serious adverse events reported to FDA."[21] OFA clarifies that the FDA's letter suggests multiple factors

[18] Citizen Petition from Novo Nordisk, Comment ID F*DA-2024-P-4937-0001* (Oct. 21, 2024) [hereinafter Novo Nordisk Petition]. at 4.
[19] *Id*. at 4. See Footnote 6.
[20] *Id*.
[21] *Id*. at 11-12.

contributing to adverse events, such as prescriber dosing practices and accelerated titration schedules. Additionally, the referenced FDA alert primarily addresses 503A facilities, which follow different regulatory standards than 503B outsourcing facilities. The risks mentioned are not inherent to compounded semaglutide or unique to specific packaging types. The petitioner conveniently left out that the risks even pertain to petitioner's product. Prescriber errors are not an inherent risk for compounded drug products, rather prescriber errors are a risk for all drug products. Here, because the active ingredient is semaglutide, risks of prescriber errors are applicable to both FDA-approved, 503A compounded, and 503B compounded drug product. This is especially true when the starting dose is considered as the risk factor. The same prescriber would be starting at that same dose regardless of the product's source from NNI or a compounder.

The petition also states, "the FDA has noted that while some compounders are incorporating additional ingredients, including pyridoxine, into their semaglutide products, the safety and effectiveness of compounding semaglutide with other ingredients has not been established."[22] Again, petitioner is misleading – what "some compounders" are doing is completely irrelevant to petitioner's requests. 503B outsourcing facilities must report to the Agency all drug products compounded and that information is publicly available on FDA's own website. The petitioner knows that and is intentionally conflating 503A pharmacies with 503Bs, and doing so after signing the sworn affidavit that is required when submitting a Citizen Petition to the FDA. The 503B Outsourcing Facility Product Report is publicly available. Seven outsourcing facilities reported compounding semaglutide during the time period of January - June 2024. None of the semaglutide reports are for products containing more than one active ingredient. Petitioner is conflating 503A and 503B compounding and doing so intentionally.

OFA responds that adverse events alone are not definitive indicators of a lack of safety or efficacy in compounded products, particularly in cases where such events may result from isolated issues unrelated to product quality. The petition references an instance involving incorrect dose administration, which does not speak to the inherent safety or effectiveness of semaglutide compounded by 503B outsourcing facilities. In fact, this argument is a reason why more compounding should be done in a 503B, which requires cGMP standards and testing requirements like potency and stability indicating assays over time (the same standards applicable to NNI), as compared to a 503A pharmacy. Furthermore, without direct, evidence-based findings demonstrating that additional ingredients like pyridoxine impact the safety profile of semaglutide, OFA argues that these safety concerns remain speculative and unfounded. Such assumptions mischaracterize the rigorous compliance requirements that 503B facilities follow, drawing attention away from the clear regulatory distinctions and compliance measures designed to address issues within specific settings rather than applying broad prohibitions based on unverified claims.

Additionally, Novo Nordisk asserts, "FDA's recent risk alert on dosing errors associated with compounded 'semaglutide' products notes that the various containers and packaging offered by compounders, including multiple-dose vials and prefilled syringes, likely contribute to medication errors."[23] OFA emphasizes that the alert specifically addresses 503A facilities, which

[22] *Id*. at 14.
[23] *Id*. at 15.

do not operate under the same standards as 503B outsourcing facilities. The cited errors arise from provider or patient mistakes and are not indicative of issues inherent to compounded semaglutide. Proper education, rather than limitations on compounding, would mitigate these risks. This is another example of the petitioner's misleading statement, in clear violation of 21 CFR § 10.30(b)(3) requiring representative information known the petitioner which is unfavorable to the petitioner's position.

Novo Nordisk also claims, "FDA received several reports of dosing errors involving compounded semaglutide injectable products in multiple-dose vials, which resulted in patients seeking medical attention or requiring hospitalization."[24] OFA highlights that these reports, again, likely relate to 503A compounding and that the incidents mainly involve human error. Without petitioner providing the data it relies on as required by 21 CFR § 10.30(b)(3), the Agency cannot evaluate the petition. Such cases do not reflect the safety standards of 503B facilities, where protocols for dosing accuracy and safety are rigorously enforced.

B. Claims Regarding Clinical Need and Dosage Forms

The petition asserts, "semaglutide does not meet the standard and criteria set forth by Congress and the FDA for inclusion on the 503B Bulks List because it is not a bulk drug substance for which a 'clinical need' to compound exists."[25] Petitioner is adopting a definition of "clinical need" opposing the statutory text. The "clinical need" for semaglutide is straightforward: the ingredient is needed in clinical treatment. It has been proven safe and effective for treating severe medical conditions, and it is in demand in medical settings across the United States. Compounded semaglutide addresses critical patient needs unmet by FDA-approved drugs. Patients who experience adverse reactions to propylene glycol in FDA-approved formulations may benefit from compounded semaglutide, as referenced in studies showing preference for propylene glycol-free versions. Additionally, OFA highlights that some patients require doses unavailable in commercial semaglutide products, emphasizing the clinical need for compounded alternatives.

Novo Nordisk's petition also argues, "current and historical use of compounded 'semaglutide' weighs against a finding of clinical need,"[26] citing the recent approval of semaglutide in 2017 for diabetes and 2021 for weight management. OFA contends that historical use of compounded semaglutide corresponds directly with legal availability and the onset of product shortages, addressing patient needs that could not otherwise be met due to market limitations.

The petition claims, "OFA's nomination does not provide specifics as to why such FDA-approved dosages might be medically unsuitable for a broad patient population."[27] OFA clarifies that its nomination explicitly highlights reasons why specific patient populations require compounded semaglutide. For instance, FDA-approved semaglutide contains propylene glycol, which has been associated with injection site irritation, with studies indicating 95% of patients

[24] *Id*.
[25] *Id*. at 2.
[26] *Id*.
[27] *Id*. at 10.

preferring formulations without it.[28] OFA emphasizes that compounded versions provide flexibility in dosage and formulation, addressing specific patient sensitivities and enhancing adherence to treatment.

Additionally, the petition argues, "OFA's unsupported claim that some patients need a lower dose of injectable semaglutide because they are 'hyper-responders' can be addressed by FDA-approved medicines."[29] OFA asserts that there is insufficient evidence that FDA-approved products can fully meet the needs of hyper-responders, who may experience adverse effects at standard doses. NNI's fixed-dose pens and non-divisible tablets limit providers' ability to adjust doses for sensitive patients, justifying the need for customized, lower-dose compounded options to avoid adverse reactions. Microdosing trends have been widely reported and allow patients otherwise intolerant to standard doses to continue treatment.[30]

Finally, Novo Nordisk claims, "OFA's nomination, however, fails to provide a good-faith estimate of the patient population with specific medical conditions that purportedly needs compounded semaglutide."[31] OFA acknowledges that while an exact population estimate may be challenging, it has clearly identified clinical groups—such as those with propylene glycol sensitivity or patients requiring dose adjustments beyond FDA-approved ranges—that would benefit from compounded semaglutide. By addressing specific medical circumstances, OFA's nomination supports the need for individualized compounded formulations to meet patient-specific clinical needs that cannot be met by the FDA approved product. That alone shows that there is a clinical need for compounding using this bulk substance.

C. Manufacturing and Compounding Process Concerns

Novo Nordisk claims, "manufacturing differences between recombinant and chemically synthesized semaglutide have been shown to yield semaglutide with different physical and chemical profiles."[32] OFA responds that while differences in manufacturing processes may introduce variations in impurities, this does not mean that chemically synthesized semaglutide is clinically different. FDA routinely evaluates and approves synthetic versions of drugs initially produced via recombinant technology when they meet equivalent safety and efficacy standards. In fact, tirzepatide, which is also a GLP-1 and approved under similar conditions as semaglutide, is a chemically synthesized drug.[33] Therefore, OFA maintains that compounded semaglutide remains a viable option, addressing patient needs without compromising quality. Furthermore, 503Bs can conduct the same testing as NNI under ICH or USP standards to ensure the impurity requirements established by FDA are met. It is important to note that if these standards are too tough for a 503B to meet under cGMP requirements they would also be tough for NNI to meet under the same cGMP requirements. Specifically, similarly regulated entities cannot be treated differently under the same regulatory standard.

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[28] *Id*. at 10. See footnote 47.
[29] *Id*.at 12.
[30] The Allure of 'Microdosing' Ozempic. The New York Times. December 5, 2024.
[31] Novo Nordisk Petition at 12.
[32] *Id*. at 2.
[33] Farzam, K. (2024) Tirzepatide, StatPearls [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK585056/ (Accessed: 13 November 2024).

The petition further argues, "testing results has shown certain compounded 'semaglutide' samples to have substantially lower strengths than labeled..."[34] OFA clarifies that the referenced examples stem from 503A pharmacies, which are subject to different regulatory oversight than 503B facilities. Again, the petitioner knowingly conflates 503A facts to use for this argument involving 503B standards. 503A testing results actually demonstrate that more compounding should be done in a 503B as compared to a 503A.

Moreover, in cases where compounded products deviate from potency standards in a 503B the product would not be distributed. Furthermore, FDA regulatory actions involving a product that did not meet a testing requirement should address specific instances rather than imposing a blanket prohibition, such as with a recall.[35] The rare occurrence of potency issues does not justify an all-encompassing restriction on compounded semaglutide, especially from 503B facilities adhering to rigorous standards. And, especially when the issue is with a product from a 503A facility, not a 503B. These examples of issues with 503A compounded product further illustrate the clinical need for 503B outsourcing facilities to compound with semaglutide. Afterall, under section 503A, compounders may lawfully compound semaglutide because semaglutide is a component of an FDA-approved drug product.[36] The petition additionally claims, "Bulk drug substance providers are manufacturing chemically synthesized versions of the "semaglutide" bulk drug substance, rather than producing semaglutide via recombinant-DNA technology, as in the FDA-approved products. Manufacturing differences between recombinant and chemically synthesized semaglutide have been shown to yield semaglutide with different physical and chemical profiles."[37] OFA asserts that 503B outsourcing facilities operate under FDA-regulated practices, ensuring consistent potency and stability. Potential minor differences due to compounding methods do not alter the core therapeutic effect of semaglutide, especially when compounded within established quality guidelines. The oversight and practices of 503B facilities are intended to mitigate the risks cited by the petitioner. For example, outsourcing facilities are subject to cGMP, the same regulatory safeguards that petitioner is subject to in the manufacturing process.

Furthermore, the petition's claim that manufacturing differences between the semaglutide used in FDA-approved formulations and the "semaglutide" used in compounded formulations lead to differences in physical and chemical stability is unsupported and lacks credibility.[38] The Petitioner references testing of samples from bulk drug substance suppliers but fails to identify the specific sources of these samples or disclose how they were obtained. This lack of transparency undermines the reliability of the results. Additionally, the Petitioner does not provide data or evidence to support the assertion that the trace metals detected—such as boron, magnesium, aluminum, chromium, manganese, iron, nickel, zinc, copper, potassium, and calcium—negatively impact the physical or chemical stability of the compounded formulations.

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[34] Novo Nordisk Petition, supra note 1, at 2.
[35] Novo Nordisk should be aware of this regulatory framework given the fact that Novo Nordisk has received 483s from FDA for its drug substance manufacturing site. *See* FDA Form 483 issued to Novo Nordisk A/S dated March 25, 2024.
[36] 21 U.S. Code § 353a(b)(1)(A)
[37] Novo Nordisk Petition, supra note 1, at 2.
[38] *Id*. at 19. *See* Morten Hach et al., *Impact of Manufacturing Process and Compounding on Properties and Quality of Follow-on GLP-1 Polypeptide Drugs*, PHARM. RSCH. (Oct. 8, 2024), https://link.springer.com/article/10.1007/s11095-024-03771-6.

Moreover, the study cited to support these claims was funded by Novo Nordisk, with all authors being employees and shareholders of the company, presenting a clear conflict of interest.[39] These financial ties cast doubt on the objectivity of the findings, particularly as they appear to target competing semaglutide products. Without independent, transparent, and verifiable data, the claim cannot be considered credible.

D. FDA's 503B Interim Policy

The petition claims, "FDA also should not categorize semaglutide under its 503B Interim Policy because the interpretations contained therein are contrary to law and should be rescinded."[40] OFA supports continued application of the 503B Interim Policy at this time as to facilitate the production compounded drugs in a safe and regulated manner, while ensuring patients receive appropriate medications on time. Simply rescinding the Interim Policy, without any contemporaneous authorization of compounding activities contemplated by the statute, would restrict patient access to compounded medications and limit outsourcing facilities' capacity to serve diverse patient needs effectively. It would be arbitrary and capricious for FDA to simply rescind the Interim Policy without considering and addressing the consequences of doing so.[41]

E. Clinical Need for Compounded Semaglutide

The petition claims, "By way of comparison, acetaminophen's (e.g., Tylenol) 500 mg tablets are 19 mm and taken by millions of adults and children."[42] OFA asserts that this comparison is irrelevant, as acetaminophen and semaglutide differ significantly in pharmacokinetics, dosing, and therapeutic indications. Acetaminophen is generally well-tolerated with minimal risk of gastrointestinal side effects, while semaglutide requires precise titration due to GI effects. The size of a tablet alone does not address the specialized dosing needs of semaglutide patients.

The petition also states, "OFA's claim that patients would face the 'daunting' task of swallowing RYBELSUS® tablets is not based on any legitimate evidence and should not serve as the basis to establish a clinical need to compound semaglutide."[43] OFA counters that difficulty swallowing is a well-documented issue, especially among older adults, with dysphagia affecting up to 33% of older adults.[44] Even more notably, dysphagia is reported in up to 80% of older adults who have Alzheimer's disease and 60% of those with Parkinson's disease.[45] These patients often need alternatives to standard oral tablets. Former FDA Commissioner Hamburg testified that compounding meets essential patient needs, such as when patients cannot swallow pills or are allergic to specific ingredients.[46]

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[39] *See* Hach et al., *supra* note 19.
[40] Novo Nordisk Petition, supra note 1, at 3.
[41] *See, e.g., Dep't of Homeland Sec. v. Regents of the Univ. of California*, 591 U.S. 1, 28–29 (2020).
[42] *Id*. at 13.
[43] *Id.*
[44] Shanojan Thiyagalingam et al., *Dysphagia in older adults*, 96 MAYO CLINIC PROCEEDINGS 488–497 (2021).
[45] *Id.*
[46] Statements Of Margaret A. Hamburg, Commissioner, Food & Drug Administration. The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before The Subcommittee On Oversight And Investigations Of

Additionally, the petition claims, "FDA's guidance is clear that 'the combination of multiple active ingredients to allow for administration of fewer products [is not] likely to represent a clinical need.'"[47] OFA clarifies that its nomination does not propose combining ingredients merely for convenience but rather to address specific patient needs. OFA emphasizes the importance of tailoring compounded medications to remove inactive ingredients for patients with sensitivities and adapting dosage forms to improve compliance and safety for those with unique requirements.

The petition asserts, "In fact, the FDA explicitly noted that it will not consider the convenience in administering a particular compounded drug in assessing clinical need."[48] OFA responds that its argument is not based on convenience but on addressing patient-specific needs, such as intolerance to inactive ingredients or challenges with certain administration devices. OFA highlights that patients who benefit from customized formulations or alternative dosing forms may not have access to these options with commercially available drugs. This is the purpose of compounding.

The petition further claims, "Current and historical use of compounded 'semaglutide' weighs against a finding of clinical need."[49] OFA argues that compounded semaglutide has been produced in response to legal availability and product shortages, directly addressing patient needs when FDA-approved options were limited. The historical use aligns with the timeline of legal authorization, underscoring clinical demand in line with regulatory allowances.

F. Efficacy and Safety Concerns Over Compounded Semaglutide

The petition references an article but misquotes it by stating, "…the article notes that while buccal or sublingual delivery of peptides have an 'appeal,' their use in peptides like GLP-1 RAs are 'less studied' compared to insulin products and future investigators must 'dig more into the generation of buccal or sublingual tablets containing GLP-1 RAs.'"[50] In reality, the article states that future investigators "are expected to dig more," not that they "must," as the petitioner inaccurately implies, thereby framing it as a necessity.[51] This again must be considered viewing the requirements for submitting a certified statement in a citizen petition to the FDA. Additionally, while the petitioner claims that "GLP-1 RAs are 'less studied' compared to insulin products," it's essential to note that GLP-1 RAs and other peptides are indeed "less studied" than insulin, primarily due to insulin's long-established role as a mainstay to traditional diabetes treatment. Furthermore, OFA emphasizes that the article does mention positive research

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The Committee On Energy And Commerce House Of Representatives One Hundred Twelfth Congress Second Session November 14, 2012 Serial No. 112–181.

[47] Novo Nordisk Petition, supra note 1, at 14.

[48] *Id*.

[49] *Id*. at 32.

[50] *Id*. at 13.

[51] Anubhav Pratap-Singh, et al., *Concept for a Unidirectional Release Mucoadhesive Buccal Tablet for Oral Delivery of Antidiabetic Peptide Drugs Such as Insulin, Glucagon-like Peptide 1 (GLP-1), and their Analogs*, 15 PHARMACEUTICS 2265 (Jul. 17, 2024), https://doi.org/10.3390/pharmaceutics15092265.

outcomes for buccal or sublingual delivery in diabetes-related peptides, indicating promise in this area of study.[52]

The petition further claims, "The article does not discuss a single successful sublingual or buccal delivery mechanism for semaglutide; it merely suggests the possibility of such a groundbreaking peptide."[53] OFA clarifies that the article serves as a theoretical discussion rather than empirical evidence, reviewing advancements in peptide delivery rather than documenting patient outcomes. The article does not need to confirm an existing delivery method to validate its exploration of future peptide delivery possibilities.

The petition asserts, "OFA's nomination provides no details about the size of the patient population that is purportedly allergic to [propylene glycol]."[54] OFA clarifies that its nomination refers to patient preferences for propylene glycol-free formulations, citing a study in which "95% of patients preferred the formulation without propylene glycol."[55] This patient preference supports the availability of propylene glycol-free options for those experiencing discomfort with standard formulations, as shown by 95% of 103 study subjects reporting pain with propylene glycol injections.[56]

Novo Nordisk claims, "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.'"[57] Again, another example of petitioner misleading the Agency. The requested actions pertain to Section 503B yet the purported support for those actions are derived from 503A compounding pharmacies. OFA highlights that under Section 503B of the FD&C Act registered "[o]utsourcing facilities shall submit adverse event reports to the Secretary in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)."[58] FAERS data for 503B products may therefore be more comprehensive than the petition suggests.

The petition further asserts, "The FDA has issued a risk alert that similarly warns the public of dosing errors associated with compounded injectable 'semaglutide' products. The FDA noted that it has received reports of adverse events, some requiring hospitalization, due to dosing errors from patients measuring and self-administering incorrect doses or healthcare providers miscalculating doses of compounded semaglutide."[59] OFA notes that such dosing issues are common with injectable medications broadly and are not unique to compounded semaglutide.

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[52] See *id*.
[53] Novo Nordisk Petition, supra note 1, at 13.
[54] *Id*.
[55] *Nomination of Semaglutide by the OUTSOURCING FACILITIES ASSOCIATION*, FDA Public Docket: Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, https://www.regulations.gov/document/FDA-2015-N-3469-0388 (last visited Nov. 11, 2024) ("OFA Nomination").
[56] *Id*.
[57] Novo Nordisk Petition, supra note 1, at 27.
[58] 21 USC 353b(b)(5).
[59] Novo Nordisk Petition, supra note 1, at 28-29.

FDA's alert suggests practical solutions such as more appropriate syringe sizes and single-dose vials, demonstrating that corrective actions can mitigate these risks. Furthermore, it should be noted that another GLP-1 drug manufacturer, Eli Lilly, is manufacturing and distributing GLP-1 product in a vial, which was approved by the FDA. If a GLP-1 can be manufactured and distributed under cGMP, that same standard applies to anyone using cGMP to manufacture a GLP-1 product. Otherwise, the agency would be arbitrarily choosing when cGMP and vial manufacturing applies and when it doesn't.

The petition claims, "Testing results has shown that certain compounded 'semaglutide' samples have substantially lower strengths than labeled."[60] The petition cites a case involving a 503A pharmacy, *Novo Nordisk Inc. v. Dr. Hank, LLC*, which concerned unapproved compounded semaglutide products from a 503A, not a 503B outsourcing facility. OFA responds that these examples pertain to 503A compounding pharmacies, not the rigorously regulated 503B outsourcing facilities. As FDA knows, 503Bs are required to conduct potency and stability testing under cGMP, the same standards applicable to NNI. Isolated potency issues are addressed through compliance measures targeting specific pharmacies rather than instituting broad prohibitions. Again, another example of petitioner misleading the Agency.

Lastly, the petition states, "inconsistencies in strengths among compounded "semaglutide" samples, even when obtained from the same clinic, underscores the importance of semaglutide products possessing certain physicochemical properties in order to properly perform as intended."[61] OFA responds that such inconsistencies are related to 503A compounding pharmacies. Potency variations in compounded medications can stem from issues with ingredient quantities rather than the active ingredient itself, underscoring the regulatory safeguards and stringent standards applied within 503B facilities.

G. Safety and Risk Mitigation in Outsourcing Facilities

The petition highlights, "the FDA has not inspected 28 newly registered outsourcing facilities, including one outsourcing facility that currently advertises compounded 'semaglutide' products."[62] OFA notes that FDA's inspection schedule is risk-based and planned to include new facilities as production commences. Lack of inspection within the early stages of a facility's

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[60] *Id*. at 30. Petitioner refers to *Novo Nordisk Inc. v. Dunklau Pharmacy Holdings LLC et al.,* No. 3:24-CV-00667, Complaint ¶ 24 (M.D. Tenn. May 2024). In *Novo Nordisk Inc. v. Dunklau Pharmacy Holdings, LLC, and Dr. Hank, LLC*, Novo Nordisk sued Dr. Hank, a 503A pharmacy, for false advertising and unfair competition for selling unapproved compounded drugs purporting to contain semaglutide, competing with Novo Nordisk's FDA-approved medications like Ozempic. On May 30, 2024, both parties settled, resulting in a court-issued permanent injunction prohibiting Dr. Hank from marketing or selling these unapproved compounds. If Dr. Hank believes it can legally market them, it must first notify Novo Nordisk. The judgment dismissed all claims against Dr. Hank without prejudice, with the court retaining enforcement jurisdiction.

[61] *Id*. at 31.

[62] *Id*. at 9. From FDA Registered Outsourcing Facility website, "Once an outsourcing facility is registered, the facility will be added to the list of facilities FDA intends to inspect according to a risk-based schedule. FDA plans to inspect outsourcing facilities within a reasonable period of time following initial registration, once it is confirmed that the facility has initiated drug production and distribution. However, the exact timing of the inspections can be affected by a number of variables, including the number of outsourcing facility registrants, other inspection priorities, and the operational status of the newly registered outsourcing facility." This supports FDA will inspect facilities within a reasonable period of time.

registration does not reflect negligence but rather demonstrates an organized inspection framework. The FDA's approach ensures that newly registered outsourcing facilities are reviewed as they establish production operations, following a structured process aligned with resource priorities.

Novo Nordisk also refers to a recent FDA observation, claiming, "In May 2024, the FDA inspected an outsourcing facility and reported the failure to measure the volume of compounded 'semaglutide' in vials with a calibrated instrument. The FDA determined that the compounded 'semaglutide' had fill-weight discrepancies, which suggests that the final compounded drug product did not accurately represent the labeled strength on the vial."[63] OFA clarifies that the FDA's Form 483 specifically noted fill-weight discrepancies due to visual checks rather than calibrated measurements, not potency or strength issues. This observation was isolated to a single facility and highlights fill volume rather than any issues with the actual active ingredient. Such findings are addressed on a facility level, reinforcing regulatory compliance without impacting other facilities. Interestingly, Novo fails to mention its own 483 observations and product recalls associated with semaglutide containing products.[64] Again, petitioner is in violation of 21 CFR § 10.30(b)(3).

Additionally, the petition asserts, "the FDA has noted that while some compounders are incorporating additional ingredients, including pyridoxine, into their semaglutide products, the safety and effectiveness of compounding semaglutide with other ingredients has not been established."[65] OFA maintains that adverse events related to additional ingredients like pyridoxine remain speculative without specific data. The example cited in the petition references a patient who experienced dosing difficulties unrelated to the ingredient itself.[66] Given the need for evidence-based conclusions, OFA argues that concerns about multi-ingredient compounded semaglutide lack sufficient data.

H. Claims of Alternative Treatments and FDA-Approved Drugs

The petition argues, "OFA's claim that patients would face the 'daunting' task of swallowing RYBELSUS® tablets is not based on any legitimate evidence and should not serve as the basis to establish a clinical need to compound semaglutide."[67] OFA contends that dysphagia—a difficulty swallowing—is a well-documented medical condition, affecting a significant portion of the older adult population.[68] This population often requires medication alternatives to standard tablets due to physical limitations. Additionally, previous FDA statements emphasize the importance of compounding for patients with unique needs, such as swallowing difficulties. OFA upholds that the availability of compounded semaglutide allows patients requiring alternative

[63] *Id*.
[64] Petitioner recalled OZEMPIC (semaglutide) injection, 2 mg/1.5mL (1.34 mg/mL) Prefilled pen on June 10, 2021 due to temperature control issues. Also, Petitioner most recently received a 483 with 8 separate observations on 03/25/2024 at their Denmark manufacturing site. See https://www.fda.gov/media/183181/download. Novo Nordisk has also received at least 8 other 483s. See https://www.accessdata.fda.gov/scripts/483inspsearch/index.cfm?action=search.search.
[65] *Id*. at 14.
[66] *Id*. See footnote 68.
[67] *Id*. at 13
[68] *Supra* note 21.

dosage forms to receive essential treatment. Novo's requests to ban 503B compounding put profits over patients.

The petition also asserts, "FDA's guidance is clear that 'the combination of multiple active ingredients to allow for administration of fewer products [is not] likely to represent a clinical need.'"[69] OFA clarifies that its position does not advocate combining ingredients solely for convenience. Instead, OFA's nomination addresses cases where individualized formulations are medically necessary. Patients with ingredient sensitivities, alternative dosing needs, or incompatibility with specific devices may benefit from tailored compounded products, emphasizing patient safety and clinical necessity over convenience.

Lastly, the petition claims, "...historical use of compounded 'semaglutide' weighs against a finding of clinical need. Because semaglutide medicines were first approved for the treatment of type 2 diabetes in 2017 and later for chronic weight management in 2021, there is no historical use associated with compounded "semaglutide." Furthermore, according to FDA's product reporting database, outsourcing facilities only began compounding "semaglutide" products in 2023."[70] OFA argues that the historical use aligns precisely with the drug's listing on the FDA shortage list. Compounded semaglutide became necessary as shortages arose, supporting the ongoing need for compounded alternatives. The demand for compounded semaglutide reflects its role in addressing patient needs that FDA-approved products cannot meet due to availability issues, not the length of its market history.

I. Regulatory Concerns and Use of Bulk Drug Substances

The petition claims, "Semaglutide is not currently included on the 503B Bulks List, yet millions of patients have taken compounded 'semaglutide' drugs."[71] OFA acknowledges that while semaglutide is not formally on the 503B Bulks List, the demand for compounded semaglutide is largely driven by patient need, especially amid shortages of FDA-approved products like Ozempic and Wegovy. Petitioner's failure to ensure adequate supply of necessary medication is Petitioner's fault alone. If Petitioner ensured there was ample supply of medication available for U.S. patients, there would not be millions of patients that have benefitted from compounded semaglutide. Instead, Petitioner has failed patients and is attempting to take access away to medically necessary medication for millions of Americans. Though estimates from industry sources suggest that compounding pharmacies may serve a significant number of patients, the data lacks concrete validation. Notably, the source of this claim itself states, "Together, the compounding pharmacies [503A and 503B] may account for up to 30% of the semaglutide sold in the U.S.," but qualifies this as a "wild ballpark figure" since "no one, including the FDA, is tracking sales in the industry."[72] The inclusion of figures that likely include 503A pharmacies, which operate under a different regulatory framework than 503B facilities, could misrepresent 503B's distinct role in the market. OFA emphasizes that compounded semaglutide addresses

[69] *Id*. at 14.
[70] *Id*. At 2-3.
[71] *Id*. At 3.
[72] Arthur Allen, *Why Millions Are Trying FDA-Authorized Alternatives to Big Pharma's Weight Loss Drugs*, KFF Health News (Jul. 23, 2024), https://kffhealthnews.org/news/article/glp1-compounding-pharmacies-wegovyzepbound- copycat-drugs-shortages/.

critical patient needs, particularly when FDA-approved drugs are inaccessible, underscoring the value of maintaining access to compounded semaglutide.

The petition further asserts, "Analysts estimate that around 20% of all prescriptions of Glucagon-like Peptide-1 receptor agonists (GLP-1 RAs) are for compounded versions of these drugs."[73] OFA notes that this claim is unverified and vague. The financial analyst cited acknowledges uncertainty, stating, "It's not clear just how many people are using compounded tirzepatide and semaglutide, because prescriptions aren't tracked through traditional channels."[74] This claim should not be taken as a reliable estimate, as the "20%" figure is described as an upper boundary rather than a definitive or verified statistic. Furthermore, the cited article appears to center on 503A compounding pharmacies rather than 503B outsourcing facilities, which adhere to different standards and practices. Misinterpreting 503A data in a 503B context can lead to misunderstandings regarding the scope and impact of 503B facilities in the market.

VI. Conclusion

OFA respectfully requests that FDA deny Novo Nordisk's Citizen Petition to exclude semaglutide from the 503B Bulks List. Removing semaglutide would unnecessarily restrict healthcare providers' ability to serve patients with specific needs, limit competition, and reduce the accessibility of individualized care. Maintaining semaglutide on the 503B Bulks List supports patient access, preserves provider autonomy, and upholds the high regulatory standards set for compounding practices.

Sincerely,

/s/ Lee H. Rosebush

Chairman, OFA

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[73] Novo Nordisk Petition, supra note 1, at 3.
[74] Meg Tirrell, *The End of a Shortage of Popular Weight-Loss Drugs May Mean Many People Lose Access to Them*, CNN (Oct. 9, 2024), https://www.cnn.com/2024/10/09/health/tirzepatide-compounded-weight-lossdrugs/index.html.