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SUBMITTED VIA REGULATIONS.GOV
Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2017-N-2562

By way of this submission, Novo Nordisk Inc. ("Novo Nordisk") nominates semaglutide products to the lists of drug products that present demonstrable difficulties for compounding pursuant to the Federal Food, Drug, and Cosmetic Act ("FDCA") Sections 503A(b)(3) and 503B(a)(6) (the "Demonstrable Difficulties for Compounding Lists" or "DDC Lists"). Semaglutide products belong on these lists due to the complexities associated with their formulations, delivery mechanisms, dosage forms, achievement of bioavailability, compounding processes, and physicochemical and analytical testing. We request that FDA convene and consult an advisory committee on compounding to discuss the addition of semaglutide products to both DDC Lists and promulgate regulations adding semaglutide products to the DDC Lists. To protect the public health posed by section 503A compounding of semaglutide products, we further request that FDA issue a direct final rule to add semaglutide products to the FDCA Section 503A DDC List. Lastly, we request joint review of this nomination by the Pharmacy Compounding Advisory Committee and Drug Safety and Risk Management Advisory Committee; the inclusion of committee members with an expertise in endocrinology, diabetes, obesity, heart disease, and immunogenicity; and participation from FDA's immunogenicity review committee.

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I. OVERVIEW

A. Statutory Authority[1]

A human drug product compounded for an identified individual patient based on a prescription is not eligible for the exemptions set forth in FDCA Section 503A(a) if, among other reasons, it is identified by regulation as a drug product that presents "demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product."[2] Before issuing such a regulation, FDA must first convene and consult an advisory committee on compounding, unless the Secretary determines that issuing regulations "before consultation is necessary to protect the public health."[3]

A human drug compounded in an outsourcing facility is not eligible for the exemptions set forth in Section 503B(a) if, among other reasons, it is identified by regulation as a drug or as a part of a category of drugs that presents "demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients," unless it is "compounded in accordance with all applicable conditions identified on the list . . . as conditions that are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties."[4] Before issuing such regulations, FDA must convene and consult an advisory committee on compounding.[5]

FDA has identified six criteria—or factors—to assess whether a drug product or category of drug products belongs on the DDC Lists: "(1) [c]omplex formulation; (2) [c]omplex drug delivery mechanism; (3) [c]omplex dosage form; (4) [b]ioavailability achievement complexity; (5) [c]ompounding process complexity; and (6) [p]hysicochemical or analytical testing complexity."[6] No single criterion is considered dispositive on whether a product is difficult to

[1] The Appendix includes the methodology, sample preparation, and testing results for drug substances and compounded drug products that are illustrative of the safety, efficacy, and quality concerns with compounded and bulk synthetic semaglutide products. *See* Appendix I to XXX. The Appendix has been submitted to FDA separately because of the confidential commercial information included in the document. *See, e.g.,* 5 U.S.C. § 552(b)(4); 18 U.S.C. § 1905; 21 U.S.C. § 331(y)(2); 21 C.F.R. § 20.61.

[2] FDCA Section 503A(b)(3)(A) [21 U.S.C. § 353a(b)(3)(A)].

[3] FDCA Section 503A(c)(1) [21 U.S.C. § 353a(c)(1)].

[4] FDCA Section 503B(a)(6) [21 U.S.C. § 353b(a)(6)].

[5] FDCA Section 503B(c)(2) [21 U.S.C. § 353b(c)(2)].

[6] *Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act*, 89 Fed. Reg. 19,776, 19,780 (Mar. 20, 2024), https://www.regulations.gov/document/FDA-2023-N-0061-0001.

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compound.[7] On July 28, 2017, the FDA established a docket to receive nominations for the DDC Lists.[8]

B. Background on Semaglutide

1. Semaglutide's Structure and Properties

Semaglutide[9] is an analog of the human Glucagon-like Peptide-1 (GLP-1), which is a hormone that stimulates insulin secretion and inhibits glucagon release in a glucose-dependent manner, thereby leading to lower glucose levels and appetite suppression.[10] GLP-1 and semaglutide share 94% amino-acid sequence homology.[11] Despite the primary-structure conservation between the native and analog peptides, the plasma half-life of each molecule is drastically different. GLP-1 has a very short half-life of about 1.5 minutes due to enzymatic inactivation, whereas semaglutide has a half-life of approximately 7 days.[12]

Semaglutide's unique molecular and pharmacological properties stem from two amino-acid substitutions—A8Aib and K34R—as well as a γGlu-2xOEG linker and a C18 fatty-diacid moiety attached via Lysine 26.[13] These characteristics affect albumin affinity and protect the peptide against fast dipeptidyl peptidase-4 (DPP-4) degradation, which accounts for semaglutide's prolonged half-life.[14] Semaglutide comprises 31 amino acids and has a molecular formula of $C_{187}H_{291}N_{45}O_{59}$ with a molecular weight of 4,113.58 g/mol.

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[7] FDA, Briefing Document: Pharmacy Compounding Advisory Committee 12 (June 17–18, 2015).

[8] *See* FDA, *Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket*, 82 Fed. Reg. 35214 (July 28, 2017).

[9] The semaglutide bulk drug substance used by compounders is not the same semaglutide used in Novo Nordisk's FDA-approved medicines. Novo Nordisk does not sell semaglutide to any entities for use in compounding. Furthermore, the semaglutide used in Novo Nordisk's FDA-approved semaglutide medicines is manufactured exclusively by Novo Nordisk and is not obtained from a third-party supplier. For the purposes of this nomination, we will refer to these products as semaglutide, even though these bulk drug substances are meaningfully different than Novo Nordisk's semaglutide.

[10] *See* T.D. Müller et al., *Glucagon-Like Peptide 1 (GLP-1)*, 30 MOLECULAR METABOLISM 72, 72–73 (2019).

[11] Arne Staby et al., *Influence of Production Process and Scale on Quality of Polypeptide Drugs: A Case Study on GLP-1 Analogs*, 37 PHARM. RES. 120, 123 (2020).

[12] *Id*. at 122.

[13] *See* Jesper Lau et al., *Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide*, 58 J. MED. CHEMISTRY 7370, 7670–73 (2015).

[14] *See id*. at 7671.

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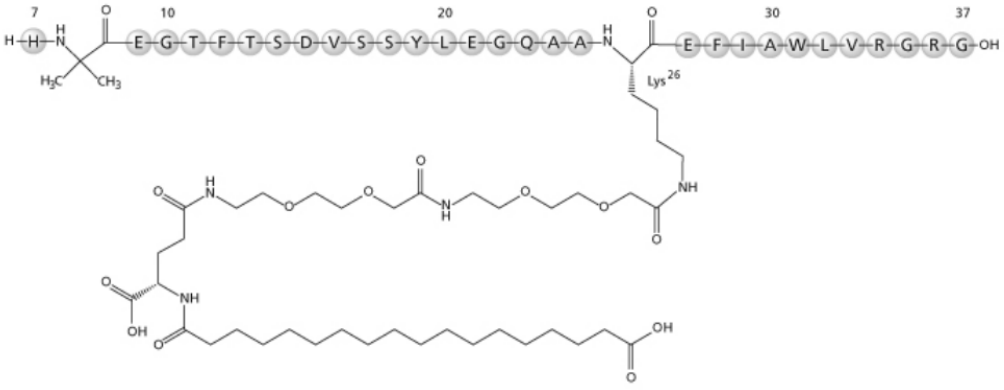

Figure 1. Structural formula of semaglutide[15]

2. FDA-approved Semaglutide Products and their Semaglutide Drug Substance

There are three FDA-approved semaglutide-based products: RYBELSUS® tablets for oral use, OZEMPIC® injection for subcutaneous use, and WEGOVY® injection for subcutaneous use. RYBELSUS® tablets for oral use contain the active ingredient semaglutide and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone and salcaprozate sodium (SNAC).[16] RYBELSUS® tablets should be stored at room temperature (20°C to 25°C) in the original bottle to protect tablets from moisture.[17] RYBELSUS® is approved to lower blood sugar levels in adults with type 2 diabetes mellitus, in addition to diet and exercise.[18]

OZEMPIC® injection for subcutaneous use is a sterile, aqueous, clear, colorless solution that has a pH of approximately 7.4.[19] OZEMPIC® contains the active ingredient semaglutide and the following inactive ingredients: disodium phosphate dihydrate, propylene glycol, phenol, and water. When necessary, the pH is adjusted by adding sodium hydroxide or hydrochloric acid. OZEMPIC® is packaged in a pre-filled pen, stored in a refrigerator from 2°C to 8°C, not frozen, and protected from heat and light.[20] It is approved to lower blood sugar levels in adults with type 2 diabetes mellitus, in addition to diet and exercise, and to reduce the risk of heart attack, stroke,

[15] WEGOVY®, Full Prescribing Information, https://www.novo-pi.com/wegovy.pdf; OZEMPIC®, Full Prescribing Information, https://www.novo-pi.com/ozempic.pdf; RYBELSUS®, Full Prescribing Information, https://www.novo-pi.com/rybelsus.pdf.

[16] RYBELSUS®, Full Prescribing Information, https://www.novo-pi.com/rybelsus.pdf.

[17] *See id*.

[18] *See id*.

[19] OZEMPIC®, Full Prescribing Information, https://www.novo-pi.com/ozempic.pdf.

[20] *See id*.

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or cardiovascular death in adults with type 2 diabetes mellitus and known cardiovascular disease.[21]

WEGOVY® injection for subcutaneous use is a sterile, aqueous, clear, colorless solutions that has a pH of approximately 7.4.[22] It contains the active ingredient semaglutide and the following inactive ingredients: disodium phosphate dihydrate, sodium chloride, and water. When necessary, the pH is adjusted by adding sodium hydroxide or hydrochloric acid. WEGOVY® is packaged in a single-dose pen, stored in the refrigerator from 2°C to 8°C, and protected from light.[23] It is approved to help adults and children aged 12 years and older with obesity or some adults with overweight, who also have weight-related medical problems, to lose weight and keep the weight off, in addition to reduced calorie diet and increased physical activity.[24] It is also approved, in combination with diet and exercise, to reduce the risk of major cardiovascular events such as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in adults with established cardiovascular disease and either obesity or overweight.[25]

The semaglutide drug substance in the FDA-approved products is produced using recombinant DNA technology in *Saccharomyces cerevisiae* (yeast).[26] The manufacturing process is complex and consists of several production steps. A fermentation step allows yeast cells to express a semaglutide precursor polypeptide. Expression in yeast cells is followed by recovery, isolation, purification, and a chemical-modification step in which the 9-37 precursor peptide backbone is acylated in the side chain via Lysine 26, by the addition of the γGlu-2xOEG linker and C18 fatty-diacid moiety. After acylation, the His-Aib dipeptide is ligated to the acylated 9-37 precursor to form the semaglutide target. Semaglutide is also modified in position 8 to provide stabilization against fast degradation by the enzyme DPP-4.

For RYBELSUS®, the semaglutide drug substance is dry mixed with microcrystalline cellulose, and povidone to form semaglutide granules.[27] Concurrently, SNAC, magnesium stearate, and microcrystalline cellulose are dry mixed to create SNAC granules. The SNAC granules and semaglutide granules are mixed together, along with more magnesium stearate, and then compressed to form semaglutide tablets.[28]

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[21] *See id.*

[22] WEGOVY®, Full Prescribing Information, https://www.novo-pi.com/wegovy.pdf.

[23] *See id*.

[24] *See id.*

[25] *See id.*

[26] *See* U.S. Patent No. 10,335,462, Use of Long-Acting GLP-1 Peptides; U.S. Patent Appl. 20100317057, Semi-Recombinant Preparation of GLP-1 Analogues; U.S. Patent No. 11,759,501, Compositions of GLP-1 Peptides and Preparation Thereof; European Medicines Agency, Ozempic® Assessment Report, Dec. 14, 2017.

[27] *See* U.S. Patent No. 11,033,499 B2, Tablet Formulation Comprising A GLP-1 Peptide and A Delivery Agent.

[28] *See id.*

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For WEGOVY® and OZEMPIC®, the semaglutide drug substance is subsequently dissolved in a solution containing the relevant excipients and diluted in sterile water. The pH is adjusted as needed by adding diluted sodium hydroxide or diluted hydrochloric acid. The solution is further purified prior to being freeze-dried as a lyophilized powder.

3. Compounded Semaglutide Products

Compounded semaglutide drugs are marketed with a variety of dosage forms, routes of administration, ingredients, packaging, and storage instructions. Compounded semaglutide dosage forms and routes of administration that differ from those of the FDA-approved semaglutide products include lyophilized powders intended for an injectable solution, tablets for sublingual use, solutions for sublingual use (some using liposomal technology), and transmucosal films. Co-active ingredients in compounded semaglutide drugs that are not present in FDA-approved semaglutide products include Body Protection Compound-157 (BPC-157), L-carnitine (levocarnitine), vitamin B-12 (cyanocobalamin or methylcobalamin), glycine, vitamin B12, pyridoxine, chromium PIC, tirzepatide, and nicotinamide adenine dinucleotide (NAD+).[29] Compounded oral semaglutide drugs typically omit the absorption enhancer SNAC. The packaging of injectable compounded semaglutide drugs, which differs from the pens used for FDA-approved semaglutide products, includes vials of solutions accompanied by syringes, vials of lyophilized powder and vials of other ingredients accompanied by syringes, prefilled syringes, and bottles. The compounded drug packaging may not provide protection from light, air, and moisture, and the storage instructions may recommend temperatures other than refrigeration for injectable drugs, such as room temperature or freezing.

II. FDA SHOULD INCLUDE SEMAGLUTIDE PRODUCTS IN THE DDC LISTS

A. Factor 1 — The Complexity of Semaglutide Products' Formulations

Semaglutide products' complex formulations present a demonstrable difficulty for compounding that may lead to adverse safety and efficacy effects. A complex formulation is one in which the active and inactive ingredients are required to possess certain unique physiochemical characteristics or properties that are necessary to achieve and maintain the proper performance and safety of the drug product.[30] The compatibility and physical and chemical stability of the API and excipients in the final dosage form may also contribute to determining whether a compounded drug has a complex formulation.[31] A complex formulation is an indicator that a drug product would be difficult to compound because the complexity

[29] *See, e.g.,* Appendix: Figures 6.1, 7.1, 12.1, 19.1, 24.1, 25.1, and 26.1; *see also* Morten Hach et al., *Impact of Manufacturing Process and Compounding on Properties and Quality of Follow-on GLP-1 Polypeptide Drugs* PHARM. RSCH. Figure 2 at 6 (Oct. 8, 2024), https://link.springer.com/article/10.1007/s11095-024-03771-6.

[30] *Supra* note 6 at 19,780.

[31] *See id.*

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increases the likelihood of an adverse effect on the safety or effectiveness of the compounded drug if the ingredients do not have the necessary characteristics.[32]

Semaglutide formulations, including the FDA-approved drug formulations, are complex. Due to its production in yeast using recombinant DNA technology, the semaglutide in the FDA-approved drug products has unique characteristics and properties that are challenging to reproduce using a synthetically produced peptide. The synthetic semaglutide itself and the compounded formulations using synthetic semaglutide have different impurity profiles and different physical and chemical stabilities than semaglutide and its FDA-approved formulations. Moreover, semaglutide has a γGlu-2xOEG linker and C18 fatty-diacid moiety that are critical to achieving its half-life. The inclusion of co-active ingredients and inactive ingredients that have not been studied in combination with semaglutide further heighten the complexities of the compounded formulations and, in turn, the safety and effectiveness risks. The lack of clinical testing, the adverse events associated with compounded semaglutide reported in FDA's Adverse Event Reporting System (FAERS), the calls to poison control centers, the measured differences between the strength of compounded semaglutide samples and the labeled strength, and *in silico* analyses on the immunogenicity of the peptide-related impurities in compounded semaglutide and bulk synthetic semaglutide samples corroborate these safety and effectiveness concerns.

1. The Semaglutide in Compounded Products

Semaglutide has unique characteristics and properties that are difficult to achieve using a synthetic semaglutide. The synthetic semaglutide—and hence, the compounded semaglutide drug products derived from that substance—can have peptide-related impurities that are not present in the recombinantly produced semaglutide or the FDA-approved semaglutide products. In addition, these differences in the manufacture of the bulk drug substance used in compounding and the semaglutide in the FDA-approved formulations lead to differences in physical and chemical stability. For example, manufacturing errors that affect modification of semaglutide at the eighth position will render the drug substance susceptible to premature degradation. Moreover, the addition of the γGlu-2xOEG linker and C18 fatty-diacid moiety and the elimination of undesirable isomers (e.g., diastereoisomers) can be difficult to achieve, and errors in the linker and fatty-diacid moiety can lead to detrimental effects on the drug's half-life. These differences increase the likelihood of adverse effects on the safety and effectiveness of the compounded formulations, including immunogenicity and sub-potency.

a) Use of Synthetic Semaglutide and Peptide-Related Impurities

Due to the inherent challenges and technical barriers associated with the biotechnological expression of recombinant therapeutic peptides from yeast cells, the vast majority of compounders are resorting to chemically synthesized versions of the semaglutide bulk drug substance.[33] But chemical synthesis of semaglutide can lead to impurities that pose several safety

[32] *Supra* note 7 at 13.

[33] Hach, *supra* note 29.

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and efficacy concerns. To mitigate the risks associated with compounded semaglutide products using chemically synthesized semaglutide, compounders would need to ensure that their bulk drug substance suppliers "fully quantify all differences in peptides produced by chemical synthesis and peptides produced by recombinant [DNA] technology and demonstrate that both products are comparable," as recommended by the European Medicines Agency ("EMA") guidance on developing and manufacturing synthetic peptides.[34] The EMA recommends quantifying these differences to ensure that the quality of the synthetic peptide is high enough to be used in a human drug product. Taking these steps would require the synthetic peptide manufacturers to "consider what analytical tests might be used to confirm comparability and to define and justify, prior to conducting these studies, the acceptance range to conclude comparability."[35] Synthetic peptide-based semaglutide may have a different impurity profile relative to the approved products with recombinant-based semaglutide. And manufacturing high-quality, clinical-grade, purified peptides via chemical synthesis requires an extensive developmental process,[36] which, at the very least, should take into account how levels of specific impurities will affect the drug substance and the final compounded formulation.

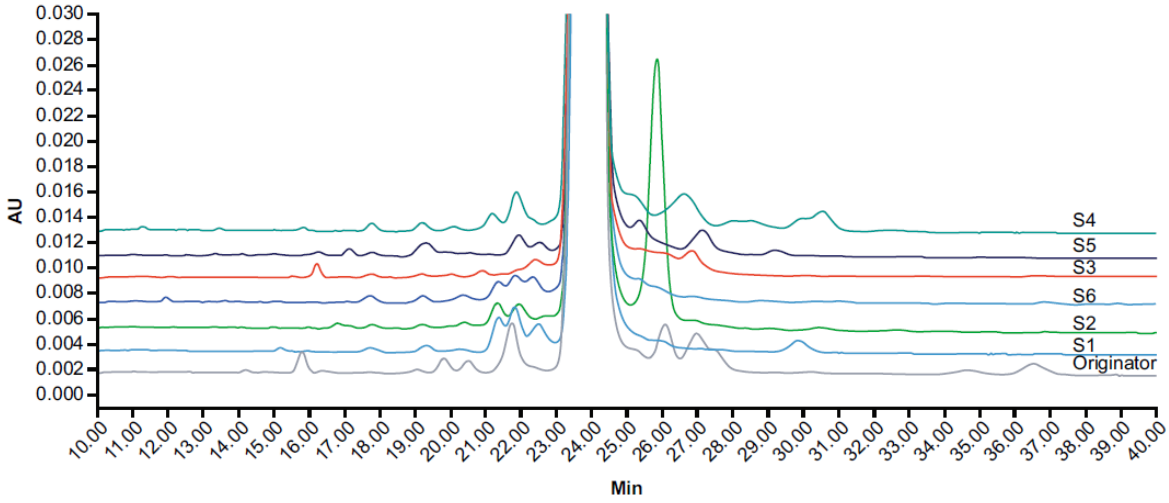

Figure 2. Overlay of chromatograms from Reverse-Phase, High-Performance Liquid Chromatography (RP-HPLC) analysis showing the impurity profile of six eluted semaglutide

[34] European Medicines Agency, *Guideline on the Development and Manufacture of Synthetic Peptides Draft* 20 (Oct. 12, 2023), https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-development-and-manufacture-synthetic-peptides_en.pdf.

[35] *Id*.

[36] *See, e.g.*, Valentijn Vergote et al., *Quality specifications for peptide drugs: A regulatory-pharmaceutical approach*, 15 J. PEPTIDE SCI. 697, 699 (Nov. 2009) ("The quality specifications for [peptide drugs require] . . . extensive developmental characterization, product design, adherence to appropriate good manufacturing practices (aGMP) consistent with the developmental stage, manufacturing process validation, starting materials testing, in-process controls, API and [finished drug product] stability testing."); U.S. Pharmacopeia, Chapter 1503, Quality Attributes of Synthetic Peptide Drug Substances, at 2, 6 (2021).

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bulk drug substances compared to the semaglutide (originator) in Novo Nordisk's FDA-approved medicines.[37]

The challenges in meeting such requirements are precisely why FDA should find semaglutide too difficult to formulate. There is currently no FDA-approved semaglutide product made from a chemically synthesized peptide that can be used as a comparator for any compounded semaglutide product on the market. Therefore, compounders cannot access bulk synthetic semaglutide with the quality and safety assurances of the semaglutide in Novo Nordisk's FDA-approved products. Furthermore, even if bulk drug substance suppliers were to sell purportedly pharmaceutical quality synthetic semaglutide, there is nothing for compounders to draw upon to determine what acceptance criteria should be imposed on their synthetic bulk drug substance suppliers to ensure that these statements are accurate. Compounders also do not perform clinical or animal testing to evaluate the safety of the synthesis-related impurities and their levels in compounded semaglutide. As a result, compounders are simply unable to ensure that the bulk synthetic semaglutide they use to compound their products will not pose adverse effects on the safety or effectiveness of the compounded drugs.[38]

Testing results have shown that bulk and compounded semaglutide have synthesis-related peptide impurities that are not present in recombinant-based semaglutide and FDA-approved semaglutide products.[39] Novo Nordisk tested bulk and compounded semaglutide from various suppliers and identified peptide synthesis-related impurities,[40] including peptides with amino

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[37] The RP-HPLC results show impurities eluting close to semaglutide's main peak in the six compounded injectable semaglutide bulk drug substances tested (all of which were synthetically produced) and the semaglutide used in Novo Nordisk's FDA-approved medicines (which was recombinantly expressed). Hach, *supra* note 29 at Figure 2 at 6.

[38] Concerns about the quality of bulk synthetic semaglutide used in compounding extend past the materials intended for pharmacy compounding. For example, testing results have also shown that a semaglutide peptide intended for reconstitution by consumers contained 54.6% of impurities and only 17% of semaglutide in the powder. *See* Appendix: Sample S-23145 (Figures 2.1-2.3, Table 2.1). Most concerningly, this retailer advertises that aesthetic spas, nurses, and doctors have purchased their powder for use in their patients for several months. *Id.* (Figure 1.4)

[39] Liquid Chromatography Mass Spectrometry (LC-MS) testing identified 32 impurities across six semaglutide bulk drug substances used in compounding that are not present in the semaglutide in Novo Nordisk's FDA-approved medicines. Seven more impurities that are present in Novo Nordisk's semaglutide drug substance were also found at increased levels in the semaglutide bulk drug substances tested. The impurities included several peptide-related impurities, like missing or truncated portions of the semaglutide peptide, amino acid additions, deletions, and substitutions. The tested semaglutide bulk drug substances also contained several unknown impurities. Hach, *supra* note 29 at Table IV at 7-8.

[40] *See* Appendix: S-9535 (Figure 3.1); *See also Novo Nordisk Inc. v. Brooksville Pharm. Inc.*, No. 8:23-cv-01503-WFJ-TGW, ECF 40, First Amended Complaint ¶21 (M.D. Fla. Nov. 29, 2023) ("[Brookville Pharmaceuticals]'s drug product is . . . adulterated . . . because . . . it contains unknown impurities and impurities with amino acid additions and deletions not found in the pharmaceutical-grade semaglutide in Novo Nordisk's FDA-approved products—all of which potentially pose safety risks to patients, including possibly serious and life-threatening reactions like anaphylaxis . . . .").

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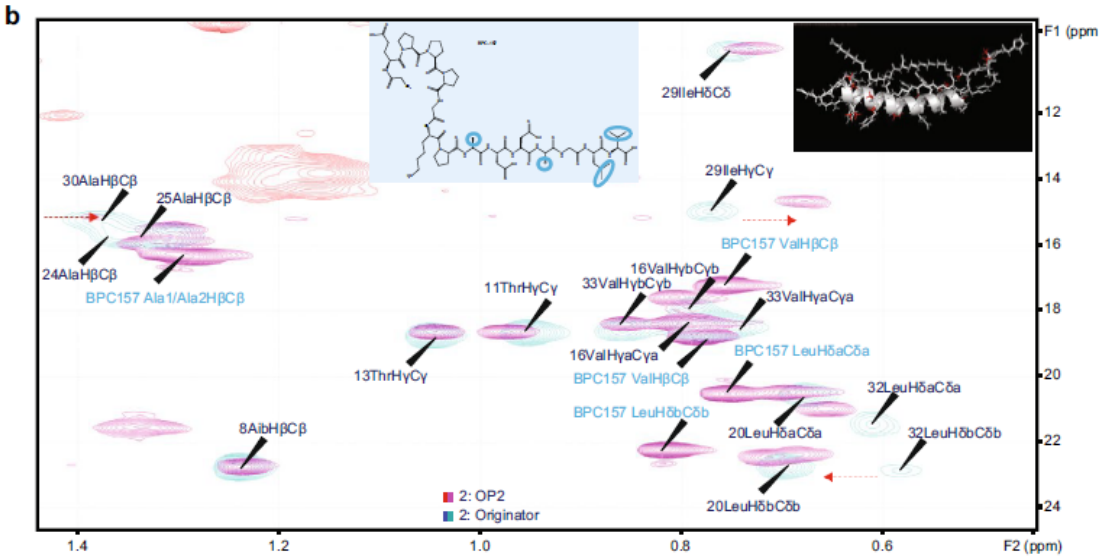
acid additions and deletions, modifications (such as tert-butylation), or no fatty di-acid side chains.[41] For example, testing of a compounded sublingual semaglutide drug product containing BPC-157 revealed that only parts of the secondary structure of the semaglutide chain overlapped with the semaglutide used in FDA-approved medicines. Specifically, an "overlay was observed from amino acid 7 to amino acid 20, whereas for the remaining part the signals of [the sample] had shifted" such that "the folding of semaglutide from amino acid 21 to amino acid 37 was different from the [semaglutide in Novo Nordisk's FDA-approved medicines]."[42]



[41] This modification is used as a protection group during peptide synthesis and constitutes a critical impurity, which must be controlled in the final product. *See* U.S. Pharmacopeia, Chapter 1504, Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides, at 2–3 (2023) ("One potential cause for critical impurities in the protected amino acid derivatives [AAD] is related to contaminants of the unprotected amino acids used to manufacture those AADs. Amino acid-related impurities, such as stereoisomers and foreign amino acids, especially, may become critical AAD-related impurities after the introduction of the protecting groups.").

[42] Hach, *supra* note 29 at Figure 5C at 10.

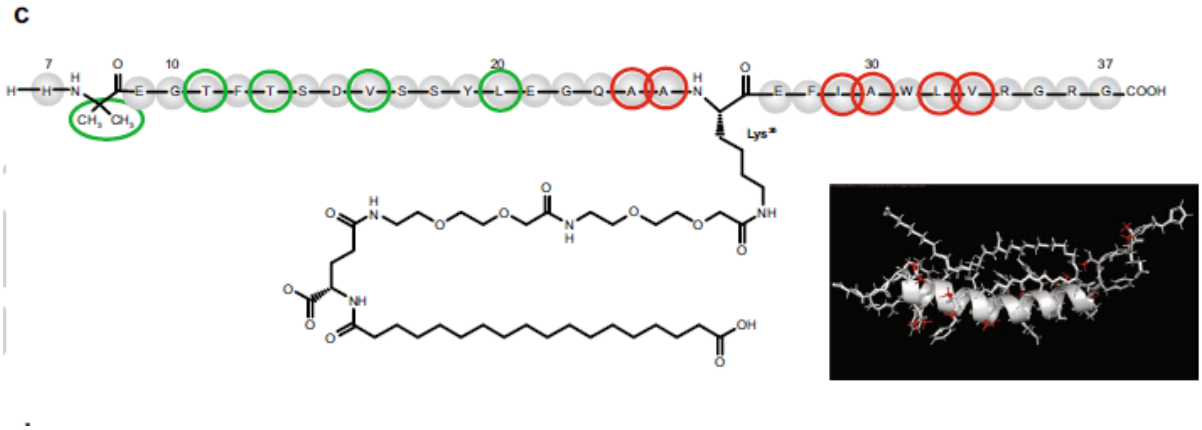


Figure 3. (b) 2D methyl HMQC ^{1}H-^{13}C NMR spectra overlay of the semaglutide used in Novo Nordisk's FDA-approved medicines (blue/green) and a compounded oral semaglutide product containing BPC-157 (red/pink). The structure in the blue box is BPC-157. (c) Mapping of the NMR spectra results to the primary structure of semaglutide. The red circles mark differences in the NMR spectra between the semaglutide in Novo Nordisk's FDA-approved medicines and the compounded semaglutide in the oral product containing BPC-157. The black box shows the corresponding data mapped to the secondary structure of semaglutide.[43]

It is well-established that changes in manufacturing techniques, such as a switch "from recombinant to peptide synthesis," "can lead to the introduction of new or duplicated amino acids or side-chain modifications, resulting in impurities that are difficult to separate from the active pharmaceutical ingredient (API), which can change the clinical profile of the drug and contribute to immunogenicity."[44] As it relates to semaglutide products, "a recent case study of impurities" showed that semaglutide derived via recombinant-DNA technology and chemical synthesis "resulted in very different impurity profiles."[45] These different impurity profiles are carried over into the formulation process of the finished drug product—another complex process that can impact the safety and efficacy of the product.[46]

FDA Guidance describes the risk that "[d]ifferences between the peptide-related impurities in a proposed generic synthetic peptide and those in [a reference listed drug] of [recombinant DNA] origin could produce different impurity profiles, which could adversely

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[43] *Id.*

[44] Anne S De Groot et al., *Immunogenicity Risk Assessment of Synthetic Peptide Drugs and Their Impurities*, 28 DRUG DISCOVERY TODAY, at 2 (2023).

[45] *Id*. (referring to Staby, *supra* note 11).

[46] *See, e.g.,* Jared R. Snell et al., *Nanobubbles in Reconstituted Lyophilized Formulations: Interaction with Proteins and Mechanism of Formation*, 109 J. PHARM. SCIS. 284 (2020) (explaining that the reconstitution process of lyophilized protein formulations may lead to formation of nanobubbles, which may contribute to protein destabilization and aggregation).

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affect the safety or effectiveness of a proposed generic synthetic peptide product, if uncontrolled." [47] FDA recognizes that the chemical synthesis of peptides can lead to "insertion, deletion, or modification of amino acid sequences or residues," and other peptide-related impurities that "create the potential for differences in immunogenicity or may otherwise affect the safety or effectiveness of a peptide drug product."[48] Amino acid insertions and deletions are known to "have the potential to impact T-cell response because changes in amino acid sequence can either create new T-cell epitopes, destroy existing epitopes or change HLA binding profiles."[49]

FDA has previously recognized that the presence of peptide-related impurities and aggregates in certain bulk drug substances pose significant safety and immunogenicity risks to patients. After reviewing nominations for other bulk drug substances proposed to be included on the 503A or 503B Bulks Lists, FDA categorized several of those bulk drug substances under Category 2 as described under the Interim Policy on Compounding Bulk Drug Substances Under 503A and 503B of the FDCA ("Interim Policy").[50] A bulk drug substance may be listed under Category 2 of the Interim Policy if FDA determines that it presents significant safety risks in compounding.[51] For example, FDA recognized that "[c]ompounded drugs containing BPC-157," a molecule that is often included in some compounded semaglutide products, "may pose risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and active pharmaceutical ingredient (API) characterization." FDA recognized similar concerns for a variety of peptide bulk drug substances including Cathelicidin LL-37, Emideltide, Epitalon, GHK-Cu, GHRP-2, GHRP-6, Ipamorelin acetate, Kisspeptin-10, Mechano growth factor pegylated, Melanotan II, MOTs-C, Semax (heptapeptide), and Thymosin beta-4, fragment (LKKTETQ).

FDA expanded on its concerns regarding immunogenicity and peptide-related impurities in the briefing documents for two peptide bulk drug substances, Ipamorelin and Kisspeptin-10, for the upcoming October 29, 2024 Meeting of Pharmacy Compounding Advisory Committee

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[47] FDA, *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin: Guidance for Industry* 7 (May 2021) [hereinafter *FDA Guideline for Synthetic Peptides*].

[48] *Id*. at 4.

[49] *See supra* note 44 at 5. HLA refers to the human-leukocyte antigen system, which plays a role in disease and immune defense.

[50] FDA, *Certain Bulk Drug Substances for Use in Compounding that May Present Significant Safety Risks,* https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks (last visited Sept. 27, 2024).

[51] FDA, *Draft Guidance for Industry, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (Rev. 2, Dec. 2023); FDA, *Draft Guidance for Industry, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Rev. 2, Dec. 2023).

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("PCAC").[52] FDA noted that these peptides pose "a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities."[53] FDA further discussed that "peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides."[54] The synthesis methods for synthetic peptides "may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions."[55] Peptide-related impurities may include "starting materials, typically protected amino acids, isomeric impurities, free amino acids, [] other species that may carry over into the drug substance," "residual solvents, coupling reagents, activators, catalysts, [] scavengers," and "peptide-related aggregates."[56] The immunogenicity risks of peptides are exacerbated due to the "inherent tendency" of peptides to aggregate.[57] "[A]ggregation is a risk factor in immunogenicity and for decreased pharmacotherapeutic effect of the drug product due to effects on bioavailability, formation of precipitates, or anti-drug antibody production."[58]

In addition to recognizing the likely presence of peptide-related impurities and the likelihood of aggregation which may cause or exacerbate immunogenicity in synthetic peptides, FDA also recognized the difficulty of fully assessing the potential immunogenicity associated with peptides and peptide-related impurities and variants in bulk drug substances "[b]ecause information is lacking about the nature and control of individual peptide-related impurities, including aggregates, and variants."[59] Peptide-related impurities "are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods."[60] FDA noted that without clinical studies assessing immunogenicity or aggregation of a bulk drug substance, there is insufficient data to conclude that the bulk drug substance does not present immunogenicity risks "due to the potential for aggregation as well as potential peptide-related impurities."[61] All of these considerations apply to compounded semaglutide drug products.

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[52] FDA, *October 29, 2024: Meeting of the Pharmacy Compounding Advisory Committee,* https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-29-2024-meeting-pharmacy-compounding-advisory-committee-10292024 (Sept. 20, 2024).

[53] FDA, *FDA Briefing Document on Kisspeptin-10* at 23*,* https://www.fda.gov/media/182089/download.

[54] *FDA Briefing Document on Ipamorelin-Related Bulk Drug Substances (Ipamorelin (free base) and Ipamorelin Acetate)* at 7*,* https://www.fda.gov/media/182088/download.

[55] *Id*.

[56] *Id*.

[57] *Supra* note 54 at 34-35; *supra* note 53 at 22-23.

[58] *Supra* note 54 at 35.

[59] Supra note 53 at 6.

[60] *Id.*

[61] *Supra* note 54 at 35.

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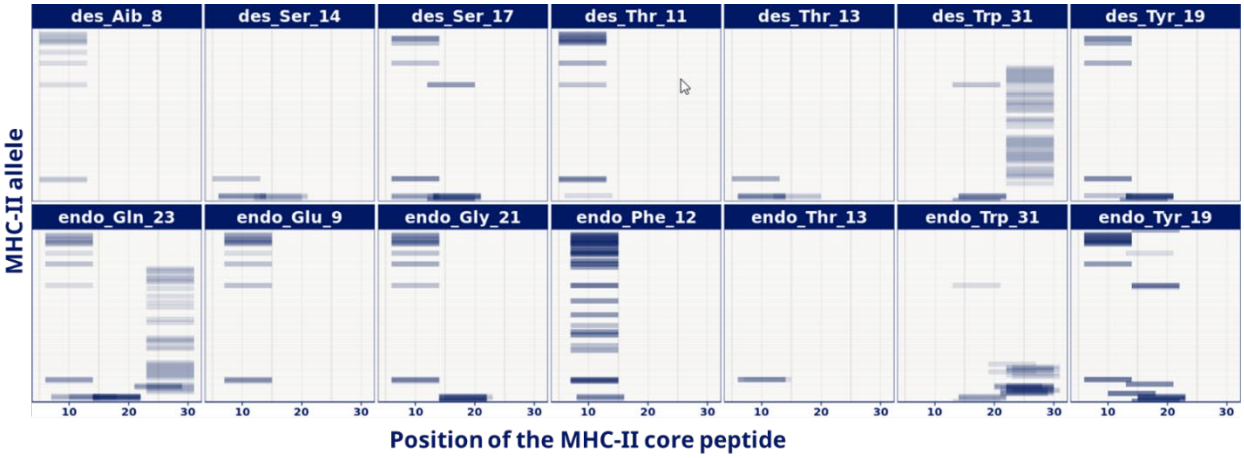
Finally, an *in silico* analysis suggests that the peptide-related impurities with amino acid additions and deletions present in the semaglutide drug substance used in compounding and the compounded semaglutide products have the potential to be immunogenic.[62] The immunogenicity potential of these impurities was assessed using *in silico* computational sequence analysis, which predicts the differential major histocompatibility complex (MHC)-II binding of impurities and identifies potential T cell epitopes.[63] The *in silico* analysis predicts that several of the peptide impurities found in the semaglutide drug substance and compounded semaglutide have the ability to bind MHC-II, which can potentially lead to activation of antigen-specific T cells and B cells and the production of antidrug antibodies. Specifically, the *in silico* analysis identified potential MHC-II-binding-T-cell epitopes for peptide sequences with Aib8, Ser14, Ser17, Thr11, Thr13, Trp31, or Tyr19 amino acid deletions, or Gln23, Glu9, Gly21, Phe12, Thr13, Trp31, or Tyr19 amino acid additions. [64] Testing has shown the presence of these peptide-related impurities in the semaglutide drug substance used by compounders and compounded semaglutide products.[65] The *in silico* analysis thus shows a potential immunogenicity risk for certain semaglutide peptide impurities in the semaglutide drug substance and compounded semaglutide.



[62] *See* Hach, *supra* note 29 at Figure 8A at 19. The *in silico* analysis specifically analyzes the peptide-related impurities present on the main peptide chain and does not include the side chain.

[63] Staby, *supra* note 11 at 125.

[64] *See* Figure 4. Because the *in silico* program cannot predict binding of the artificial amino acid Aib, in this analysis, the Aib was replaced with Alanine, both in the semaglutide reference standard and in the compounded and related bulk synthetic semaglutide. The *in silico* analysis is only considering differences between Novo Nordisk's semaglutide and the impurity sequences used in the compounded and bulk synthetic semaglutide, so the Aib/Ala replacement is expected to have limited effect on the comparison. *See* Hach, *supra* note 29 at Table 3 at 6.

[65] *See, e.g.*, Appendix: In-Silico Analysis (Table 4.1); S-23009 (Figures 5.1-5.2, Table 5.1); S-23046 (Figures 6.1-6.2, Table 6.1); S-23166 (Figures 7.1-7.3, Table 7.1); S-23032 (Figure 8.1, Table 8.1); S-23036 (Figure 9.1, Table 9.1).

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Figure 4. *In silico* immunogenicity assay showing predicted MHC II-binding T-cell epitopes for the backbone sequence of impurities with amino-acid additions (endo) or deletions (des) in several compounded semaglutide products. Each bar represents a distinct peptide, with its position in the backbone sequence (X axis) and its binding affinity to a given MHC II allele (Y axis).[66]

b) Manufacturing Differences and Physical and Chemical Stability

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. Samples from bulk drug substance suppliers contained trace metals, such as boron, magnesium, aluminum, chromium, manganese, iron, nickel, zinc, copper, potassium, and calcium.[67] These trace metal impurities are not present, or not present in similar amounts, in the semaglutide used in the FDA-approved formulations. Such trace metal impurities, especially elevated levels of iron, can impact the physical and chemical stability of the drug products and promote the formation of dimers or other high molecular weight proteins ("HMWPs"), which in turn may impact drug immunogenicity and cause other safety and efficacy adverse-related effects.[68]

Testing results for samples of bulk synthetic semaglutide used in compounding also differ from the semaglutide in Novo Nordisk's FDA-approved products in terms of subvisible particle concentration when prepared as a solution and tested using micro flow imaging. One sample of bulk synthetic semaglutide had a significantly higher concentration of subvisible particles over 2 μm in size than the semaglutide in FDA-approved products.[69] Subvisible protein particles in the

[66] Novo Nordisk's semaglutide has been set as the reference. *See* Hach, *supra* note 29 at Figure 8A at 19.

[67] *See* Appendix: S-23032 (Figures 8.2-8.3), S-23036 (Figures 9.2-9.3), S-23033 (Figures 10.2-10.3).

[68] *See* Staby, *supra* note 11 at 126, 136. While the quantity of copper and magnesium found in the bulk synthetic semaglutide samples to date have not reached levels that likely would cause formation of HMWPs, the quantities of other trace metals have been high enough to pose this risk and the lack of adequate controls over the quantities of trace metals remain a significant concern for the bulk synthetic semaglutide used in compounding. *See also* FDA, *Immunogenicity Assessment for Therapeutic Protein Products* 20 (Aug. 2014); Hach, *supra* note 29 at Table VI at 13. This table shows testing results demonstrating the concentration of impurities found in the semaglutide in Novo Nordisk's approved medicines as compared to the five semaglutide bulk drug substances used in compounding. Different concentrations are seen for chloride (≤ 10 to ≤ 30 μg/g for semaglutide bulk drug substances vs 190 μg/g for Novo Nordisk's semaglutide), phosphate (≤ 19 to 100 μg/g for S1, S2, and S3, and 5700 μg/g for S4, vs 630 μg/g for Novo Nordisk's semaglutide), calcium (660 μg/g for S5 vs ≤ 9.7 μg/g for Novo Nordisk's semaglutide), and iron (36 μg/g for S4 and 2.5 μg/g for S1 and S5 vs 0.49 μg/g for Novo Nordisk's semaglutide). Similarly, the concentration of residual buffers TRIS and 2-(N-mor-pholino)ethanesulfonic acid (MES) are higher in S2 and S3 than Novo Nordisk's semaglutide (≤ 200 for both vs 60 μg/g, and ≤ 200 for both vs ≤ 40 μg/g, respectively). The ranges of dissolved pH values for four semaglutide bulk drug substances (S1, S2, S3, and S5) are more acidic than the semaglutide in Novo Nordisk's approved medicines (6.89–7.23 vs 7.45/7.33, respectively), but the dissolved pH for S4 (7.33) is the same as Novo Nordisk's semaglutide.

[69] *See* Appendix: S-23033 (Figure 10.5, Table 10.2).

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0.1–10 μm range have the potential to impact the safety and efficacy of a therapeutic protein product over its shelf life.[70] Subvisible particles consisting of aggregated proteins in a drug substance can enhance immunogenicity risks in the final drug product.[71]

In addition, the bulk synthetic semaglutide used in compounding included different anions and elevated levels of some anions compared to the semaglutide in the FDA-approved products.[72] The samples of semaglutide bulk drug substances used in compounding contain acetate and nitrate, which are not present in FDA-approved semaglutide products, and elevated levels of phosphate, compared to the semaglutide used in the FDA-approved drug products. A compounded semaglutide product with unknown anion concentrations has the potential to adversely impact the stability of semaglutide and thus its safety and efficacy.

Likewise, manufacturing differences between FDA-approved semaglutide formulations and compounded semaglutide formulations can and do lead to differences in physical and chemical stability.[73] For example, small changes in the pH of the semaglutide formulation can induce fibrillation.[74] Lowering the pH of semaglutide from 7.4 to 6.7 has been shown to induce the formation of semaglutide fibrils.[75] An error in the synthesis process leading to an incorrect polypeptide sequence that lacks fatty di-acid side chains would potentially contribute to pH-dependent destabilization of the semaglutide product due to the absence of ionizable groups targeted for protonation or deprotonation.[76]

Beyond changes in pH levels, other factors such as net charge, concentration, chemical degradation (e.g., deamidation, hydrolysis, or oxidation), process-related impurities, excipients, and contact with air or hydrophobic surfaces can generally influence the chemical and physical stability of peptide formulations, which could also apply to semaglutide peptides.[77] Even the materials used in primary packaging of a product can lead to differences in chemical and

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[70] *See* John F. Carpenter et al., *Overlooking Subvisible Particles in Therapeutic Protein Products: Gaps that May Compromise Product Quality*, 98 J. PHARM. SCI. 1201 (Apr. 2009).

[71] *See id.*

[72] *See* Appendix: S-23032 (Figure 8.4), S-23036 (Figure 9.4), S-23033 (Figure 10.4); *See also* Hach, *supra* note 29 at Table VI at 13.

[73] *See* Staby, *supra* note 11 at 126–28 (demonstrating that trace metals—particularly iron, copper, and magnesium—found in follow-on semaglutide products increased high molecular weight protein formation).

[74] *See id*.

[75] *See id*.

[76] *See* Karolina L. Zapadka et al., *A pH-Induced Switch in Human Glucagon-like Peptide-1 Aggregation Kinetics*, 138 J. AM. CHEM. SOC'Y 16259, 16259 (2016) (suggesting that the protonation state at the N-terminus of GLP-1 peptides contributes to pH-induced aggregation).

[77] *See* Karolina L. Zapadka et al., *Factors Affecting the Physical Stability (Aggregation) of Peptide Therapeutics*, 7 INTERFACE FOCUS Art. 1, 1–2 (2017).

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physical stability of therapeutic peptides.[78] At every step, facilities, equipment, and processes must be assessed to ensure that the semaglutide in a finished product does not increase the likelihood of adverse effects on safety and effectiveness. Testing of bulk synthetic semaglutide used in compounding and compounded semaglutide indicates that such steps are not being taken and the physical and chemical stability of the API is being compromised.[79] According to testing results, both bulk synthetic semaglutide used in compounding and compounded semaglutide contain a variety of impurities that affect drug stability. Testing has detected formaldehyde adducts, acetaldehyde adducts, and butyraldehyde adducts; oxidations and di-oxidations; isomers; and dimers.[80] At times, the percentages of the stability-indicating impurities in the samples were exceedingly high. For example, multiple samples contained more than 15% of formaldehyde adducts.[81] Formaldehyde adducts are known to pose immunogenicity risks.[82]

Unknown impurities were detected in both the bulk samples used in compounding and compounded semaglutide samples. Results from testing one sample of a compounded semaglutide product revealed it contained 33% unknown impurities that are absent from the semaglutide in Novo Nordisk's FDA-approved semaglutide products.[83] Compounding pharmacies do not routinely take on the complex tasks of characterizing and justifying these unknown impurities to ensure they do not adversely impact physical and chemical stability and immunogenicity.

Lastly, some compounding pharmacies have used bulk synthetic semaglutide that is labeled for research use to produce sterile injectable drug products for patient use.[84] An ingredient that is not for pharmaceutical use will very likely contain higher levels of impurities

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[78] *See* Jared S. Bee et al., *Effects of Surfaces and Leachables on the Stability of Biopharmaceuticals*, 100 J. PHARM. SCIS. 4158 (2011) (reporting that adsorption to interfaces or interactions with leachables and/or particles can lead to protein aggregation or particle formation).

[79] *See* Hach, *supra* note 29 at Table V at 9-11.

[80] *See id.*; Appendix: S-23007 (Figures 11.1 and 11.2, Table 11.1); S-22002 (Figures 12.1 and 12.2, Table 12.1).

[81] *See Novo Nordisk Inc. v. WellHealth Inc.*, No. 3:23-cv-00782-TJC-LLL, ECF 44, Amended Complaint (M.D. Fla. July 31, 2024) (reporting more than 24% impurities, including formaldehyde adduct, dimers, and other unknown impurities).

[82] *See* Thomas J.M. Michiels et al., *Novel Formaldehyde-Induced Modifications of Lysine Residue Pairs in Peptides and Proteins: Identification and Relevance to Vaccine Development*, 17 MOLECULAR PHARM. 4375, at 4376 (2020), https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.0c00851 ("It has been shown that endogenous formaldehyde induces immunogenic adducts…").

[83] *See Novo Nordisk Inc. v Wells Pharmacy Networks, LLC*, No. 5:23-cv-00689, Complaint ¶¶ 30, 40–41 (M.D. Fla. Nov. 29, 2023).

[84] *See* FDA, *Form 483 for TMC Acquisition LLC dba Tailor Made Compounding* (Mar. 14, 2022), https://www.fda.gov/media/162642/download.

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compared to compendial or pharmaceutical grade equivalents.[85] These impurities could be dangerous to patient health because the levels of impurities have not been shown to be safe in humans.[86]

c) Fatty Acid Modification

Semaglutide's pharmacological action depends on the chemical composition of the peptide, which requires a precise amino-acid sequence, inclusion of the A8Aib and K34R substitutions, and the presence of the K26-derivatized γGlu-2xOEG linker and C18 fatty-diacid moiety. Incorporation of the A8Aib modification, as well as the linker and fatty-diacid moiety, is a complex process that requires advanced equipment, quality-control processes, and regulatory oversight. The process used to incorporate these modifications can differ between the semaglutide used in Novo Nordisk's FDA-approved drugs and synthetic semaglutide drug substance used in compounding. Suppliers making synthetic semaglutide might gradually synthesize each amino acid unit in the chain, including the side chain with the fatty-diacid moiety and linker, couple the units together, and acylate each group to obtain the final peptide. In contrast, Novo Nordisk recombinantly expresses the semaglutide precursor (9-37) in yeast cells, acylates the 9-37 semaglutide precursor with the linker and fatty-diacid moiety to the Lys26, and then ligates the His7-Aib8 to the acylated precursor using lipid phase synthesis to obtain the final semaglutide. Confirming the integrity of these modifications is crucial to ensuring the pharmacological effects of semaglutide-formulated products. Furthermore, the differences in the processes for making these modifications, especially without the quality control processes and Agency review used in the approval process, are highly likely to result in the synthetic semaglutide having a different impurity profile than Novo Nordisk's recombinantly expressed semaglutide drug substance that could very well adversely impact the finished drug's safety and efficacy.

The C18 fatty di-acid moiety plays an important role in albumin binding and may sterically hinder the cleavage by the DPP-4 enzyme, while the A8Aib modification protects semaglutide against fast DPP-4 degradation, thereby prolonging semaglutide's half-life.[87] Similarly, the semaglutide linker has been shown to have a significant impact on potency and receptor binding, and both the fatty-diacid moiety and linker are key features that contribute to high albumin binding affinity and GLP-1 receptor potency.[88] Compounded products using bulk synthetic semaglutide that lack the correct and precise combination of the A8Aib/K34R modifications, γGlu-2xOEG linker, and C18 fatty-diacid moiety would have a much shorter half-

[85] *See* FDA, *Insanitary Conditions at Compounding Facilities: Guidance for Industry* (Nov. 2020), https://www.fda.gov/media/124948/download.

[86] *See supra* note 83.

[87] Staby, *supra* note 11 at 122; *see also* Yun Ding et al., *Impact of Non-Proteinogenic Amino Acids in the Discovery and Development of Peptide Therapeutics*, 52 AMINO ACIDS 1207 (2020) (noting that peptides incorporating non-proteinogenic amino acids can exhibit a longer circulating plasma half-life compared to native peptides).

[88] *Supra* note 13 at 7370–71.

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life and diminished potency. Chemical synthesis of peptide therapeutics featuring chemical linkers could lead to potential genotoxicity in vivo effects.[89] Furthermore, acylating the entire peptide rather than acylating the precursor alone makes purifying semaglutide more difficult. Failure to remove undesirable isomeric impurities associated with the C18 fatty-diacid moiety can adversely impact the biological activity of the compounded semaglutide. Thus, unless the bulk synthetic semaglutide used by compounders has the precise structure necessary to trigger the pharmacological action and has all the isomeric impurities controlled, the safety and efficacy of the finished product cannot be guaranteed.

2. Co-Active Ingredients

Co-active ingredients in compounded semaglutide drugs that are not present in FDA-approved semaglutide products include BPC-157, L-carnitine, glycine, vitamin B12, pyridoxine, chromium PIC, tirzepatide, and NAD+. Combining ingredients that have not been studied with semaglutide heightens the complexity of compounded semaglutide formulations and introduces some known risks, and critically, a myriad of unknown risks.[90] Developing a fixed-dose combination product is an extremely complex process and requires a careful safety and effectiveness assessment of the individual drugs alone and when used in combination. According to FDA, a fixed-dose combination "may present greater risk compared to clinical development of an individual drug" and "should ordinarily be reserved" for circumstances where there is a (a) combination intended to treat a serious disease or condition, (b) strong biological rationale for use of the combination, (c) full nonclinical characterization of the activity of both the combination and the individual drugs, or a short-term clinical study on an established biomarker that suggests the combination may provide a significant therapeutic advantage over an available therapy and is superior to the individual agents, and (d) compelling reason why the new drugs cannot be developed independently.[91] These circumstances do not exist for the compounded fixed-dose combination products purporting to contain semaglutide.

Moreover, the testing conducted on these compounded samples revealed impurities and degradants caused by the interactions between the semaglutide and the co-active ingredient, underscoring how complex it is to create such a formulation. For instance, testing revealed that a sample from one pharmacy contained BPC-157. The compounded product's marketing indicated

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[89] *See* Doris Zane et al., *Development and Regulatory Challenges for Peptide Therapeutics*, 40 INT'L J. TOXICOLOGY 108, 116 (2021).

[90] *See* FDA, *FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products* (Jul. 26, 2024), https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded ("FDA is aware that some compounders incorporate additional ingredients, such as cyanocobalamin (Vitamin B-12), pyridoxine (Vitamin B-6), levocarnitine (L-Carnitine) and nicotinamide adenine dinucleotide (NAD), into their semaglutide products. The safety and effectiveness of combining semaglutide with other ingredients has not been established.").

[91] FDA, Guidance for Industry, *Codevelopment of Two or More New Investigational Drugs for Use in Combination* 3 (June 2013), https://www.fda.gov/media/80100/download.

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that BPC-157 "is based on a protective compound present in the human stomach," which "works by triggering the formation of new blood vessels (angiogenesis)," and "may promote healing and induce faster regeneration for cells."[92] BCP-157 is not a component of any FDA-approved drug, and FDA has determined that BPC-157 should not be used in compounding because it raises significant safety and immunogenicity risks.[93] In addition, testing of the sample revealed the presence of dimers, including semaglutide–BPC-157 dimers.[94] Such dimers can further negatively affect the immunogenicity and safety profiles of compounded semaglutide products.[95]

Another formulation that revealed safety and efficacy concerns involved a compounded drug containing semaglutide and NAD+, an oxidized form of NAD. NAD and NAD+ "substantially degrade when exposed to light, moisture, alkaline pH, or standard room temperatures; therefore, [they] will not be stable under ordinary storage conditions."[96] Testing results for the sample showed extremely high levels of oxidations and di-oxidations, likely due to the NAD+ reacting with the semaglutide peptide.[97] These testing results indicated that the stability of semaglutide was compromised, which may adversely impact its effectiveness. In addition, the oxidation may result in the formation of aggregates with the potential to induce or enhance immune responses. FAERS includes one report associated with semaglutide and NAD+ where a patient suffered a liver injury, was hospitalized, and ultimately died. Considering the absence of clinical data, this adverse event report (although limited in number and information) may suggest a potential safety signal and should be thoroughly investigated.[98]

Finally, several compounding pharmacies are marketing a compounded drug containing semaglutide and tirzepatide in a fixed dose combination. We are not aware of any clinical research demonstrating the safety or efficacy of treatments combining tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, with

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[92] *Wells Pharmacy Networks LLC*, Complaint ¶ 24.

[93] Appendix XIX; FDA, *Safety Risks Associated with Certain Bulk Drug Substances Nominated for Use in Compounding* (last updated on Sept. 29, 2023), https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks; *Wells Pharmacy Networks LLC*, Complaint ¶¶ 42–43. The same immunogenicity concern that prompted FDA to place BPC-157 in Category 2 should motivate the Agency to place semaglutide products on the DDC Lists.

[94] Appendix S-22002 (Figure 12.2, Table 12.1); S-23014 (Figure 26.2, Table 26.1); *Wells Pharmacy Networks LLC*, Complaint ¶ 43.

[95] Staby, *supra* note 11.

[96] *Supra* note 7 at 4.

[97] *See* Appendix: S-23084 (Figures 19.1-19.3, Table 19.1).

[98] Unlike sponsors of FDA-approved medicines, compounding pharmacies do not do surveillance, evaluation, or reporting of adverse events to FDA. FDA has warned that "adverse events from compounded versions of these drugs are underreported." FDA, *FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss* (Oct. 2, 2024), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss.

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semaglutide, another GLP-1 receptor agonist. Without proper clinical studies to confirm that this combination is safe and effective, this product poses enhanced risks to patient safety. Indeed, the compounding of such product is in direct violation of the instruction on the FDA-approved labels for WEGOVY®, a semaglutide product, and ZEPBOUND®, a tirzepatide product, which each state that these products should not be co-administered with other GLP-1 receptor agonists.[99]

3. Inactive Ingredients

With respect to oral dosage forms, unlike RYBELSUS®, most of the compounded oral formulations purporting to contain semaglutide that have been tested do not contain SNAC, an absorption enhancer that elevates the local pH environment in the stomach and leads to increased semaglutide solubility and decreased proteolytic degradation.[100] SNAC also promotes semaglutide monomerization and fluidizes the plasma membrane of the gastric epithelium.[101] Many compounded semaglutide products for oral use are missing this critical ingredient altogether and there is no ingredient with similar properties added to the formulation.

Some compounded sublingual formulations claiming to contain semaglutide incorporate an anhydrous base that supposedly forms liposomes when exposed to saliva, which will allegedly aid in the delivery of sublingual medications. This liposomal semaglutide drug product has never been clinically tested in humans. FDA has also already proposed that liposome drug products be included on the lists of drug products that present demonstrable difficulties for compounding under both section 503A and section 503B.[102] In the proposed rule, the Agency highlighted the risk that the improper selection of inactive ingredients or improper mixing of liposomes with active ingredients could cause the drug product to be potentially ineffective or hazardous.[103] Novo Nordisk urges FDA to finalize the proposal to include liposomal drug products, including those formed by combining/compounding semaglutide with an anhydrous base, on the DDC Lists.[104]

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[99] The WEGOVY® label states "WEGOVY® contains semaglutide. Coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended." Novo Nordisk, *WEGOVY® Semaglutide Injection,* novo-pi.com/wegovy.pdf. The ZEPBOUND® label states "ZEPBOUND contains tirzepatide. Coadministration with other tirzepatide-containing products or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended." Eli Lily and Company, *ZEPBOUND – Tirzepatide Injection, solution,* https://uspl.lilly.com/zepbound/zepbound.html#pi.

[100] *See* Hwi Seung Kim et al., *Oral Semaglutide, the First Ingestible Glucagon-Like Peptide-1 Receptor Agonist: Could It Be a Magic Bullet for Type 2 Diabetes?*, 22 INT'L J. MOLECULAR SCI. 9936 (2021).

[101] *See* Vanita R. Aroda et al., *A New Era for Oral Peptides: SNAC and the Development of Oral Semaglutide for the Treatment of Type 2 Diabetes*, 23 REVS. IN ENDOCRINE & METABOLIC DISORDERS 979, 982 (2022).

[102] *Supra* note 6 at 19,785.

[103] *See id.*

[104] Comment by Novo Nordisk, No. FDA-2023-N-0061-0021 (Jun. 18, 2024), https://www.regulations.gov/comment/FDA-2023-N-0061-0021.

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4. Safety and Effectiveness Risks Associated with Compounded Semaglutide Formulations

The safety and efficacy concerns associated with compounded semaglutide are not merely theoretical. The peptide-related impurities observed in the compounded samples tested pose serious safety risks to patients because they "have the potential to stimulate an immunological reaction upon repeated injections."[105] Even in small quantities, pharmaceutical impurities can negatively impact the safety and efficacy of a drug product.[106] Such changes may impact the immunogenicity potential of compounded semaglutide products and pose severe safety risks, including anaphylaxis, injection site reactions, and delayed immune reactions including type-III hypersensitivity and immune complex deposition causing fever, rash, arthralgias, myalgias, and hematuria.[107] Moreover, neutralizing antibodies to semaglutide may decrease semaglutide's effectiveness, and more critically, antibodies to semaglutide may cross react to endogenous GLP-1, neutralizing the activity of this essential incretin hormone.

Also, with regard to efficacy, testing results have shown that certain compounded semaglutide samples have substantially lower or higher strengths than labeled.[108] Many samples had strengths outside the 90-110% range of the labeled strength and one sample had no semaglutide whatsoever.[109] While the strengths of these compounded drugs are inconsistent across pharmacies, they can also be inconsistent from the same clinic. One weight loss clinic that distributed compounded semaglutide to patients sold one sample was superpotent (111% of the labeled strength) while another sample was subpotent (70% of the labeled strength).[110] Given the differences in the impurity profiles, it is likely that these samples came from two different API suppliers. The compounding pharmacy that made these two products are unknown, because the

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[105] Staby, *supra* note 11 at 135.

[106] *See* Kavita Pilaniya et al., *Recent Trends in the Impurity Profile of Pharmaceuticals*, 1 J. ADVANCED PHARM. TECH. & RSCH. 302, 302 (2010).

[107] *See* FDA, *Immunogenicity Assessment for Therapeutic Protein Products* 33 (Aug. 2014).

[108] *See, e.g.*, Appendix: S-23114 (Table 20.1); Appendix: S-24031 (Table 21.1); *Brooksville Pharm. Inc.*, First Amended Complaint ¶ 21 ("[Brookville Pharmaceuticals]'s drug product is . . . misbranded because . . . its strength is at least 19 percent less than what is reported on its label."); *Novo Nordisk Inc. v. MediOAK Pharmacy LLC,* No. 4:24-cv-02032, ECF 1, Complaint ¶¶ 25-26 (S.D. Tex. May 30, 2024) ("Defendant markets and sells to patients certain non-FDA approved compounded drugs that claim to contain '2.4MG/0.75 ML' of semaglutide. However, testing of Defendant's compounded drugs performed on Novo Nordisk's behalf has revealed that Defendant's drug product is misbranded because its 'semaglutide' content is calculated at 1.91 mg/0.75 mL, which is at least 20 percent less than its labeled strength."); *Novo Nordisk Inc. v. Live Well Drugstore, LLC*, No. 3:23-cv-808, ECF 70, First Amended Complaint ¶¶ 45-46 (M.D. Fla. July 15, 2024) ("Defendant's "4mg vial" is labeled as "2ml," which equates to a labeled strength of 2 mg/mL. Novo Nordisk's testing of Defendant's drugs, however, has revealed that they contain only 1.75 mg/mL of semaglutide, which is at least 12 percent less than its labeled strength.").

[109] *Novo Nordisk Inc. v. Dunklau Pharmacy Holdings, LLC et al.,* No. 3:24-CV-00667, Complaint ¶ 24 (M.D. Tenn. May 2024).

[110] *See* Appendix: S-23114 (Table 20.1); S-24031 (Table 21.1).

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clinic sold patients compounded semaglutide, in unlabeled, prefilled syringes via mail. The inconsistencies in strengths between batches, even from the same clinic, underscores exactly why compounded semaglutide products are difficult to compound.

Inconsistent strengths are also an issue for compounded sublingual or transmucosal semaglutide products. Testing results from compounding pharmacies marketing sublingual semaglutide products reveal high levels of impurities and inconsistencies between the labeled strength and calculated semaglutide content. One compounded sublingual semaglutide sample contained 170% of the labeled strength, while testing results from a different pharmacy's compounded sublingual semaglutide contained only 42% of the labeled strength.[111] Some of these compounded sublingual samples had total impurities up to 41% of the sample.[112] Transmucosal films claiming to contain semaglutide also have strength and purity issues. The strength of compounded transmucosal semaglutide films varied among the different films within the same package. Some strips contained only 12% of semaglutide in the formulation compared to the labeled claim, while other strips in the same package contained 20% of the labeled claim.[113] These strips also contained up to 75% impurities.[114]

Subpotent and superpotent samples pose serious risks to patients. The reduced strength of compounded semaglutide formulations render such products potentially less effective than the FDA-approved semaglutide products.[115] This lack of efficacy also poses a safety risk. When patients believe that their chronic condition is being treated by a compounded drug, they lose out on the opportunity to use a product that has been found to be consistently safe and effective, like an FDA-approved drug indicated for their condition. However, if the compounded drug is less effective or ineffective, the patients' condition will go untreated. For patients with type 2 diabetes or cardiovascular disease, the consequences of not treating their conditions can be life-threatening. A sample whose strength is higher than labeled is also potentially dangerous. Administering too much compounded semaglutide could lead to serious adverse events or even hospitalization, especially if the patient accidentally overdoses on a superpotent product.[116]

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[111] Appendix: S-24043 (Table 15.1); S-24045 (Table 17.1).

[112] Appendix: S-24043 (Table 15.2); S-24045 (Table 17.2). This sum of impurities is an integration of peaks within the retention time window where Novo Nordisk has typically observed semaglutide-related impurities. Due to signal interference from excipients, the impurity profile of this sample could not be further analyzed by LC-MS..

[113] *See* Appendix: S-24050 (Table 13.1).

[114] Appendix: S-24050 (Table 13.2). The percent impurities for the sample were calculated by integrating the peaks in the retention time window where semaglutide-related impurities typically elute, except peaks in the retention time window where large hydrophobic impurities typically elute.

[115] *Id*.

[116] *Supra* note 90.

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Despite the historic underreporting of adverse events associated with compounded drugs,[117] a significant number of adverse events associated with compounded semaglutide have been reported. Based on data as of June 30, 2024, FAERS reported 542 cases of adverse events associated with compounded semaglutide since 2018.[118] Of those cases, 388 were classified as "serious" adverse events, 124 involved hospitalization, and 10 involved deaths.[119] The database includes reports of adverse events associated with compounded semaglutide that are not present on the labels for Novo Nordisk's FDA-approved products, such as hematuria (blood in urine) and myalgia (muscle pain or discomfort). Hematuria and myalgia may be immunogenicity related adverse events.[120] Given the lack of clinical data, and this historic underreporting, these reports (despite their well-recognized limitations), raise concerns regarding the safety and effectiveness risks associated with compounded semaglutide drugs.

Compounded semaglutide is also associated with several product quality and dosing issues. FAERS includes several reports on product quality and dosing issues, and lack of efficacy associated with compounded semaglutide drugs. A recent publication highlighted administration errors where patients accidentally self-administered doses of compounded semaglutide up to 10 times greater than the intended amount.[121] FDA has similarly issued a risk alert on dosing errors associated with injectable compounded semaglutide that warns the public that several patients had mistakenly administered 5 to 20 times more than the intended dose of compounded semaglutide.[122] Many of these patients reported several adverse events, sought medical attention, or were hospitalized after overdosing on the compounded semaglutide.

Furthermore, in a letter sent by FDA to Alliance for Pharmacy Compounding, the Federation of State Medical Boards, the National Association of Boards of Pharmacy, the National Council of State Boards of Nursing and the Outsourcing Facilities Association, the Agency flagged additional factors that it believes may have contributed to the adverse events

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[117] Unlike sponsors of FDA-approved medicines, compounding pharmacies do not perform surveillance, evaluation, or reporting of adverse events to FDA. FDA has warned that "adverse events from compounded versions of these drugs are underreported." *Supra* note 98. As a result, the number of 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. *See* Janet Woodcock and Julie Dohm, *Toward Better-Quality Compounded Drugs — An Update from the FDA*, 377 NEW ENG. J. MED. 2509, 2510 (2017).

[118] FDA, *FAERS Public Dashboard*, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

[119] *Id.*

[120] *Supra* note 107.

[121] Joseph E. Lambson et al., *Administration Errors of Compounded Semaglutide Reported to a Poison Control Center — Case Series*, 63 J. AM. PHARMACISTS ASS'N 1643–45 (2023).

[122] *Supra* note 90.

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reported to FDA.[123] First, FDA noted 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.[124] Compounded semaglutide products were also prescribed to be administered twice a week instead of once weekly, which is the recommended frequency of administration for FDA-approved semaglutide medicines. Last, prescribers titrate patients' doses "every one to two weeks instead of every four weeks," which is the recommended titration schedule for FDA-approved semaglutide medicines.[125] FDA encouraged providers and compounders to consider the possible adverse events that could arise when varying from the doses, dose frequencies, and titration schedules used in the FDA-approved products and weigh the risks versus benefits of deviating from the approved products' dosing.

* * *

In sum, semaglutide products' *complex formulations* present a demonstrable difficulty for compounding that is reasonably likely to lead to adverse safety and efficacy effects.

B. Factor 2 — The Complexity of Semaglutide Products' Delivery Mechanisms

Semaglutide products present a demonstrable difficulty for compounding because the delivery mechanisms of the FDA-approved semaglutide products are complex and designed to release semaglutide in a precise way and limit administration errors, while the use of different delivery mechanisms for compounded semaglutide is likely to lead to an adverse effect on the safety or efficacy of the drug product. A complex drug delivery mechanism refers to "the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect."[126] Complex drug delivery mechanisms include, for example, formulations designed to release the drug at specific onset, rate, and extent through specific region(s) within the gastrointestinal (GI) tract; formulations designed to achieve permeation through the skin at a specific rate; and formulations containing coated beads or liposomes.[127] FDA-approved injectable and oral semaglutide products involve complex, site-specific, dosage-delivery mechanisms, and compounders are risking patient safety by compounding injectable and oral products purporting to contain semaglutide without these delivery mechanisms.

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

[124] *Id.*

[125] *Id.*

[126] *Supra* note 6 at 19,780.

[127] *Id.*

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1. The Complex Delivery Mechanism of Injectable Semaglutide Products

The delivery mechanism used by FDA-approved injectable semaglutide products is complex, and failure to use such a suitable delivery mechanism adversely impacts patients' ability to safely use the products, especially since they are self-administered. Novo Nordisk's injectable semaglutide products come in a single-patient-use pen injector, which accurately dispenses the correct dose and comes with fulsome instructions to reduce the risk that patients will accidentally overdose. In contrast, compounders typically use unapproved, multi-dose vials and insulin syringes, prefilled syringes, or compounding kits with highly variable instructions. These differences significantly increase the risk of significant administration errors, which have been reported for compounded semaglutide products.

To date, there have been multiple reports of patients overdosing on injectable compounded semaglutide as a result of administration errors.[128] For instance, a 50-year-old male with type 2 diabetes who obtained semaglutide from a specialty compounding pharmacy incorrectly self-administered 50 units (0.5 mL), instead of 5 units (0.05 mL), of semaglutide co-formulated with cyanocobalamin subcutaneously.[129] The patient consistently vomited for 2 days and had ongoing nausea for 1 week. Similarly, a 37-year-old female with a history of obesity incorrectly self-administered 10 times the correct dose of semaglutide co-formulated with cyanocobalamin that she received from a compounding pharmacy, which dispensed the medication in a vial with syringes for self-administration.[130] She experienced frequent vomiting, a persistent headache, decreased appetite, weakness, and fatigue. Another 33-year-old female went to a hospital's emergency department with nausea, vomiting, and abdominal pain after receiving a subcutaneous injection at an aesthetic spa of what was reported to be compounded semaglutide of an unknown source.[131]

The above-documented dosage-administration errors involving compounded semaglutide likely resulted from the differences between the delivery mechanism used by the compounding pharmacies and the delivery mechanism of the FDA-approved semaglutide products. Novo Nordisk's semaglutide products are supplied as a clear, colorless solution in a prefilled, disposable, single-patient-use pen injector, which accurately dispenses precise semaglutide doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg.[132] The prescribing information further instructs that

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[128] *See, e.g.*, *supra* note 121 at 1643–45 (2023); Brenda Goodman, *Poison Centers See Nearly 1,500% Increase in Calls Related to Injected Weight-Loss Drugs as People Accidentally Overdose*, CNN, https://www.cnn.com/2023/12/13/health/semaglutide-overdoses-wellness/index.html (Dec. 18, 2023) (stating that between January and November 2023, US poison control centers reported nearly 3,000 calls of accidental semaglutide-related overdoses involving symptoms such as severe nausea, vomiting, and stomach pain, which represents a 1,500% increase since 2019).

[129] *Supra* note 121 at 1644.

[130] *Id*.

[131] *Id*.

[132] *See supra* note 19; *supra* note 22.

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patients should initiate treatment of approved semaglutide with a 0.25 mg subcutaneous injection once weekly for 4 weeks, followed by an increase to 0.5 mg once weekly for another 4 weeks. The dosage may be further increased after the third month to 4 weeks to 1 or 2 mg once weekly for OZEMPIC® and to 1.7 mg and 2.4 mg in the fourth and fifth months, respectively, for WEGOVY®. The semaglutide solution comes in a prefilled cartridge, so that the drug is never in contact with the injecting device. Each pen injector is manufactured for use with NovoFine® Plus or NovoFine® disposable needles up to 8 mm in length and delivers precise doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg, which ensure proper titration of the drug according to the prescribing information. The use of needles of appropriate length is important because semaglutide should be injected subcutaneously (under the skin) into a patient's abdomen, thigh, or upper arm and should not be injected intramuscularly (into a muscle) or intravenously (into a vein). Furthermore, Novo Nordisk's pen injector features various components and special characteristics, including a dose button, end-of-content stop, torque limiter to protect the mechanism from overload, end-of-dose click, and a maximum possible dose. The pen injector ensures that (1) the correct amount of semaglutide product is delivered into the precise area of a patient's body, and (2) the integrity of the semaglutide product is preserved by not exposing it to air, light, and other elements that could degrade it.

Unlike FDA-approved semaglutide products, which are supplied as prefilled injection pens that deliver a specific dose to patients, compounders often provide insulin syringes and a multi-dose vial from which patients must draw up the correct amount of medication themselves. These methods used by compounders have not been reviewed by FDA as an effective or safe method to deliver semaglutide. Vials containing large volumes of medication enable the dangerous delivery of large overdoses that have been documented (up to 10 times the prescribed dosage) with compounded semaglutide products.[133] The use of conventional syringes, as opposed to the disposable needles in Novo Nordisk's products, compounded by the lack of approved labeling, further contributes to patient confusion about the proper dosing units and procedures for self-administration. Moreover, the delivery mechanism associated with compounded semaglutide increases the likelihood of administration errors because patients must figure out the correct amount of milliliters, units, and milligrams that need to be injected.[134] Similar dosage and delivery errors have been reported among other medications when pen injectors are replaced with manual delivery using a syringe.[135]

FDA has also warned health care providers, compounders, and patients of dosing errors associated with compounded injectable semaglutide products. FDA noted that it has received

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[133] *Supra* note 128.

[134] *See supra* note 121.

[135] *See, e.g.*, Daniella Asch et al., *Benefit of Epinephrine Autoinjector for Treatment of Contrast Reactions: Comparison of Errors, Administration Times, and Provider Preferences*, 209 AM. J. ROENTGENOLOGY 363, 366 (2017) (reporting a nearly 50% *physician* administration error rate in the dosage and delivery of epinephrine when pen injectors were replaced with traditional needle-mediated manual delivery, which suggests an even higher error rate for patient self-administration).

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reports of adverse events, some requiring hospitalization, due to dosing errors from patients measuring and self-administering incorrect doses or health care providers miscalculating doses of compounded semaglutide.[136] The Agency received reports that patients administered five to 20 times more than the intended dose of semaglutide.[137] Health care providers have also incorrectly calculated the doses when converting between milligrams to units or milliliters. For example, one provider prescribed 20 units instead of 2 units of compounded semaglutide. The provider's patients received 10 times the intended dose and experienced nausea and vomiting.[138] Even patients that are health care providers have inadvertently self-administered a dose 10 times higher than intended.[139]

The Agency indicated that the likely cause of these dosing errors relates to the use of various containers and packaging, including multi-dose vials and prefilled syringes, and varying product concentrations associated with compounders of semaglutide products.[140] Many reports indicated that patients were unfamiliar with how to measure the intended dose using a syringe. Furthermore, FDA noted that the instructions that accompany the compounded drug, if any are provided, instructs users to administer semaglutide injections in "units" rather than milligrams or milliliters, and that the insulin syringes provided are much larger than the prescribed volume of semaglutide.[141] This lack of clarity has resulted in dangerous outcomes. A patient who received compounded semaglutide from a telemedicine provider without clear dosing instructions was forced to conduct an online search for medical advice that ultimately led to the patient's accidental overdose.[142]

In circumstances where the compounded semaglutide product is dispensed in a prefilled syringe, the labeling may be missing key information for patient use. For example, two different companies have sent compounded semaglutide drug samples to patients through the mail that arrived in prefilled syringes with no indication of when the product was made or the beyond-use date ("BUD").[143] Furthermore, in two cases, the container falsely included the trade name OZEMPIC®.[144] The delivery mechanism, coupled with the labeling and packaging of this compounded drug, pose patient safety risks. Patients will not know the BUD of the compounded

[136] *Supra* note 90.

[137] *See id*.

[138] *See id*.

[139] *See id*.

[140] *See id.*

[141] *See id.*

[142] *See id.*

[143] *See* Appendix: S-23114 (Figure 20.2); S-24031 (Figure 21.2); S-24013 (Figures 22.1 and 22.2).

[144] Appendix: S-23114 (Figure 20.1); S-24031 (Figure 21.1).

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drug, may assume that the compounded drug shares the duration of expiry of OZEMPIC®, and could take the compounded drug well past the BUD.

The potential for erroneous delivery and overdosing is not limited to injecting semaglutide solutions. Novo Nordisk's research further reveals that compounders and other providers send patients "compounding kits," which require patients to reconstitute the peptide themselves.[145] This is concerning because the preparation of lyophilized, parenteral medications in a patient's home environment can lead to serious consequences based on how much the patient deviates from the manufacturer-provided dosage and delivery instructions in favor of preparation techniques that are more compatible with the patient's previous experiences and expectations (i.e., "mental models.").[146] Shifting dosage and delivery burdens to patients with little to no experience in reconstituting lyophilized drugs—especially peptide drugs—poses serious safety risks even if unapproved instructions are provided. Patients, for example, could accidentally fail to fully resuspend the lyophilized powder, which would affect the dose delivered; introduce contaminants into the resuspended solution due to improper handling and use of unsterile equipment; or incorrectly measure the proper dose necessary to ensure the safety and efficacy of the medication. Additionally, patients could introduce air bubbles in the resuspended solution, which could lead to injection-mediated air embolisms.[147] Furthermore, as discussed in Factor 5, the exposure of semaglutide to air bubbles, which may occur with a multi-dose vial, can degrade the semaglutide and result in peptide-related impurities.[148] Using a dosing pen injector to administer semaglutide significantly improves the safety and efficacy of the product.

The complexities associated with reconstituting semaglutide powder and ensuring sterility are also present when physicians compound semaglutide products in a medical spa or weight loss clinic. Physicians engaged in in-office compounding may fail to fully resuspend the lyophilized powder or incorrectly measure the proper dose necessary. Additionally, physicians compounding these products in medical spas or weight loss clinics are unlikely to have hoods or

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[145] Appendix XXIV; *see, e.g.*, FDA, *Inter-governmental Working Meeting on Drug Compounding* (Nov. 1–2, 2022), https://www.fda.gov/drugs/human-drug-compounding/inter-governmental-working-meeting-drug-compounding-november-1-2-2022 (expressing concerns about new trends involving delivery of "compounding kits" to patients, "who are then expected to prepare their own drugs with supplied ingredients and instructions, sometimes even for injection.").

[146] *See* Chris Franzese et al., *The Burden of At-Home Preparation of Lyophilized Parenteral Medications: An Analysis of Contributing Factors and Implications for Chronic Disease Patients and Caregivers*, 16 EXPERT OPINION ON DRUG DELIVERY 187, 194 (2019).

[147] *See* Hajime Yano et al., *Cerebral Air Embolism as a Complication of Subcutaneous Injection*, 130 AM. J. MED. E443–44 (2017).

[148] *See* Appendix: S-22002 (Figure 12.2, Table 12.1); *infra* Factor 5.

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other equipment necessary for sterile compounding.[149] In fact, boards of medicine have warned that many physicians are compounding semaglutide using a drug substance that is not prescription quality powder (i.e., research grade powder) and do not compound using USP's quality standards for sterile injectable products.[150] Given the prevalence of medical spas and weight loss clinics as sources of compounded semaglutide, a significant number of patients could be adversely impacted by compounded semaglutide improperly prepared in these settings.

Thus, compounded semaglutide products lack the complex safety features inherent in the design of Novo Nordisk's FDA-approved prefilled pen injectors. The absence of such safety features increases the likelihood that patients will be unable to adhere to complex dosing requirements and will suffer from dosage-related administration errors.

2. The Complex Delivery Mechanisms of Oral, Sublingual, or Transmucosal Semaglutide Products

RYBELSUS® has an inherently complex drug delivery mechanism. RYBELSUS® is co-formulated with SNAC, which facilitates the absorption and bioavailability of semaglutide after oral administration.[151] The absorption of semaglutide following orally dosing of RYBELSUS® predominantly occurs in the stomach. The exposure to semaglutide in RYBELSUS® increases in a dose-proportional manner, as assessed through population pharmacokinetics studies.[152] The maximum concentration of semaglutide is reached one-hour post-dose, and steady state exposure is achieved following 4-5 weeks of administration.[153]

The drug delivery mechanisms used by compounded semaglutide products are significantly different than that used by RYBELSUS®. The compounded formulations intended for swallowing do not contain SNAC or a comparable absorption-enhancing ingredient and have not been the subject of by population-pharmacokinetics studies performed on drugs like RYBELSUS®, which casts serious doubt about whether, and how much, compounded semaglutide is being absorbed in the stomach. Furthermore, compounders are using other delivery mechanisms, such as sublingual routes of administration for tablets and solutions (including with liposomes) and transmucosal routes of administration for films. There are no FDA-approved sublingual tablets or solutions or transmucosal films with semaglutide or any other comparable molecule. Developing safe and effective products with sublingual and

[149] *See* Federation of State Medical Boards, *White Paper on Compounding of Medications by Physicians* (posted in 2020), https://www.fsmb.org/siteassets/advocacy/publications/white-paper-on-physician-compounding-2020-for-posting.pdf (encouraging physicians to limit compounding activity to non-sterile preparations unless they have all equipment, materials, and space necessary to comply with applicable standards).

[150] *See* Alabama State Board of Medical Examiners, *Declaratory Ruling of the Alabama State Board of Medical Examiners* (Aug. 8, 2024), https://www.albme.gov/uploads/pdfs/BOPSemaglutide.DeclaratoryRuling_.pdf.

[151] *Supra* note 16.

[152] *See id.*

[153] *See id.*

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transmucosal routes of administration is complex, especially for complicated peptides like semaglutide.

Sublingual administration typically results in lower drug absorption than orally administered medications that are swallowed, especially for large molecules, because of the thick mucinous fluid secreted by sublingual glands and the underlying tight epithelial junctions.[154] It is generally recommended that a drug formulated for sublingual administration should have a molecular weight of less than 500 g/mol to facilitate its diffusion.[155] A large molecule with similar characteristics to a protein, like semaglutide, which has a molecular weight of about 4,113 g/mol, likely would require a significant amount of time to be absorbed via this route of administration, if it is absorbed at all. For a sublingual tablet, patients would need to allow the tablet to fully dissolve under the tongue without swallowing and the semaglutide would need to be absorbed via the oral mucosa. Similarly, the limited information available indicates that the compounded sublingual tablets must be held under the tongue for an indeterminate amount of time for full absorption. Given the possible unpleasant taste or texture, [156] patients may struggle to keep the product under the tongue for full absorption and instead swallow it. If the drug is swallowed and makes its way to the GI tract, it will likely not be absorbed. Additionally, the systemic bioavailability of peptides is typically less than 5% of the administered dose with transmucosal delivery due to the physicochemical barrier of the oral mucosa, which contains enzymes that break down peptides.[157]

In addition, several pharmacies are compounding sublingual semaglutide products by mixing crushed RYBELSUS® tablets or semaglutide from other sources with a patent-pending anhydrous base that reportedly, allegedly utilizes liposomes to carry drugs with a high molecular weight. Entities marketing these products claim that the anhydrous base has self-emulsifying properties such that when the vehicle hits the aqueous environment of the mouth, it results in the instantaneous formation of a mixed micelle liposomal system without mechanical energy.[158] This emulsion allegedly has mucoadhesive properties which help transport the molecule into the mucosal tissue under the tongue, ensuring that the drug is absorbed more efficiently and prolonging contact time between the drug and the mucosal tissues.

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[154] *See* Jiamin Wu et al., *Systemic delivery of proteins using novel peptides via the sublingual route*, 368 J. OF CONTROLLED RELEASE 290 (Apr. 2024).

[155] *See* Vilayat A. Sayeed and Muhammad Ashraf, *Considerations in Developing Sublingual Tablets – An Overview*, 38 PHARMA. TECH. (Nov. 2, 2014), https://www.pharmtech.com/view/considerations-developing-sublingual-tablets-overview.

[156] *See* Parma Verma et al., *Routes of Drug Administration*, INT. J. OF PHARMA. STUDIES AND RES. (2020), https://romanpub.com/resources/ijpsr%20v11-2020-7.pdf.

[157] Hao Zhang, et al., *Oral Mucosal Drug Delivery—Clinical Pharmacokinetics and Therapeutic Applications,* 41 CLINICAL PHARMACOKINETICS 661, 664 (2002), https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=f1cc5e280a3ae90701121861afaba4d2349e780f.

[158] *See* Appendix XXX.

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Entities marketing these products claim that the products have enhanced bioavailability as compared to RYBELSUS®; however, the flux rates of these compounded products, reported to be up to 1 ng/cm²/hr, likely do not allow for any meaningful absorption of semaglutide.[159] The animal study that tested this anhydrous base with semaglutide is also unconvincing to show the bioavailability of this dosage form. The *in vivo* study was conducted in rats, which are a poor model for determining the bioavailability of sublingual products.[160] Rats exhibit a thin, keratinized epithelium with low epithelial extensions; this pronounced keratinization of the oral mucosa may result in a possible physical barrier that minimizes the penetration of sublingual products into the bloodstream.[161] Minipigs and monkeys, in contrast, have a thick, non-keratinized mucosal lining with large epithelial extensions, similar to humans. Therefore, because of these differences between the oral mucosae in rodents versus humans, using rodents for these kinds of studies will not be able to adequately gauge the impact of such dosage and administration schemes in humans.

Additionally, purported studies of this anhydrous base did not show the absorption of semaglutide into and through the artificial tissue used for *in vitro* testing until 15 minutes post-application of the sublingual compounded formulation.[162] However, we have seen several compounding pharmacies direct patients to hold the product in their mouths for anywhere between 90 seconds to 5 minutes. Consequently, even if the sublingual technology is effective, under the prescribed instructions, it will not be held in place for sufficient time to take effect. Considerations like these are why FDA has stated that the delivery mechanism of liposomal drug products is inherently complex because "it involves precisely designing and formulating a system that delivers a specific amount of API per unit time and, in most cases, in a specific region."[163] Furthermore, in order to successfully use liposomes as a drug delivery mechanism, compounders need "precise control of raw materials, the manufacturing process, and the final product," which compounders, even those operating under CGMP, cannot maintain.[164]

Other compounders are selling transmucosal or sublingual semaglutide films to patients. This film purportedly must permeate through a specific region (i.e., the buccal mucosa or lining inside the cheek or the oral mucosa under the tongue) at a certain rate into the bloodstream

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[159] *See id*. A 3 mg RYBELSUS® tablet with a fasting period of 0.5 hours corresponds to an absorption of 0.01 * 3 mg = 0.03 mg = 30,000 ng with 1% bioavailability. A compounded product with a flux rate of 1 ng/cm²/h in an oral cavity area of 50 cm² with the same absorption window of 0.5 hours results in significantly lower absorption of 1 ng/cm²/h * 50 cm² * 0.5 h = 25 ng.

[160] *See id*.

[161] *See* Catherine Thirion-Delalande et al., *Comparative analysis of the oral mucosae from rodents and non-rodents: Application to the nonclinical evaluation of sublingual immunotherapy products*, 12 PLOS ONE (Sep. 8, 2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5590855/.

[162] *Supra* note 158.

[163] *Supra* note 6 at 19,783.

[164] *Id.*

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through the thin mucosal membranes. Using this type of delivery mechanism with semaglutide requires an assessment of whether semaglutide possesses the physiochemical properties necessary for such routes of administration and whether a semaglutide film can overcome barriers in the oral cavity, including the intrinsic enzyme activity, the relative permeability of the oral mucosa, and the small fluid volume required for dissolution and absorption.[165] Compounding such a film would also require a mucoadhesive to increase the contact time of the formulation and minimize any accidental ingestion of the product and a careful balancing of the dose to ensure it is appropriate for a given patient.[166] As noted above, there is no approved transmucosal or sublingual semaglutide film that compounders can use as a guide for their products, and semaglutide's size makes permeating the mucosa in the mouth extremely challenging. Extensive testing, which compounders do not perform, is necessary to ensure that the complexities with this delivery mechanism do not lead to adverse effects on safety and efficacy.

Thus, the delivery mechanism of RYBELSUS® is complex, and the delivery mechanisms of the compounded oral, sublingual, or transmucosal semaglutide products, including the tablets, solutions, and films, present significant complexities and safety and effectiveness risks.

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In sum, the *delivery mechanisms* necessary for safe and effective injectable and oral, sublingual, or transmucosal semaglutide-containing products are complex, and the semaglutide products with different delivery mechanisms are difficult to compound and pose significant safety and effectiveness risks.

C. Factor 3 — Semaglutide Products' Dosage Forms Are Complex

Semaglutide products present a demonstrable difficulty for compounding because the dosage forms used by compounders are complex and likely to lead to an adverse effect on the safety and efficacy of the drug product. A complex dosage form refers to "physical dosage units with unique characteristics that are difficult to consistently achieve or maintain," and "container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system."[167] Drug products may have very simple formulations, such as a single API, and a simple delivery mechanism, such as an injection, but the drug product may be complex because the physical properties of the dosage form are difficult

[165] Jenny K.W. Lam et al., *Oral transmucosal drug delivery for pediatric use*, 73 ADVANCED DRUG DELIVERY REVIEWS 50 (Jun. 2014).

[166] *See id.*

[167] *Supra* note 6 at 19,780-81.

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to achieve or maintain, such as coated beads, osmotic-controlled release systems, and liposomes.[168]

As discussed above, while many compounding pharmacies compound injectable solutions or oral tablets (the dosage forms of FDA-approved semaglutide products), some compounders are using other dosage forms like lyophilized powders intended for an injectable solution, dissolvable tablets, tablets for a sublingual route, solutions for a sublingual route, films for a buccal or sublingual route, and troches for oral use. All of these dosage forms present significant safety and efficacy issues when compounded, especially for peptides like semaglutide. Many of the complexities described above for the drug delivery mechanisms are relevant to the complexities for the dosage forms. This section will focus on additional complexities posed by the compounded dosage forms.

The injectable compounded semaglutide differs from the injectable FDA-approved semaglutide products in meaningful ways. The use of a multi-dose vial and normal insulin syringes that have not been approved by FDA for use with a particular drug product increases sterility assurance risks and make it difficult to achieve a consistent dose. Injectable drug products already pose a serious risk of harm to patients because "they bypass many of the body's natural defenses against toxic ingredients, toxins, or dangerous organisms that can lead to serious and life-threatening conditions such as septicemia or sepsis."[169] These risks are exacerbated by the compounders' untested use of multi-dose vial and insulin syringes, which lack the sterility assurances of injectable FDA-approved semaglutide products. As discussed in Factor 2, vials containing large volumes of compounded semaglutide enable patients to overdose on compounded semaglutide products.[170] Similarly, patients can accidentally over-or-underdose themselves by erroneously determining how many units of solution correspond to their proper dose in the units listed on the insulin syringes. There is a higher likelihood that a patient could extract the incorrect dosage if the patient is also responsible for calculating a new dose titration. Because the product is injected and medications administered via injections are generally absorbed more quickly compared to oral injection,[171] these dosing errors can impact patients even more quickly than in oral dosage forms.

The compounded oral, sublingual, or transmucosal dosage forms also present complexities and dangers to patients. Testing has demonstrated significant inconsistencies with products in these dosage forms. For example, when tested, the strength of compounded transmucosal semaglutide films varied among the different films within the same package. Some strips contained only 12% of semaglutide in the formulation compared to the labeled claim,

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[168] *Id.*

[169] FDA, *Warning Letter: www.semaspace.com* (Oct. 2, 2023), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/wwwsemaspacecom-665848-10022023.

[170] *See, supra* note 121 at 1643–45.

[171] *See* CLAIRE EAU, *Chapter 18: Administration of Parenteral Medications in* NURSING SKILLS (2021), https://www.ncbi.nlm.nih.gov/books/NBK593214/.

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while other strips contained 20% of the labeled claim.[172] Other sublingual dosage forms, especially those using liquid anhydrous formulations, had similar issues with inconsistent strengths. Some compounded sublingual semaglutide solutions were superpotent and contained between 135%-170% of the labeled strength.[173] Other compounded semaglutide solutions were subpotent and contained only 42% of the labeled strength.[174] Most concerningly, a sublingual oral solution purporting to contain 1 mg/ml of semaglutide contained no semaglutide at all.[175] The inconsistent strengths per dosage form will lead to inconsistent efficacy of the finished product. Furthermore, the use of crushed RYBELSUS® tablets to compound sublingual oral dosage forms of semaglutide using liquid anhydrous formulations raises concerns regarding quality and stability. The labeling of RYBELSUS® includes a "Do not . . . crush tablets" instruction,[176] and the constituents in RYBELSUS® tablets have not been demonstrated to be compatible in a liquid state or suspension. Therefore, these products pose significant risk to patients. Patients taking a less effective or ineffective drug purporting to contain semaglutide are losing the opportunity to receive treatment that would be effective at treating their condition and leaving their underlying disease improperly treated or wholly untreated.

Thus, these differences and inconsistencies illustrate that compounding semaglutide *dosage forms* is a complex endeavor and are likely to lead to an adverse effect on the safety and efficacy of the drug products.

D. Factor 4 — Semaglutide Products' Complexity in Achieving and Assessing Bioavailability

Semaglutide products present a demonstrable difficulty for compounding due to the complexity in achieving and assessing semaglutide bioavailability. Bioavailability refers to "the rate and extent to which the active ingredient . . . is absorbed from a drug product and becomes available at the site of action."[177] According to FDA, "drug products may present demonstrable difficulties for compounding if bioavailability is challenging to achieve because of the characteristics of the API or compounded formulations such as low permeability or low solubility."[178] Examples of drug products for which consistent bioavailability is difficult to achieve include Biopharmaceutics Classification System (BCS) Class II drugs and Class IV drugs.[179] Because semaglutide is a large peptide, ensuring absorption is difficult in any form, and

[172] *See* Appendix: S-24050 (Table 13.1).

[173] *See* Appendix: S-24042 (Table 14.1); Appendix: S-24043 (Table 15.1); Appendix: S-24049 (Table 16.1).

[174] Appendix: S-24045 (Table 17.1).

[175] *See Dunklau Pharmacy Holdings LLC*, Complaint ¶ 24.

[176] *Supra* note 16.

[177] *Supra* note 6 at 19,780–81.

[178] *Id.*

[179] *Id.*

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its oral bioavailability is low.[180] In fact, based on the low solubility and low bioavailability, the semaglutide drug substance in RYBELSUS® was classified as a BCS Class IV compound.[181] Thus, it is difficult to achieve bioavailability in all compounded semaglutide products, and particularly challenging in oral semaglutide products.

1. The Complexities with Achieving and Assessing Bioavailability of Injectable Semaglutide Products

Improper compounding and dosing of injectable semaglutide products may limit the bioavailability of semaglutide. According to the FDA-approved labeling of OZEMPIC® and WEGOVY®, the absolute bioavailability of semaglutide following subcutaneous administration is 89%.[182] Subsequent studies have suggested that subcutaneous administration of a semaglutide product in the abdomen, thigh, or upper arm can achieve 94% bioavailability when administered in accordance with approved labeling.[183] It is imperative that the correct dose of the semaglutide formulation be administered to patients, especially because exposure to semaglutide increases proportionately as patients titrate up the formulation. Semaglutide exposure increases in a dose-dependent manner for once-weekly doses of 0.5 mg and 1 mg, and steady-state exposure is achieved following 4–5 weeks of once-weekly administration.[184] Furthermore, it is extremely important to tightly control oligomers in order to prevent any negative impacts to semaglutide's bioavailability.[185]

Compounded semaglutide products for injection have a different formulation, delivery mechanism, and labeling than the FDA-approved injectable semaglutide medicines; are not evaluated by pharmacokinetics or pharmacodynamic studies; and may not be appropriately dosed pursuant to the titration schedule in the FDA-approved labeling. As a result, there is no guarantee that administration of compounded semaglutide for injection will achieve the absolute bioavailability of 89% for semaglutide following subcutaneous administration or the 94% bioavailability that is achieved by the injectable FDA-approved semaglutide medicines.

2. The Complexities with Achieving and Assessing Bioavailability of Oral, Sublingual, or Transmucosal Semaglutide Products

Oral, sublingual, or transmucosal semaglutide formulations present particular complexities with bioavailability that make them difficult to compound. The low rate of oral

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[180] *See* Rune V. Overgaard et al., *Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials*, 60 CLINICAL PHARMACOKINETICS 1335, 1343 (2021).

[181] *See* FDA, *Product Quality Reviews (Application Number: 21305Orig1s000)*, (Feb. 19, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213051Orig1s000ChemR.pdf.

[182] *See supra* note 19; *supra* note 22.

[183] *Supra* note 13 at 7376.

[184] *Supra* note 16.

[185] *See supra* Factor 1, Part 2.

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bioavailability for peptide molecules generally stems from the limited membrane permeability in the gastrointestinal tract, as well as the chemical- and enzyme-mediated degradation in the low pH environment of the stomach.[186] Microorganisms that colonize the intestine can further degrade orally administered, therapeutic peptides.[187] Oral semaglutide absorption can also be impaired by the presence of food and large amounts of water in the stomach.[188] Due to these challenges, most therapeutic peptides, including semaglutide products, are formulated as injectable products, rather than oral-dosage medications.[189] Approved semaglutide products undergo testing to ensure consistent bioavailability, while compounders and suppliers of bulk drug substances used in compounding do not measure the bioavailability of their products, increasing the likelihood that the products distributed to patients have reduced bioavailability or none at all.

The bioavailability of semaglutide following oral dosing is approximately 0.8%.[190] Progress toward improving the bioavailability of semaglutide following oral administration led to the first FDA-approved, oral-semaglutide formulation, RYBELSUS®.[191] To overcome the barriers in the gastrointestinal environment, RYBELSUS® requires co-formulation with SNAC and a proper pharmacokinetic profile to help ensure the efficacy of the product. Compounders using bulk synthetic semaglutide are not compounding oral semaglutide products that contain SNAC or other ingredients that are indispensable to ensuring semaglutide's bioavailability.

Compounders also market sublingual and transmucosal semaglutide products. Researchers continue the search for breakthrough technologies toward the development of these alternative routes for semaglutide delivery.[192] Despite modest progress in recent years, there is still no approved form of sublingual or transmucosal semaglutide, and the bioavailability, safety, and efficacy of these delivery routes has not been established. That has not, however, prevented compounders from marketing semaglutide products with sublingual and transmucosal routes of administration and claiming the superiority of these products over RYBELSUS®. In fact, one

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[186] *See* Yajie Zhang et al., *Just How Prevalent Are Peptide Therapeutic Products? A Critical Review*, 587 INT'L J. PHARM. 119491 (2020).

[187] *See* Christina Lamers, *Overcoming the Shortcomings of Peptide-Based Therapeutics*, 4 FUTURE DRUG DISCOVERY 4–5 (2022).

[188] *See id*.

[189] *See supra* note 186 at 119491.

[190] *Supra* note 180 at 1343.

[191] *See supra* note 16.

[192] *See, e.g.*, 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 Art. 2265 (2023); U.S. Patent Appl. 20190388513, Oil Based Formulations for Sublingual and Buccal Delivery; Anne-Lise Paris et al., *Sublingual Protein Delivery by a Mucoadhesive Patch Made of Natural Polymers*, 128 ACTA BIOMATERIALIA 222 (2021).

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compounding pharmacy that made such claims was purporting to sell a sublingual form of semaglutide that included no semaglutide at all.[193]

One significant risk to patients taking a compounded semaglutide product with low bioavailability is that they will experience a lack of efficacy, which can be dangerous for patients. Left untreated or undertreated, long-term incidence rates of obesity-related complications, like congestive heart failure, heart attack, stroke, and osteoarthritis, might double over time.[194] Untreated diabetes can lead to heart disease, stroke, blindness and other eye problems, kidney disease, nerve damage, amputations, and other serious medical conductions.[195] And failing to address the risk of major adverse cardiovascular events in patients with established cardiovascular disease and obesity can result in cardiovascular death, non-fatal myocardial infarction, and non-fatal strokes. These potential adverse events make it imperative that semaglutide drug products are formulated correctly to achieve bioavailability. Ensuring consistent *bioavailability* is too complex for compounded semaglutide.

E. Factor 5 — The Complexity of Semaglutide Products' Compounding Process

A complex compounding process includes multiple, complicated, or interrelated steps and/or specialized facilities or equipment to compound the appropriate drug product.[196] Compounders attempting to make products containing semaglutide should use a complex process to ensure that the final drug product is unlikely to lead to adverse safety and efficacy effects.

Compounders often receive bulk synthetic semaglutide as a lyophilized powder that requires resuspension in a solution. FDA has previously concluded that "there is a complex technology associated with the manufacture and control of a lyophilized pharmaceutical dosage form… [including] the formulation of solutions; filling of vials and validation of the filling operation; sterilization and engineering aspects of the lyophilizer; and testing of the end product."[197] For example, a major concern when filling a vial is the assurance of fill volume. Unlike with a powder or liquid fill, a lower than specified fill may not be readily apparent after lyophilization but could lead to a sub-potent product.[198] Another complexity is ensuring that the solution used for reconstitution is appropriate for reconstituting the lyophilized powder. For example, some compounding kits instruct patients to use bacteriostatic water for injection for

[193] *See Dunklau Pharmacy Holdings LLC*, Complaint ¶ 24.

[194] *See* Novo Nordisk, *Module 1: Recognize the Impact – Why obesity and weight management matter to your organization*, https://www.novonordiskworks.com/content/dam/nnw/resource-library/pdf/TWF_Module_1_Recognize_the_Impact.pdf.pdf.

[195] *See* CDC, *Put the Brakes on Diabetes Complications* (last reviewed May 15, 2024), https://www.cdc.gov/diabetes/prevention-type-2/stop-diabetes-complications.html.

[196] *Supra* note 6 at 19,781.

[197] FDA, *Lyophilization of Parenterals* (Apr. 18, 1986), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/lyophilization-parenterals.

[198] *See id.*

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reconstitution. However, FDA recommends that sterile water for injection is used instead to reduce potential toxicities associated with bacteriostatic water.[199] Besides determining whether the reconstituting agent will inherently bring potential toxicities, compounders must also understand whether the reconstituting agent will impact the safety and efficacy of the semaglutide peptide, which is already a temperature and pH sensitive molecule. Ensuring that the compounding process is sensitive to semaglutide's particular issues is especially difficult when compounders do not run the battery of tests listed in Factor 6 to confirm that the compounding process is working as intended.

Compounders must also ensure that their compounding process does not cause the contamination of the drug products. Improperly cleaned equipment could lead to the contamination of the compounded drug with other active or inactive ingredients compounded in the same location. Testing of a sample from a foreign compounding pharmacy importing products to U.S. patients showed that the sample contained undisclosed tirzepatide in the solution.[200] Because the label did not disclose that the product would include tirzepatide mixed with semaglutide, and the pharmacy advertises compounded tirzepatide, it is likely that pharmacy cross-contaminated its equipment with the other peptide. Furthermore, the labels for RYBELSUS®, OZEMPIC®, and WEGOVY® all warn that coadministration of this product with any other GLP-1 receptor agonist is not recommended.[201]

Compounders must also have adequate procedures to assure the sterility of any sterile compounded drugs. In March 2022, FDA inspected a compounding pharmacy and discovered several concerning sterility issues. For example, the Agency noted that pharmacy had five sterility failures on its sterile injectable drug products within the past year and the pharmacy routinely released sterile injectable drug products prior to obtaining sterility results.[202] Following the inspection, the compounding pharmacy voluntarily recalled over 15,000 injectable semaglutide products due to a lack of assurance of sterility.[203] In August 2023, the same compounding pharmacy had to voluntarily recall more compounded semaglutide products for lack of assurance of sterility.[204]

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[199] *See id.*

[200] *See* Appendix: S-23166 (Figures 7.2-7.3, Table 7.1).

[201] *Supra* note 15.

[202] *Supra* note 84.

[203] *See* Notice to California Board of Pharmacy on Tailor Made Compounding LLC Recall (Apr. 6, 2022), https://www.pharmacy.ca.gov/about/recall_alerts/040622_taylor.pdf; *See* FDA, *Enforcement Report – Week of August 30, 2023*, *See* FDA, *Enforcement Report – Week of July 20, 2022*, https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=194736 (5,842 vials of compounded semaglutide recalled); https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=194737 (9,993 vials of compounded semaglutide recalled).

[204] *See* FDA, *Enforcement Report – Week of August 30, 2023*, https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=202834.

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Sterility issues are not limited to traditional compounding pharmacies. In August 2024, FDA inspected an outsourcing facility and discovered several sterility issues with its semaglutide products compounded between March and June 2024.[205] Shortly after the inspection, the outsourcing facility voluntarily recalled around 13,000 vials of compounded semaglutide products due to a lack of assurance of sterility.[206] Most concerningly, this facility had not even reported to FDA that they had manufactured any compounded semaglutide products between January and June 2024.[207] Injectable drug products where sterility cannot be assured can pose serious health risks, such as the introduction of infectious diseases to patients using the product.

The purification and processing steps in compounding semaglutide may also introduce impurities that impact semaglutide's efficacy. In addition to the impurities impacting physical and chemical stability described in relation to Factor 1, such as formaldehyde adducts, semaglutide-related impurities with acetaldehyde adducts and butyraldehyde adducts were detected in bulk drug samples used for compounding and compounded semaglutide samples;[208] these impurities may impact immunogenicity via the generation of high molecular weight protein of semaglutide. Furthermore, compounded and bulk synthetic semaglutide samples also included acrylonitril additions, which may have unknown impacts on the efficacy and safety of the peptide.[209] These impurities likely stem from additional agents used to purify and process the semaglutide drug substance and are not being adequately controlled through the drug substance manufacturing process or the compounding process.

It is also imperative that compounders establish appropriate procedures for production and process controls to assure that its compounded drug products have the identity, strength, purity, and quality that they are purported or represented to possess. For example, in May 2024, FDA inspected an outsourcing facility and discovered that a vial of compounded semaglutide was visually inspected by the facility, rather than measuring the volume with a calibrated instrument.[210] FDA concluded the compounded semaglutide had fill weight discrepancies. If a compounded drug product does not have the proper fill weight, it may not accurately represent the labeled strength on the vial.

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[205] *See* FDA, Registered Outsourcing Facilities, https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities; FDA, *Enforcement Report – Week of September 11, 2024*, https://www.pharmacompass.com/pdf/news/enforcement-report-week-of-september-11-2024-67667.pdf.

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

[207] *See* FDA, *Outsourcing Facility Product Reports (2024-1)*, https://dps.fda.gov/outsourcingfacility/searchresult?year=2024-1&type=active_ingredients&name=semaglutide.

[208] *See* Appendix: S-23007 (Figure 11.2, Table 11.1); S-23036 (Figure 9.1; Table 9.1).

[209] *See* Appendix: S-23032 (Figure 8.1; Table 8.1).

[210] *See* FDA, *Form FDA-483 for Olympia Compounding Pharmacy* (May 29, 2024), https://www.fda.gov/media/180579/download.

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Moreover, compounders must ensure that the compounding process maintains the proper storage conditions for the semaglutide peptide. Semaglutide is temperature sensitive. If the temperature at which semaglutide is formulated rises above 86°F, it can potentially affect the chemical and physical stability of the semaglutide product. Once the semaglutide peptide is in a solution, the solution must be stored in the refrigerator between 36°F and 46°F.[211] Unless the solution is stored safely in the pen,[212] the solution's stability can be compromised after about 20-30 hours at room temperature.[213] The semaglutide solution should also be discarded if it has been frozen or exposed to temperatures above 86°F.[214] Novo Nordisk has encountered several compounded drug products purporting to contain semaglutide that do not follow these guidelines. For example, the labeling for a compounded sublingual oral solution instructed patients to keep the solution at room temperature.[215] Testing ultimately showed that this solution contained no semaglutide at all.[216] Other pharmacies instructed patients to freeze their compounded drug products instead, despite the recommendations against freezing in OZEMPIC® and WEGOVY®'s label.[217] One pharmacy instructed patients to freeze their vial of reconstituted semaglutide solution and then defrost it at room temperature before each weekly dose.[218] Exposing the semaglutide peptide to alternating freezing temperatures then room temperature environments will likely impact the stability of the peptide and risk the drug's efficacy and safety.

Another complexity with the compounding process is ensuring that each sample has an appropriate BUD. Because compounded drugs should be intended for administration immediately or following short term storage, their BUDs should be assigned conservatively and with the help of drug-specific and general stability documentation and literature.[219] For sterile products with the highest microbial risk, only terminally sterilized, sterility tested compounded sterile preparations (CSP) that have passed all applicable tests for Category 3 CSPs can have a *maximum* BUD date of 120 days for a sample that requires refrigeration.[220] Longer BUDs can increase the likelihood that the compounded semaglutide degrades and aggregates in the formulation. Novo Nordisk has identified several compounded products sold to patients with

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[211] *Supra* note 22.

[212] *See id.*

[213] *See* FDA, *Clinical Pharmacology and Biopharmaceutics Reviews (Application Number 209637Orig1s000)*, at 102 (Dec. 3, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209637Orig1s000ClinPharmR.pdf.

[214] *See id.*

[215] *See Dunklau Pharmacy Holdings LLC*, Complaint ¶ 24.

[216] *See id.*

[217] *See* Appendix: S-23071 (Figures 24.1-24.2); S-22001 (Figures 25.1-25.2); S-23014 (Figure 26.1).

[218] *See* Appendix: S-23071 (Figure 24.2).

[219] U.S. Pharmacopoeia, Chapter 795, Pharmaceutical Compounding – Nonsterile Preparations, at 358 (2013).

[220] U.S. Pharmacopoeia, Chapter 797, Pharmaceutical Compounding – Sterile Preparations (2023).

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long BUDs. For example, many compounding pharmacies have selected BUDs that far surpass the 180-day maximum[221] established by USP for *frozen* CSPs.[222] In fact, one pharmacy routinely assigns its semaglutide products a BUD that extends for nearly 365 days after the date of compounding.[223]

Finally, compounders must ensure that the container they use to store the semaglutide and the location where the finished product is stored are suitable. Novo Nordisk's FDA-approved semaglutide injections are enclosed in a complex container closure system. The semaglutide solution comes in a prefilled cartridge, so that the drug is never in contact with the injecting device. Each pen injector is manufactured for use with NovoFine® Plus or NovoFine® disposable needles up to 8 mm in length and delivers precise doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg, which ensure proper titration of the drug according to the prescribing information. Furthermore, Novo Nordisk ensures that the semaglutide solution is adequately protected from light, exposure to air, and leachables from the manufacturing process.

These storage conditions are not used for the injectable compounded products currently on the market. Compounded semaglutide drugs are frequently stored in clear or light-colored glass vials or prefilled syringes that do not protect the product from light, air, or moisture, which can degrade the peptide. In particular, the accidental exposure to air is clearly evident from the many oxidation and di-oxidation peptide-related impurities present in several samples, especially those that utilize multi-dose vials.[224] Aside from exposing the semaglutide solution to potentially extreme environmental conditions, the container itself may impact the peptide's stability. Many of the samples come in containers made of polystyrene, industrial polypropylene, polycarbonate, or glass with polystyrene or cellulose acetate beads, which can cause spontaneous emulsification and further destabilizes the semaglutide solution.[225] Finally, testing of a different compounded semaglutide drug showed the presence of silicone oil, which is likely attributable to leaching from the container closure system used.[226] All of these factors negatively impact semaglutide's chemical and physical stability, which can lead to serious adverse effects on a patient's safety and product efficacy.

Compounded semaglutide oral tablets may arrive in standard pharmacy bottles, which may expose the tablets to air, light and moisture; this is unlike RYBELSUS®, which contains a special blue cap that is equipped with a drying agent to protect the tablets from moisture and

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[221] *See, e.g.,* Appendix: S-23008 (Figure 27.1) (364-day expiration); Appendix: S-23166 (Figure 7.1) (183-day expiration).

[222] *Supra* note 220.

[223] Appendix: S-23008 (Figure 27.1); S-23153 (Figure 28.1); S-24012 (Figure 29.1).

[224] Appendix: S-23009 (Figure 5.2, Table 5.1); S-23014 (Figure 26.2, Table 26.1).

[225] Qi Li et al., *Surface-mediated spontaneous emulsification of the acylated peptide, semaglutide,* 121 PROC. NAT'L ACAD. SCI. USA (Jan. 30, 2024), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10835113/.

[226] Appendix: S-23007 (Figure 11.3).

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preserve the tablets.[227] The packaging for compounded sublingual and transmucosal semaglutide drugs all vary. The sublingual liquid comes in a bottle with a separate, oral dispenser, while the films are stored in a clear, peelable container.[228] There are no FDA-approved storage conditions for dosage forms with these routes of administration.

Therefore, the *compounding process* for semaglutide products presents significant difficulties that increase the likelihood of adverse effects on safety and effectiveness.

F. Factor 6 — Compounding Semaglutide Requires Complex Physicochemical or Analytical Testing

Any drug product containing semaglutide requires a complex array of physicochemical and analytical testing to ensure the integrity of the semaglutide molecule, thereby ensuring the proper safety and efficacy of the product. Physiochemical and analytical testing complexity refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics.[229] Drug products may demonstrate testing complexity when specialized analytical instruments or special training is necessary to show that the drug product will perform as expected, such as cell-based assays, nuclear magnetic resonance, or mass spectrometry.[230] Complex testing involves testing for batch-to-batch uniformity, potency, purity, and quality presents challenges. Even minimally adequate batch testing requires specialized analytical instruments and/or special training. FDA-approved semaglutide products undergo a variety of tests by specially trained personnel to ensure that the drug product has the appropriate uniformity, potency, purity, and quality. Compounders are not taking such extensive precautions when testing their compounded semaglutide products. To ensure the safety and efficacy of its FDA-approved semaglutide products, Novo Nordisk performs the following tests (among others) as part of its research and development or release criteria:

- Glu-C peptide mapping and proton NMR to confirm the identity of the semaglutide primary sequence;
- Evaluation of microbial contamination and plasmid rearrangement at the start of the yeast-fermentation process;
- Chemical stability assays using Reversed-Phase, High-Performance Liquid Chromatography (RP-HPLC);
- Physical stability assay using Thioflavin T assays;
- Immunogenicity testing using a semaglutide antibody assay;

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[227] Novo Nordisk, *Important instructions about RYBELSUS® (semaglutide) to share with patients* (last reviewed Oct. 17, 2024), https://www.novomedlink.com/diabetes/products/treatments/rybelsus/dosing-administration/storage-and-administration.html#storing.

[228] *See*, *e.g.*, Appendix: S-24050 (Figure 13.1); S-24024 (Figure 13.1); S-24043 (Figure 15.1); S-24049 (Figure 16.1); S-24045 (Figure 17.1).

[229] *Supra* note 6 at 19,781.

[230] *See id.*

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- Evaluation of hydrophilic and hydrophobic impurities, as well as the total sum of impurities using RP-HPLC with UV detection;
- Characterization of HMWP formation;
- Product-bioavailability assessment;
- Testing for loss on drying;
- Evaluation of the semaglutide's primary structure and molecular mass using mass spectrometry;
- Testing for batch homogeneity using RP-HPLC;
- pH measurements at several stages of the manufacturing and compounding processes; and
- Testing for the presence of trace metals using Inductively coupled plasma mass spectrometry (ICP-MS) and Inductively coupled plasma - optical emission spectrometry (ICP-OES).

The above complex *physicochemical and analytical tests* are crucial for establishing the quality, efficacy, safety, and identity of FDA-approved semaglutide products. Compounders are not specially trained to, and do not routinely, perform such tests. Accordingly, compounders cannot ensure that the compounded products they market possess the proper physical and chemical characteristics and do not pose significant safety and effectiveness risks.

III. BENEFIT/RISK ANALYSIS

The risks with compounding semaglutide products are numerous and outweigh any actual or potential benefit of compounded semaglutide products. For one, there are a number of serious immunogenicity risks created by compounders' use of bulk drug substance, regardless of whether the drug is compounded by a traditional pharmacy or an outsourcing facility. The bulk drug substance accessed by compounders contains peptide-related impurities, such as amino acid additions and deletions, which have the potential to stimulate an immune reaction against semaglutide itself with repeated injections.[231] The immunogenicity risk is exacerbated by the different manufacturing processes used to make the bulk drug substance. For example, testing results showed that bulk synthetic semaglutide contained elevated levels of trace metals, which can lead to the formation of HMWPs.[232] These HMWPs are aggregates that are known to trigger immune responses.[233]

Furthering the concern about these peptide-related impurities and elevated levels of trace metals, compounded semaglutide products may lead to significant hypersensitivity reactions, including type I immediate hypersensitivity responses like anaphylaxis and potentially type III hypersensitivity reactions, characterized by fever, rash, arthralgia, myalgia, hematuria,

[231] Staby, *supra* note 11.

[232] *See* Appendix: S-23032 (Figures 8.2-8.3), S-23036 (Figures 9.2-9.3), S-23033 (Figures 10.2-10.3).

[233] *See, e.g.*, Staby, *supra* note 11; Amy S. Rosenberg, *Effects of protein aggregates: An immunologic perspective*, 8 THE AAPS J. (2006), https://pmc.ncbi.nlm.nih.gov/articles/PMC2761057/.

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proteinuria, serositis, central nervous system complications, and hemolytic anemia.[234] Notably, therapeutic proteins or peptides causing severe hypersensitivity reactions have resulted in sponsors terminating the development of otherwise efficacious protein or peptide products due to the immunogenicity risk.[235] This underscores how essential premarket research on the immunogenicity risks in peptides is to ensure the peptide product manufactured will not harm patients. For example, during its phase 3 trials, Novo Nordisk regularly assessed anti-semaglutide antibody formation throughout the trial period and MedDRA searches were performed on all the AEs reported in the trials to capture and summarize all events *potentially* related to antibodies, including allergic reaction events, immune complex diseases, and injection site reaction events.[236] Only after this thorough review did the Agency conclude that Novo Nordisk's semaglutide posed a low immunogenicity risk.[237] The safety information obtained from these clinical trials cannot simply be assumed to apply to compounded semaglutide.

Even more, the use of peptide synthesis, rather than recombinant DNA technology, to create the semaglutide drug substance used by compounders may lead to a higher immunogenicity risk for compounded semaglutide. While there are no Phase 3 clinical trials for a synthetic semaglutide product available, the clinical trials for taspoglutide may be instructive on the immunogenicity risk presented by synthetic semaglutide. Taspoglutide was produced synthetically and is a GLP-1 receptor agonist with 93% sequence homology to GLP-1.[238] While taspoglutide was able to significantly reduce hemoglobin A1C compared with a competitor, adverse events were reported among 92-94% of patients treated with taspoglutide.[239] Among the taspoglutide patients experiencing severe adverse events, 6% were caused by injection site reactions and 4% were hypersensitivity reactions.[240] Immune system disorders (including hypersensitivity, anaphylactoid, or anaphylactic reactions) and injection-site adverse events were also reasons for withdrawal more often in the taspoglutide groups compared to its comparator.[241] It is possible these events are related to the anti-drug antibodies that developed in 39% of patients. Ultimately, the sponsor decided to discontinue the development of the product after the Phase 3 trials due to the hypersensitivity reactions and high discontinuation rate.[242] Therefore,

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[234] *Supra* note 107.

[235] *Id.* at 2.

[236] FDA, *Clinical Review(s) Application Number: 209637Orig1s000* 397-408 (Nov. 22, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209637Orig1s000MedR.pdf.

[237] *See id.*

[238] *See* Julio Rosenstock et. al., *The Fate of Taspoglutide, a Weekly GLP-1 Receptor Agonist, Versus Twice-Daily Exenatide for Type 2 Diabetes*, 36 DIABETES CARE 498, 498 (Feb. 2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579343/.

[239] *See id.* at 500.

[240] *See id.*

[241] *See id.*

[242] *See id.* at 503.

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given the possible immunogenicity risks associated with a synthetic GLP-1 receptor agonist with high sequence homology to GLP-1, it is imperative that any synthetic semaglutide in a drug product be rigorously tested to determine its impact on patients' immune systems. Compounders cannot and do not ensure that the drug they compound using synthetic semaglutide has been subjected to this necessary testing.

Using synthetic semaglutide that has not undergone FDA review also may lead to the formation of semaglutide anti-drug antibodies (ADAs) that bind to semaglutide and neutralize its activity and bind to native GLP-1 and neutralize the activity of endogenous GLP-1. As part of its premarket drug development, Novo Nordisk has demonstrated that patients receiving its semaglutide products have a low incidence of developing anti-semaglutide antibodies.[243] However, because of the impurity profile associated with synthetic semaglutide, other differences between synthetic and recombinantly produced semaglutide, and the chemical alterations that might occur from the presence of co-actives (e.g., aggregations, oxidations, or deamidation), there is a risk that patients using compounded semaglutide products could develop ADAs. Neutralization induced by the use of compounded "semaglutide" drugs may also render FDA-approved semaglutide medicines less effective in the future among these patients. Semaglutide neutralization may lead to significant safety and effectiveness concerns, especially for patients who need these medications to treat chronic conditions, like type 2 diabetes or obesity, or reduce the risk of major adverse cardiovascular events. These antibodies might also cross-reactively bind to native GLP-1 and neutralize the activity of the endogenous GLP-1 incretin.[244] Because GLP-1, which binds only to the GLP-1 receptor, plays such an important role in the body with respect to fasting glucose, glucose-dependent insulin secretion, ß cell signal transduction, islet size and ß cell neuronal apoptosis,[245] the neutralization of native GLP-1 could have severe and long-term consequences on patient health. Of further concern is the potential difficulty in initially detecting the neutralization of native GLP-1 among those patients taking compounded semaglutide drugs: patients taking semaglutide medicines typically titrate up until they reach the maintenance dose, often without realizing the impacts of the neutralization of either the therapeutic or endogenous GLP-1.

More broadly and as detailed in other sections of this nomination, the potential quality, effectiveness, and safety concerns caused by the differences between the injectable FDA-approved drugs and the compounded drugs with respect to the strength, formulation, delivery mechanism, and dosage form are all more appropriately evaluated in a premarket approval process. Compounding pharmacies dispense compounded semaglutide drugs that do not resemble the FDA-approved medicines and are likely to lead to patient harm. Compounders use co-actives in a fixed-dose combination with semaglutide that have not been tested or approved

[243] *See supra* note 19; *supra* note 22.

[244] *Supra* note 107 at 5.

[245] *See* Tanya Hansotia & Daniel J. Drucker, *GIP, and GLP-1 as Incretin Hormones: Lessons From Single and Double Incretin Receptor Knockout Mice*, 128 REGUL. PEPTIDES 125 (June 2005), https://www.glucagon.com/pdfs/Hansotia2005RegPeptides.pdf.

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by FDA in any drug, including BPC-157 and NAD+, and, in some cases, these fixed dose combinations have led to serious degradations of the semaglutide, which may increase its aggregation in the products. Because fixed-dose combination products are more complicated than individually formulated drugs, extensive testing, which compounders do not conduct, is essential to ensure that all ingredients in the drug product work together to provide the expected safety and efficacy profile.

These quality, effectiveness, and safety concerns exist for compounded oral, sublingual, or transmucosal semaglutide formulations as well. Because many of these compounded formulations lack SNAC or an equivalent absorption enhancer, it is unlikely that any of these oral compounded formulations will be bioavailable or appropriately deliver the semaglutide active ingredient as intended to a patient. Choosing an alternative absorption enhancer or developing a formulation without one where the drug is still bioavailable requires significant research and drug development that compounders do not perform. Furthermore, for the compounders using liposome drug products as a mechanism to deliver semaglutide, FDA has already indicated that liposome drug products are too complex for any compounder to make due, in part, to the risks that the improper selection of inactive ingredients and improper mixing of liposomes with the active ingredient could cause the drug product to be potentially ineffective or hazardous.[246]

With regard to benefit, we have not identified any actual or potential benefit that would outweigh the risks presented by compounded semaglutide products. Exacerbating this concern, pharmacies and outsourcing facilities widely claim that their compounded drugs can be used as substitutes for injectable FDA-approved semaglutide drugs because the compounded drugs allegedly contain the same active pharmaceutical ingredient as Novo Nordisk's therapies approved by FDA. We are not aware of any evidence to suggest that compounded drugs purporting to contain semaglutide have the safety, effectiveness, or quality of RYBELSUS®, OZEMPIC®, and WEGOVY®. Instead, as our testing results have shown, the active ingredient used in compounding is not the same as the semaglutide in the FDA-approved medicines, and there are substantial complexities in the formulation, drug delivery mechanism, dosage form, bioavailability, compounding process, and testing that make it unlikely the product will be as safe and efficacious as advertised.

Compounders also attempt to justify their compounding of semaglutide products based on supposed clinical needs of patients. However, no clinical need, as argued by the compounders, supports the serious risks associated with allowing semaglutide to be compounded. As described in detail in the Citizen Petition submitted by Novo Nordisk on October 21, 2024 in opposition to semaglutide's nomination to the list of bulk drug substances that may be used by outsourcing facilities in compounding, there is no legitimate clinical need to compound using semaglutide.[247] The FDA-approved semaglutide medicines come in a variety of strengths and dosage forms to meet the needs of many patients. For example, in an effort to

[246] *Supra* note 6 at 19,784.

[247] *See* Comment from Novo Nordisk Inc., Docket No. FDA-2015-N-3469 (Oct. 21, 2024).

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assert there is a clinical need to compound using semaglutide, some compounding pharmacies offer prescribers options like the ability to "add Vitamin B6 or Vitamin B12 to semaglutide to prevent nausea or . . . request a formulation of the drug that is delivered under the tongue,. . . which is different from the injectables marketed by [Novo Nordisk] . . . ." [248] However, in those cases where a prescriber determines that a patient needs another drug to complement their therapy, such as vitamin B-6 or B-12, the patient could easily be separately prescribed that vitamin B-6 or B-12 medication alongside an FDA-approved semaglutide medicine, rather than be prescribed an unapproved compounded semaglutide product in which the semaglutide is mixed with vitamin B-12. There is no clinical evidence that using these products in a fixed-dose combination will improve patient outcomes; to the contrary, there are significant unknown risks to patient safety from patients taking such unapproved compounded fixed-dose combination products. Similarly, patients who need a non-injectable formulation of semaglutide can be prescribed RYBELSUS®. It is unknown what group of patients would ever need a compounded sublingual liquid or transmucosal film of semaglutide particularly given the various safety and efficacy risks posed by such products. There also is no reliable evidence or data suggesting that RYBELSUS® or other FDA-approved medications or treatments for type 2 diabetes, chronic weight management, or major adverse cardiovascular events would truly be medically unsuitable for patients taking such compounded drugs.

Finally, if FDA were to place semaglutide drug products on the DDC Lists, it would not be alone in determining that the risks of using compounded semaglutide products outweigh the benefits. The Australian government through its Therapeutic Goods Administration (TGA) recently took action to protect patients from potentially unsafe and dangerous compounded drugs purporting to contain semaglutide. On May 22, 2024, the Australian government announced that new regulations would be issued to remove GLP-1 receptor agonists from the pharmacy-compounding exemption to "protect Australians from the clear risk to human health posed by the large-scale manufacture of compounded injections."[249] Despite noting the valid place for compounding in certain circumstances, and the ongoing shortage of OZEMPIC® and WEGOVY® in Australia,[250] the Minister of Health and Aged Care noted that the "risk of not acting is far greater [than the consequences of banning GLP-1 receptor agonists from compounding]," and cited "the recent reports of individual[s] impacted by large scale compounding" to underscore the dangers posed by semaglutide compounders.[251] The

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[248] David Wainer, *The War Over Cheaper Ozempic Won't End Well for Some Investors*, WALL ST. J. (June 26, 2024).

[249] Honorable Mark Butler MP, *Protecting Australians from unsafe compounding of replica weight loss products*, Ministers: Department of Health and Aged Care (May 22, 2024), https://www.health.gov.au/ministers/the-hon-mark-butler-mp/media/protecting-australians-from-unsafe-compounding-of-replica-weight-loss-products?language=en.

[250] *See* Therapeutic Goods Administration, *About the Ozempic (semaglutide) shortage 2022 and 2024* (last updated Aug. 29, 2024), https://www.tga.gov.au/safety/shortages/information-about-major-medicine-shortages/about-ozempic-semaglutide-shortage-2022-and-2024.

[251] *Supra* note 249.

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government highlighted the dangers of "commercial-like scale and quality standards of compounded weight loss drugs," and increasing reports of adverse events related to GLP-1 receptor agonists, including "the hospitalization of a patient in Australia due to a serious adverse event."[252] The Pharmacy Board of Australia finalized these revisions to the compounding provisions of the *Therapeutic Goods Act 1990*, effective October 1, 2024.[253] Under a similar set of circumstances to ours, the Australian government was able to determine that the risks with compounding purporting to contain semaglutide are too high to justify the benefits. Novo Nordisk urges FDA to make the same determination and act similarly to prevent a future public health crisis that its peer regulators have already identified and addressed.

On balance, the risks to patient safety presented by semaglutide products compounded under section 503A or 503B far outweigh any actual or potential benefit.

IV. CONCLUSION

The complexities associated with semaglutide's formulation, delivery mechanism, dosage, bioavailability, compounding process, and physicochemical and analytical testing raise serious concerns about the safety and efficacy of compounded semaglutide products. Therefore, we request that FDA convene and consult an advisory committee to discuss the addition of semaglutide products to the Section 503A and 503B DDC Lists. After consultation with the advisory committee, we ask that FDA promulgate regulations to add semaglutide products to the DDC Lists. To protect the public health from section 503A compounding, we respectfully request that FDA issue a direct final rule to add semaglutide products to the FDCA Section 503A DDC List. Lastly, we request joint review of this nomination by the Pharmacy Compounding Advisory Committee and Drug Safety and Risk Management Advisory Committee; the inclusion of committee members with an expertise in endocrinology, diabetes, obesity, heart disease, and immunogenicity; and participation from FDA's immunogenicity review committee.

[252] *Id.*

[253] *See* Therapeutic Goods Act 1990, https://www.legislation.gov.au/F1996B00406/latest/text (effective date Oct. 1, 2024); The Pharmacy Board of Australia, *Guidelines on compounding of medicines* (Aug. 2024), https://www.ahpra.gov.au/documents/default.aspx?record=WD24%2f33815&dbid=AP&chksum=e85eWDHxss0KwfOkm5wEGg%3d%3d.

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