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U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Response in Opposition to Novo Nordisk's Nomination of Semaglutide to Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act
Docket No. FDA-2017-N-2562

To Whom It May Concern:

This law firm and the undersigned represent the Alliance for Pharmacy Compounding ("APC") and its members. APC is a national trade association advocating on behalf of millions of patients who benefit from compounded medications. APC's more than 5,000 members, located in all 50 states, include compounding pharmacists, pharmacy technicians, educators, students, researchers, and suppliers. APC further represents the interests of physicians, veterinarians, nurse practitioners, and other medical professionals who prescribe compounded medications to their patients.

APC is the voice for state-licensed compounding pharmacies ("503A pharmacies") and FDA-registered outsourcing facilities ("503B outsourcing facilities") throughout the country and works to ensure the availability of—and access to—customized medications for patients for whom manufactured drugs are not suited. Its mission is to preserve the rights of physicians to prescribe, pharmacists to prepare, and patients to take personalized medication solutions to meet their unique healthcare needs for a range of issues, including women's health, autism, oncology, dermatology, ophthalmology, pediatrics, and others. As such, APC not only represents the interests of compounders but just as importantly, it also represents the interests of patients who rely upon their services for access to life-enhancing medications they cannot obtain from any other source.

This letter is written in response to Novo Nordisk's nomination of semaglutide to the FDA's lists of drug products that present demonstrable difficulties for compounding under 21 USC § 353a(b)(3)(A) and 21 USC § 353b(a)(6) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (the "DDC Lists").

As noted by the FDA, approximately 70% of American adults have obesity or are overweight, and many of those who are overweight have a weight-related condition.[1] Losing 5% to 10% of body weight through diet and exercise has been associated with a reduced risk of cardiovascular disease in adults with obesity or overweight. *Id.* GLP-1 drugs like semaglutide are critical tools in the fight against the national obesity epidemic, which is a contributing factor to countless other medical issues afflicting tens of millions of Americans. Due to extraordinary demand generated in no small party by Novo Nordisk's aggressive advertising of its drugs, semaglutide injection has been on the FDA's Drug Shortage list since March 31, 2022, and it continues to be listed as "Currently in Shortage" to this day.

Throughout the shortage, patients who have been unable to obtain commercially manufactured semaglutide have relied upon 503A pharmacies and 503B outsourcing facilities to provide access to compounded versions of this life-changing medication. Now, two and a half years later, after hundreds of thousands of doses of compounded semaglutide have been dispensed to satisfied patients throughout the country, the drugmaker is suddenly asking the FDA to declare that semaglutide products are too difficult to compound, which would eliminate patients' access to compounded semaglutide literally overnight, even as the commercially manufactured drug remains in shortage.

The two and a half-year delay in the drugmaker's nomination of semaglutide to the DDC Lists calls into question the veracity of its claim that its nomination is motivated by a concern for patient safety. Moreover, the drugmaker's speculation that that the synthetic active pharmaceutical ingredient (API) used by compounders is somehow inferior to the drugmaker's recombinant API is unpersuasive. As an initial matter, by statute 503A pharmacies and 503B outsourcing facilities may only use API that are supplied by FDA-registered manufacturers and that are accompanied by valid certificates of analysis.[2] Semaglutide is not demonstrably difficult to compound, is not prepared from inferior API, and should not be placed on the FDA's DDC Lists.

The drugmaker's primary basis for contending that semaglutide is demonstrability difficult to compound has little to do with the actual *compounding* of semaglutide drug products.

[1] See https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014

[2] See 21 USC § 353a(b)(1)(A)(ii) and (iii); 21 USC § 353b(a)(2)(C) and (D)

Rather, the drugmaker contends that the synthetic semaglutide API used by compounders is inferior because it contains a different impurity profile than the recombinant semaglutide API used in its commercially manufactured drug products. However, the drugmaker fails to note that in several respects, synthetic semaglutide API presents a more favorable impurity profile than recombinant semaglutide API. While we presume that the drugmaker selected the six (6) synthetic semaglutide APIs that it likely believed would present test results most favorable to its nomination purposes, even those APIs do not support the drugmaker's desired conclusion. As shown in Table II of the drugmaker's own study, of the six (6) synthetic semaglutide APIs tested, four (4) had *lower* total percentages of hydrophilic impurities than the drugmaker's recombinant API, four (4) had *lower* total percentages of hydrophobic impurities 1 than the drugmaker's recombinant API, and four (4) had *similar* total percentages of hydrophobic impurities 2 to the drugmaker's recombinant API.[3]

Moreover, the figures shown in Table II reflect percentage levels related to the *total* impurities for each API– not the levels of *individual* impurities. The drugmaker has failed to disclose any individual impurity levels, which are the key considerations for assessing the impurities' potential effect on immunogenicity, safety, and effectiveness. It has long been the FDA's position, and industry standard, that an ANDA applicant need not identify or study the safety profile of an impurity unless the individual impurity exceeds 0.1% of the drug substance.[4] The drugmaker has failed to provide any evidence whatsoever that any *individual* impurity found in any of the six (6) synthetic semaglutide API samples exceeded the 0.1% threshold. Under FDA and industry standards, impurities below 0.1% of the drug substance do not warrant further investigation as to their identity or their effect on immunogenicity, safety, or effectiveness. *Id.*

Synthetic production allows for high levels of precision and a highly predictable impurity profile. In contrast, because recombinant semaglutide API production relies on host cells from biological organisms, the production process is inherently less controllable and less predictable than chemical synthesis. Synthetic semaglutide API production does not rely on host cells from biological organisms. As a result, chemically synthesized semaglutide API has none of the host-cell impurities found in recombinant semaglutide API, including potential biological agents such as viruses and prion. The peptide-related impurities found in synthetic semaglutide API are more controllable and more predictable than in recombinant semaglutide API, and the level of peptide-

[3] Hach, Morten, et al., *Impact of Manufacturing Process and Compounding on Properties and Quality of Follow-On GLP-1 Polypeptide Drugs*. Pharmaceutical Research (Oct. 8, 2024). https://doi.org/10.1007/s11095-024-03771-6

[4] See e.g. *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin,* (May 2021) https://www.fda.gov/media/107622/download; see also *ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits,* (August 2016) https://www.fda.gov/files/drugs/published/ANDA-Submissions-%E2%80%94-Refuse-to-Receive-for-Lack-of-Justification-of-Impurity-Limits.pdf.

related impurities is largely determined by the level of controls implemented by the API manufacturer.

The FDA's treatment of synthetic peptides in evaluating the adequacy of API for use in Abbreviated New Drug Applications (ANDA) is instructive. In its November 2022 guidance document, titled *Sameness Evaluations in an ANDA – Active Ingredients Guidance for Industry*,[5] the FDA explains that, pursuant to 21 CFR 314.92(a)(1),"[f]or determining the suitability of an abbreviated new drug application, the term 'same as' means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." *Id. at fn. 9.* In its guidance, the FDA noted that in the preamble to the final rule that implemented the Hatch-Waxman Amendments (1992 Final Rule), the FDA specifically declined to require that ANDA applicants show active ingredient sameness by demonstrating that their active ingredients "exhibit the same physical and chemical characteristics [as the RLD's], that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered." *Id.* Instead, FDA adopted "a more flexible approach in assessing whether a proposed generic drug product contains the same active ingredient as that of the RLD." *Id.*

Novo Nordisk's claim that the FDA has never evaluated synthetic semaglutide API is simply false. In order to receive ANDA approval for a generic drug, an ANDA applicant must identify the manufacturer of its API, and the FDA must review the API manufacturer's Drug Master File (DMF) and confirm that the API is adequate for use in the proposed generic drug. The FDA has already evaluated two synthetic semaglutide APIs and has found them to be adequate for use in supporting ANDA applications for generic semaglutide products. Specifically, on December 10, 2023, following a full scientific review, the FDA issued a First Adequate Letter to Sinopep-Allsino Biopharmaceutical Co. Ltd. for its synthetic semaglutide DMF (No. 036273).[6] Similarly, in May 2022, the FDA issued a First Adequate Letter to Shenzen JYMed Technology Co., Ltd. for its synthetic semaglutide DMF (No. 036009).[7] According to the FDA's Master Formularies Available for Reference Report (updated November 15, 2024), seven (7) other API manufacturers have also submitted synthetic semaglutide DMFs that are presently undergoing review by the FDA.[8]

Like the drugmaker's claim related to the synthetic APIs used by compounders, its second and third grounds for contending that semaglutide injection is demonstrably difficult to

[5] See https://www.fda.gov/media/163018/download
[6] See https://www.sinopep.com/news/company/46
[7] See https://www.peptidejymed.com/news/semeglutide-api-of-shenzhen-jymed-accepted-by-the-first-batch-of-domestic-nmpa-and-registered-in-us-fda-dmf-no-036009-with-status-a/
[8] See https://www.fda.gov/media/85138/download

compound also have little to do with the actual *compounding* of semaglutide drug products. The drugmaker contends that the most common delivery methods and dosage forms for compounded semaglutide — vials with syringes or pre-filled syringes, are unreliable. However, these delivery mechanisms and dosage forms, along with their labeling and instructions for self-administration, are no different than the self-administered insulin injections that have been dispensed for decades to diabetes patients.

It is noteworthy that Novo Nordisk' nomination letter in which it disingenuously asserts that vials with syringes or pre-filled syringes are unreliable and unsafe delivery mechanisms for patients, comes on the heels of its announcement that it intends to transition away from injection pens for its own insulin drug product and will begin utilizing the same vial and syringe delivery mechanism it now purports to have such grave concerns about.[9] Novo Nordisk cannot in good faith take the position that the vial-and-syringe delivery mechanism that has been used throughout the world for decades is appropriate for its own insulin drug product, but at the same time assert that vials with syringes or pre-filled syringes are unsafe and unreliable for compounders to use. Specious contentions like this undercut Novo Nordisk's credibility.

APC fully agrees that all compounded semaglutide products should include appropriate instructions for use, and that prescribers and pharmacists should provide their patients with the instructions and counseling necessary to enable them to properly self-administer their medications. However, existing federal and state rules and regulations sufficiently protect this important patient interest. The drugmaker's contention that the commonly used vials and syringes dispensed to semaglutide patients are dangerously unreliable simply lacks merit.

With respect to the drugmaker's claims related to oral, sublingual, and transmucosal delivery mechanisms and dosage forms, APC would note that state laws and United States Pharmacopeia (USP) <795> and <797> standards already provide sufficient guidelines for ensuring that compounded drug preparations are within acceptable potency tolerances. 503B outsourcing facilities are subject to similar CGMP guidelines. APC expects all compounders to comply with applicable state laws and USP or CGMP guidelines, as applicable, to ensure that all compounded drug products they dispense or distribute are within acceptable potency tolerances. Ensuring the proper potency of a compounded drug product is part of the everyday practice of pharmaceutical compounding. It is not unique to compounded semaglutide and it is not a valid basis for contending that semaglutide is demonstrably difficult to compound.

The drugmaker's speculative allegation that compounded semaglutide injection "may" lack consistent bioavailability also lacks merit. The drugmaker provides no evidence that the bioavailability of compounded semaglutide injection is materially less than that of its own commercially manufactured products. To the extent the drugmaker contends that patients taking

[9] See https://endpts.com/novo-nordisk-to-decrease-some-insulin-pen-manufacturing-transition-supply/

compounded semaglutide injection may experience an unexpected lack of efficacy due to low bioavailability, prescribers and their patients are fully aware that compounded drug products are not FDA-approved and, therefore, compounders do not make any claims of efficacy. However, it can be presumed that if compounded semaglutide injection did not meet the reasonable expectations of prescribers or their patients, they would transfer their prescriptions to a different compounder or stop prescribing compounded semaglutide injection altogether. Yet, over the two-and-a-half years that Novo Nordisk's FDA-approved drug has been in shortage, doctors have continued to prescribe, and their satisfied patients have continued to request, hundreds of thousands of doses of compounded semaglutide injection. Anecdotally, it would appear that this contention by the drugmaker is also without merit.

Only near the end of Novo Nordisk's lengthy nomination letter does it finally assert that the actual process of *compounding* semaglutide drug products is complex. This unsupported contention is simply false. The "complexities" asserted by the drugmaker simply reflect the everyday considerations that define the scientific profession of pharmaceutical compounding. Did it really take Novo Nordisk two-and-a-half years to suddenly determine that semaglutide is demonstrably difficult to compound? Or did Novo Nordisk simply decide to follow the lead of its competitor, Eli Lilly, by nominating compounded semaglutide for inclusion on the FDA's DDC Lists in an opportunistic attempt to stifle what it improperly perceives to be competition from 503A pharmacies and 503B outsourcing facilities? 503A pharmacies and 503B outsourcing facilities are not the commercial drugmaker's competitors, and semaglutide is not demonstrably difficult to compound. 503A pharmacies and 503B outsourcing facilities regularly compound drug preparations whose compounding processes are more complex than preparing semaglutide.

It is noteworthy that Novo Nordisk references deficiencies at a single 503A pharmacy and a single 503B outsourcing compounding pharmacy to paint all compounders with a broad brush. Yet, the drugmaker ignores the fact that on March 25, 2024, its own Kalundborg, Denmark production facility for FDA-approved semaglutide products received an FDA Form 483 in which the FDA noted eight (8) different observations.[10] Those observations included concerns about the quality and purity of the water used by Novo Nordisk in its manufacturing process and its inability to demonstrate that the water was adequately controlled for microbial counts and objectionable organisms. *Id.* The FDA inspectors raised additional concerns regarding Novo Nordisk's use of unauthorized equipment and deficiencies in its critical process parameters and in-process controls. *Id.* Moreover, FDA inspectors found that the drugmaker's quality control unit was not fully following its responsibilities and quality control procedures. *Id.* In addition, the inspectors found that the drugmaker's laboratory controls do not include the establishment of

[10] See https://www.fda.gov/media/183181/download

scientifically sound and appropriate sampling plans designed to assure that production cultures conform to appropriate standards of identity, strength, quality, and purity. *Id.* APC is confident Novo Nordisk would caution the FDA against using a handful of Form 483 observations from a single production facility to make an overly broad and unfair generalization of its overall drug production activities at all of its facilities. So too would APC caution the FDA against imputing isolated events at a single 503A pharmacy and a single 503B outsourcing facility to the entire compounding industry.

The drugmaker claims that compounding semaglutide requires complex physicochemical or analytical testing. However, in so doing, the drugmaker improperly seeks to hold compounders to standards that only apply to commercial drug manufacturers. For appropriate reasons, 503A pharmacies and 503B outsourcing facilities are governed by different regulations promulgated by state boards of pharmacy.

Contrary to Novo Nordisk's assertions, there is no factual support for its claim that compounded semaglutide poses an unacceptable risk to the public safety. In referencing adverse events data posted on the FDA's Adverse Events Reporting System (FAERS) Public Dashboard, the drugmaker notes that there have been 542 *total* adverse events reported for compounded semaglutide since 2018, including 124 hospitalizations and 10 deaths. However, to give those figures context, it is necessary to compare them to the adverse events reported for Novo Nordisk's own FDA-approved semaglutide products during that same time period.[11] From 2018 through September 30, 2024, there were **35,722** reported adverse events related to Novo Nordisk's commercially manufactured semaglutide products.[12] This includes **26,233** adverse events related to Novo Nordisk's FDA-approved Ozempic, **5,735** adverse events related to Novo Nordisk's FDA-approved Wegovy, and **3,903** adverse events related to Novo Nordisk's FDA-approved Rybelsus. *Id*. Of those **35,722** total adverse events, there have been **5,619** hospitalizations and **455** deaths reported. *Id.*

While these numbers related to Novo Nordisk's FDA-approved drugs might initially appear alarming, the FAERS public dashboard, itself, specifically states that a report in the database does *not* mean that the drug *caused* the adverse event:

> [W]hile FAERS contains reports on a particular drug or biologic, this does not mean that the drug or biologic caused the adverse event. Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug or

[11] APC acknowledges that 503A pharmacies are not required by federal law to report adverse events to FDA. APC has proposed implementing in law the mandatory reporting of serious adverse events by 503A pharmacies – and a framework for that reporting – but the FDA has yet to respond to that proposal.

[12] See https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis

> biologic. Some additional limitations to note include: . . . **Existence of a report does not establish causation**: For any given report, there is no certainty that a suspected drug caused the event. While consumers and healthcare professionals are encouraged to report adverse events, the event may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.[13] (Emphasis in original).

The difficulty of establishing a causal link between a drug and a reported adverse event is highlighted by the fact that, although Novo Nordisk's Ozempic and Wegovy are essentially the same drug, four and a half-times as many adverse events have been reported for Ozempic than for Wegovy. This disparity is not surprising given the differences in the patient populations those drugs are prescribed to treat. Ozempic is FDA approved to treat patients with Type 2 diabetes, whereas Ozempic is FDA approved to treat obesity and other weight-related conditions. Certainly, Novo Nordisk would not agree that Ozempic is four and a half-times riskier for patients than its Wegovy product, simply because four and a half-times as many adverse events have been reported for Ozempic than for Wegovy.

Moreover, attempting to draw conclusions from FDA's FAERS public dashboard is also problematic because the database includes reports related to the known side effects of the drug. According to Novo Nordisk's website, its FDA-approved semaglutide products are known to cause "serious side effects," including thyroid C-cell tumors, pancreatitis, diabetic retinopathy complications, hypoglycemia, acute kidney injury, hypersensitivity reactions (e.g., anaphylaxis and angioedema), acute gallbladder disease, change of vision in people with Type 2 diabetes,

[13] See https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

increased heart rate, and depression or thoughts of suicide.[14,15,16] The most common adverse reactions are known to be nausea, vomiting, diarrhea, abdominal pain, constipation, stomach (abdomen) pain, headache, tiredness (fatigue), upset stomach, dizziness, feeling bloated, belching, low blood sugar in people with Type 2 diabetes, gas, stomach flu, heartburn, and runny nose or sore throat. *Id.* A close examination of the FAERS database reveals that the adverse events reported for compounded semaglutide products largely mirror the known side effects of the FDA-approved, commercially manufactured semaglutide products.

Contrary to the contentions set forth in Novo Nordisk's self-serving nomination letter, semaglutide injection is not demonstrably difficult to compound, it is not prepared from inferior API, and it should not be placed on the FDA's DDC Lists. Accordingly, on behalf of the many 503A pharmacies and 503B outsourcing facilities across the country that have successfully compounded hundreds of thousands of doses of semaglutide injection since the commercially manufactured drugs were placed on the FDA's Drug Shortage List in March 2022, APC strongly opposes Novo Nordisk's nomination of semaglutide for addition to the FDA's DDC Lists.

Thank you for your consideration of this matter. If you would like to discuss this matter further, APC welcomes the opportunity to do so.

Sincerely,

Stephen T. Snow

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[14] See https://www.novomedlink.com/diabetes/products/treatments/ozempic/efficacy-safety/safety-profile.html?showisi=true&&utm_source=google&utm_medium=cpc&utm_term=ozempic%20side%20effects&utm_campaign=1_All_Shared_BR_Ozempic_2022_Refresh&mkwid=s-dc_pcrid_621307270744_pkw_ozempic%20side%20effects_pmt_e_slid__product_&pgrid=140570076385&ptaid=kwd-391207467799&gad_source=1&gclid=CjwKCAiA9IC6BhA3EiwAsbltOH_w3liGhXt-iS21jS4YbFr52-tF-0HtBRPcR9XzHkzlZ6s1Jx1IXBoC1V4QAvD_BwE&gclsrc=aw.ds

[15] See https://www.wegovy.com/taking-wegovy/side-effects.html?showisi=true&&utm_source=google&utm_medium=cpc&utm_term=wegovy%20side%20effects&utm_campaign=1_All_Shared_BR_Wegovy_Resources&mkwid=s-dc_pcrid_645289260617_pkw_wegovy%20side%20effects_pmt_e_slid__product_&pgrid=146393445018&ptaid=kwd-1296426950362&gad_source=1&gclid=CjwKCAiA9IC6BhA3EiwAsbltOFXbQw31u8MFjCTiF_oJOrVa071JpJHwm6KPnlqloqGvtm38bfgE9RoCvIUQAvD_BwE&gclsrc=aw.ds

[16] See https://www.google.com/search?q=rybelsus+side+effects&rlz=1C1GCEU_enUS878US878&oq=rybelsus+sid&gs_lcrp=EgZjaHJvbWUqCggAEAAYsQMYgAQyCggAEAAYsQMYgAQyBggBEEUYOTIHCAIQABiABDIHCAMQABiABDIHCAQQABiABDIGCAUQRRg8MgYIBhBFGD0yBggHEEUYPdIBCDU2NjNqMGo0qAIAsAIA&sourceid=chrome&ie=UTF-8