TABLE 1—PROPOSED EXEMPT CLASS II DEVICES SUBJECT TO GENERAL LIMITATIONS AND PARTIAL LIMITATIONS—Continued

| 21 CFR section | Generic device type | Exempt product code | Non-exempt product codes | Current partial limitations | Proposed partial limitations |
|---|---|---|---|---|---|
| 862.3640 ..... | Morphine test system. | PVG ..... | DIQ, DJJ, DLR, DMY, DNA, DNK, DOE, DOK, DPK, NGI. | Exemption is limited to test systems intended to measure morphine and its analogs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing, and does not include devices intended for Federal drug testing programs. | Exemption is limited to test systems intended to measure morphine and its analogs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing. |
| 862.3650 ..... | Opiate test system | PVH ..... | DJF, DJG, DKT, DLT, LAH, LAI, NGL. | Exemption is limited to test systems intended to measure any of the addictive narcotic pain-relieving opiate drugs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing, and does not include devices intended for Federal drug testing programs. | Exemption is limited to test systems intended to measure any of the addictive narcotic pain-relieving opiate drugs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing. |
| 862.3700 ..... | Propoxyphene test system. | PVI ..... | DPN, JXN, LAJ, LAK, QBF. | Exemption is limited to test systems intended to measure propoxyphene for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing, and does not include devices intended for Federal drug testing programs. | Exemption is limited to test systems intended to measure propoxyphene for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing. |
| 862.3870 ..... | Cannabinoid test system. | PVJ ..... | DKE, LAT, LDJ, NFW. | Exemption is limited to test systems intended to measure any of the cannabinoids for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing, and does not include devices intended for Federal drug testing programs. | Exemption is limited to test systems intended to measure any of the cannabinoids for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing. |
| 862.3910 ..... | Tricyclic antidepressant drugs test system. | PVK ..... | LFG, LFH, LFI, MLK, QAW. | Exemption is limited to test systems intended to measure any of the tricyclic antidepressant drugs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing, and does not include devices intended for Federal drug testing programs. | Exemption is limited to test systems intended to measure any of the tricyclic antidepressant drugs for employment and insurance testing and for which the test system labeling includes a statement that the device is intended solely for employment and insurance testing. |

## V. Paperwork Reduction Act of 1995

While this notice contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The collections of information in part 807, subpart E, regarding premarket notification submissions, have been approved under OMB control number 0910–0120.

## VI. Reference

The following reference is on display at the Dockets Management Staff (see **ADDRESSES**) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at *https://www.regulations.gov.* Although FDA verified the website address in this document, please note that websites are subject to change over time.

1. FDA Guidance, ''Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff,'' February 19, 1998, available at *https://www.fda.gov/media/72685/download.*

**Grace R. Graham,**

*Deputy Commissioner for Policy, Legislation, and International Affairs.*

[FR Doc. 2026–08499 Filed 4–30–26; 8:45 am]

**BILLING CODE 4164–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2018–N–3240]**

### List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA, the Agency, or we) is evaluating substances that have been nominated for inclusion on a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need for outsourcing facilities to use in compounding (the 503B Bulks List). This notice identifies three bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List: semaglutide, tirzepatide, and liraglutide. Additional bulk drug substances nominated for inclusion on this list are under consideration and may be the subject of future notices.

**DATES:** Either electronic or written comments on the notice must be submitted by June 30, 2026.

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before June 30, 2026. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of June 30, 2026. Comments received by mail/hand delivery/courier (for written/paper submissions) will be

considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

*Electronic Submissions*

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

*Written/Paper Submissions*

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

*Instructions:* All submissions received must include the Docket No. FDA–2018–N–3240 for ''List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

**FOR FURTHER INFORMATION CONTACT:** Tracy Rupp, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 240–402–0260, *compounding@fda.hhs.gov.*

**SUPPLEMENTARY INFORMATION:**

## I. Background

Section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b) describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and section 582 of the FD&C Act (21 U.S.C. 360eee–1) (concerning drug supply chain security requirements).[1]

Compounded drug products that meet the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).[2] Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.[3] Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for ''office stock,'' to hold in their offices in advance of patient need.[4]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for the exemptions under section 503B of the FD&C Act is that the outsourcing facility does not compound a drug using a bulk drug substance unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List) or (2) the drug compounded from the bulk drug substance appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.[5]

Section 503B of the FD&C Act directs FDA to establish the 503B Bulks List by: (1) publishing a notice in the **Federal Register** proposing bulk drug substances to be included on the list, including the rationale for such proposal; (2) providing a period of not less than 60 calendar days for comment on the notice; and (3) publishing a notice in the **Federal Register** designating bulk drug substances for inclusion on the list.[6]

FDA has published a series of **Federal Register** notices addressing bulk drug substances nominated for inclusion on the 503B Bulks List.[7] This notice

[1] Section 503B(a) of the FD&C Act.

[2] Compare section 503A(a) of the FD&C Act (21 U.S.C. 353a(a)) (exempting drugs compounded in accordance with that section from CGMP requirements) with section 503B(a) of the FD&C Act (not providing an exemption from CGMP requirements).

[3] Section 503B(b)(4) and (5) of the FD&C Act.

[4] Section 503B(d)(4)(C) of the FD&C Act.

[5] Section 503B(a)(2)(A) of the FD&C Act.

[6] Section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.

[7] See **Federal Register** of August 28, 2018 (83 FR 43877), March 4, 2019 (84 FR 7383), September 3, 2019 (84 FR 46014), July 31, 2020 (85 FR 46126), March 24, 2021 (86 FR 15673), January 27, 2022 (87

identifies three bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List.

For purposes of section 503B of the FD&C Act, *bulk drug substance* means an active pharmaceutical ingredient as defined in § 207.1 (21 CFR 207.1).[8] *Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of the substance.[9] [10]

## II. Methodology for Developing the 503B Bulks List

### *A. Process for Developing the List*

In the **Federal Register** of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. FDA reopened the nomination process in the **Federal Register** of July 2, 2014 (79 FR 37747), and provided more detailed information on what FDA needs to evaluate nominations for the list. In the **Federal Register** of October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA–2015–N–3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances, renominate substances with sufficient information, or submit comments on nominated substances.

As FDA evaluates bulk drug substances, we intend to publish notices for public comment in the **Federal Register** that describe FDA's proposed position on each substance along with the rationale for that position.[11] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making our determination, and if so, we will seek PCAC input.[12] Depending on our review of the docket comments and other relevant information before the Agency, FDA may finalize the proposed determination without change, or we may finalize a modification to the proposal to reflect new evidence or analysis regarding clinical need. FDA intends to then publish in the **Federal Register** a final determination identifying the bulk drug substances for which we have determined there is a clinical need and our rationale in making that final determination. FDA also intends to publish a final determination in the **Federal Register** for those substances which we considered but found that there is no clinical need to use in compounding and our rationale in making this decision.

FDA maintains a list of all bulk drug substances we have evaluated on our website and separately identify bulk drug substances we have placed on the 503B Bulks List and those we have decided not to place on the 503B Bulks List. This list is available at *https://www.fda.gov/drugs/human-drug-compounding/503b-bulk-drug-substances-list.* FDA will only place a bulk drug substance on the 503B Bulks List when we have determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place the bulk drug substance on the 503B Bulks List.

FDA is evaluating bulk drug substances nominated for the 503B Bulks List on a rolling basis. FDA intends to evaluate and publish the proposed and final determinations in the **Federal Register** in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List.[13]

### *B. Analysis of Substances Nominated for the List*

As noted above, the 503B Bulks List includes bulk drug substances for which the Agency has determined there is a clinical need. The Agency is evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the clinical need standard provided by the statute.[14] In applying this standard to develop the proposals in this notice, FDA interprets the phrase ''bulk drug substances for which there is a clinical need'' to mean that the 503B Bulks List may include a bulk drug substance if: (1) there is a clinical need for an outsourcing facility to compound the drug product and (2) the drug product must be compounded using the bulk drug substance. FDA does not interpret supply issues, such as backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance. Section 503B of the FD&C Act separately provides for compounding from a bulk drug substance under the exemptions discussed above if the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Additionally, FDA does not consider convenience in administering a particular compounded drug product (*e.g.,* a ready-to-use form) or the cost of the compounded drug product as compared with an FDA-approved drug product when assessing ''clinical need.''

For purposes of this analysis, FDA assumes without deciding that semaglutide, tirzepatide, and liraglutide are components of FDA-approved drug

FR 4240), November 23, 2022 (87 FR 71642), April 6, 2023 (88 FR 20531), and August 21, 2023 (88 FR 56837).

[8] See section 503B(a)(2) of the FD&C Act, which defines bulk drug substances used in compounding under section 503B according to 21 CFR 207.3(a)(4) ''or any successor regulation.'' Section 207.1 is the successor regulation.

[9] Section 503B(a)(2) of the FD&C Act and § 207.1.

[10] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3) of the FD&C Act, inactive ingredients used in compounding must comply with the standards of an applicable U.S. Pharmacopeia or National Formulary monograph, if a monograph exists.

[11] This is consistent with procedure set forth in section 503B(a)(2)(A)(i) of the FD&C Act. Although the statute only directs FDA to issue a **Federal Register** notice and seek public comment when it proposes to include bulk drug substances on the 503B Bulks List, we intend to seek comment when the Agency has evaluated a nominated substance and proposes either to include or not to include the substance on the list.

[12] Section 503B of the FD&C Act does not require FDA to consult the PCAC before developing the 503B Bulks List.

[13] FDA's guidance for industry titled ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (January 2025) provides additional information regarding FDA's policies for bulk drug substances nominated for the 503B Bulks List pending FDA's evaluation under the ''clinical need'' standard. This guidance is available on the FDA guidance web page at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents.*

[14] In March 2019, FDA announced the availability of a final guidance titled ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (84 FR 7390). This guidance describes FDA policies for developing the 503B Bulks List and the Agency's interpretation of the phrase ''bulk drug substances for which there is a clinical need'' as it is used in section 503B of the FD&C Act. The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's guidance.

products.[15] We begin our evaluation of bulk drug substances which are components of an FDA-approved drug by asking one or both, as applicable, of the following questions:

1. Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that: (a) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (b) the drug product proposed to be compounded is intended to address that attribute?

2. Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

The reason for question 1 is that unless an attribute of the FDA-approved drug makes it medically unsuitable for certain patients, and a drug product to be compounded using a bulk drug substance that is a component of the FDA-approved drug is intended to address that attribute, there is no clinical need to compound a drug product using that bulk drug substance. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question 2 is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product. When it is feasible to compound a drug product by starting with an FDA-approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including that FDA-approved drugs have undergone premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection, as well as routine post-approval, risk-based inspections. In contrast, FDA does not conduct a premarket review of the quality standards, specifications, and controls for bulk drug substances used in compounding and does not conduct a premarket assessment of the manufacturer of the bulk drug substance.

If the answer to both of these questions is ''yes,'' there may be a clinical need for outsourcing facilities to compound using the bulk drug substance, and we would evaluate the substance further, applying the factors described below. Each of the following factors is considered in the context of the others, balancing them to determine whether the statutory ''clinical need'' standard has been met:

- the physical and chemical characterization of the substance;
- any safety issues raised by the use of the substance in compounding;
- the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.[16]

If the answer to either of these questions is ''no,'' we generally would not include the bulk drug substance on the 503B Bulks List, because there would not be a basis to conclude that there may be a clinical need to compound drug products using the bulk drug substance instead of administering or starting with an FDA-approved drug product.

FDA did not answer ''yes'' to both of the threshold questions for the bulk drug substances we are addressing in this notice. Accordingly, as explained below, we did not proceed further in our evaluation of these substances and are proposing not to include these bulk drug substances on the 503B Bulks List.

In this notice, FDA evaluated certain nominated bulk drug substances for potential inclusion on the 503B Bulks List either alone or in combination with other bulk drug substances. FDA does not intend to consider comments raising different bulk drug substances or combinations of bulk drug substances other than those evaluated by FDA in this notice to be within the scope of this notice. New bulk drug substance nominations may be submitted to Docket No. FDA–2015–N–3469. The docket is available on *https://www.regulations.gov.*

To assess whether there is a clinical need for outsourcing facilities to use a bulk drug substance in compounding, FDA must consider the drug products that have been proposed to be made from the nominated bulk drug substances. Therefore, FDA's evaluation of a bulk drug substance includes detailed consideration of the drug products that are proposed to be compounded, including the conditions justifying clinical need under the applicable statutory standard. Comments on FDA's preliminary evaluation of a bulk drug substance should include adequate support for the commenter's position. For example, a commenter writing to support inclusion of a nominated bulk drug substance on the 503B Bulks List should include sufficient information to permit a meaningful clinical need evaluation by FDA of the proposed product. Commenters writing in favor of or in opposition to a proposal to include or not to include an entry on the 503B Bulks List should address, for each proposed compounded drug product, the factors FDA evaluated in making our proposal.[17] After FDA publishes a **Federal Register** notice making a final determination regarding whether a bulk drug substance will be placed on the 503B Bulks List, FDA will no longer consider comments submitted to the docket regarding that bulk drug substance, but interested parties may submit a citizen petition to FDA requesting specific action or relief (see 21 CFR 10.30).

## III. Substances Evaluated and Not Proposed for Inclusion on the 503B Bulks List

This notice identifies three bulk drug substances that FDA has evaluated and is proposing not to include on the 503B Bulks List: semaglutide, tirzepatide, and

[15] The nominators take the position that the nominated semaglutide, tirzepatide, and liraglutide are the active ingredient in the approved drug products. For purposes of this analysis, FDA assumes without deciding that these substances are components of FDA-approved drug products, as proposed in the nominations. Part 1 of the clinical need analysis primarily concerns attributes of the relevant FDA-approved drugs. Specifically, under the clinical need standard, FDA considers in Part 1 of its analysis whether there is a clinical need for an outsourcing facility to compound a drug with a bulk drug substance because the FDA-approved drug is medically unsuitable. Here, irrespective of any differences in the attributes of the bulk drug substances used in the FDA-approved drug products compared to compounded drug products, FDA has not identified a basis to conclude that an attribute of the approved products makes them medically unsuitable such that a compounded drug is needed to address any such attribute. The commenters' arguments, and nominator's responses, about safety and quality concerns with the nominated bulk drug substances for use in compounding would be addressed in Part 2 of the clinical need analysis, which we do not reach here.

[16] See section 503B(a)(2)(A) of the FD&C Act and FDA's guidance titled ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act.''

[17] See also FDA's guidance for industry, ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (March 2019), and our **Federal Register** notice of October 27, 2015 (80 FR 65770).

liraglutide. The reasons for FDA's proposals are set forth below.

*A. Semaglutide*

Semaglutide has been nominated [18] for use in compounded drug products for ''Type 2 diabetes mellitus,'' as ''an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus''; [19] ''[t]o reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight''; ''to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease''; ''[t]o reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 12 years and older with obesity [and] adults with overweight in the presence of at least one weight-related comorbid condition''; ''to reduce the risk of sustained eGFR [estimated Glomerular Filtration Rate] decline, end-stage kidney disease, and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease''; and for ''related health conditions as determined appropriate by medical provider.''

Semaglutide is an active ingredient in FDA-approved drug products: 2 mg/3 mL, 4 mg/3 mL, and 8 mg/3 mL solutions for subcutaneous (SC) injection which contain propylene glycol (Ozempic, NDA 209637); 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, 2.4 mg/0.75 mL, and 7.2 mg/0.75 mL solutions for SC injection which do not contain propylene glycol (Wegovy and Wegovy HD, NDA 215256); 1.5 mg, 4 mg, 9 mg, and 25 mg oral tablets (Wegovy, NDA 218316); and 1.5 mg, 3 mg, 4 mg, 7 mg, 9 mg, and 14 mg oral tablets (Rybelsus and Ozempic, NDA 213051).[20] [21]

Semaglutide was nominated and evaluated for the SC injection, sublingual, buccal, and oral routes of administration in various strengths. The nominations provide examples of such strengths and state that different strengths may be compounded ''depending on medical provider requests.'' [22] In addition, the nominations propose to compound semaglutide as an injectable product without propylene glycol and as ''combination injectables including those doses above combined with [p]yridoxine or an antiemetic medication'' (Ref. 1).

1. Suitability of FDA-Approved Drug Product(s)

The nominations propose to compound a ''subcutaneous injection, oral sublingual, buccal, and oral tablet or capsule'' in various strengths.[23] The nominators indicate that semaglutide might also be used to compound other drug products, but the nominators do not identify those products. To assess clinical need, we consider whether the nomination identifies an attribute of the approved drug that makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation. With respect to the nominator's statement that the compounded products will be used for ''related health conditions as determined appropriate by medical provider,'' we cannot find that there is a clinical need for an outsourcing facility to compound semaglutide for unidentified health conditions.

''Oral Sublingual'' and Buccal Products

For ''oral sublingual'' products, the nominators identify concentrations of 1.5 mg/mL, 2 mg/mL, 2.5 mg/mL, and 3 mg/mL as examples; the nominators do not provide a proposed concentration for buccal administration. One nominator states that ''the challenge of swallowing this tablet . . . can be daunting and can discourage [patients] from using the tablet'' and that ''difficulty swallowing is a well-documented issue . . . with dysphagia affecting up to 33% of older adults.'' [24] The nominator further states that the injection route of administration is ''linked to patient discomfort and is subject to refrigerated storage.'' The nominator states that the buccal and sublingual routes ''are recognized as valid alternatives'' and that these routes ''in varying strengths would satisfy this clinical need.''

For the reasons below, FDA has not identified a basis to conclude that the oral and injectable routes of administration of the FDA-approved semaglutide products cause those products to be medically unsuitable for certain patients and that a compounded buccal or sublingual product would address such an attribute. While we have no reason to disagree with the proposition that difficulty swallowing is a ''well-documented issue'' and that compounded drugs can serve an important need for patients who cannot swallow tablets, the nominators refer to concerns about oral routes of administration generally; they do not identify any unsuitability with approved semaglutide products. Nor do they explain why the injectable drug products would be medically unsuitable for patients who cannot swallow a tablet.

One nominator refers to an article, Pratap-Singh et al. (2023), that the authors characterize as ''a guideline for future investigators in creating buccal or sublingual tablets for the delivery of [peptide] drugs used to treat diabetes.'' The article explains that ''clinical use [of peptides for diabetes mellitus] is limited by the challenges of subcutaneous injection,'' referencing ''patient discomfort as well as being subjected to refrigerated storage and the requirement for efficient supply chain logistics.'' The article states that ''[t]he oral route is possibly the most common and the most acceptable for patients'' but that ''oral delivery faces challenges such as low permeation, proteolysis enzymes in the upper gastrointestinal tract, low gastric pH, and bioavailability.'' The article further states that ''the gastrointestinal route is unpredictable and usually involves high losses of the delivered drug.'' The paper

[18] See Docket No. FDA–2015–N–3469, document nos. FDA–2015–N–3469–0388 and FDA–2015–N–3469–0411.

[19] One nomination proposes to compound semaglutide for ''type 2 diabetes mellitus.'' For purposes of this evaluation, we have interpreted this proposed use to be as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

[20] Ozempic is FDA-approved as a single-patient-use pen in the listed concentrations, and Wegovy and Wegovy HD are FDA-approved as a single-dose pen in the listed concentrations.

[21] According to the ''Dosage and Administration'' section of the FDA-approved labeling for NDA 213051, there are two formulations that are not substitutable on a milligram per milligram basis. Formulation R1 (Rybelsus) includes strengths 3 mg, 7 mg, and 14 mg and Formulation R2 (Rybelsus and Ozempic) includes strengths 1.5 mg, 4 mg, and 9 mg.

[22] Nominators included the following examples of strengths for injectable products: 2 mg/3 mL (0.68 mg/mL), 4 mg/3 mL (1.34 mg/mL), 8 mg/3 mL (2.68 mg/mL), 0.00067 g/1 mL, 0.00167 g/1 mL, 0.0025 g/1 mL, 5 mg/1 mL, 8 mg/2 mL, 8 mg/1 mL, and 16 mg/1 mL. For the sublingual route of administration, the nominators included the following example strengths: 1.5 mg/mL, 2 mg/mL, 2.5 mg/mL, and 3 mg/mL. For oral tablets or capsules, the nominators provided the following example strengths: 25 mg and 50 mg.

[23] Some of the proposed concentrations are the same as the FDA-approved injectable product (*i.e.,* 2 mg/3 mL (0.68 mg/mL), 4 mg/3 mL (1.34 mg/mL), 8 mg/3 mL (2.68 mg/mL)) or the FDA-approved oral tablet (*i.e.,* 25 mg)).

[24] OFA cites Shanojan Thiyagalingam et al., *Dysphagia in older adults,* 96 Mayo Clinic Proceedings 488–497 (2021); Statements of Margaret A. Hamburg, Commissioner, Food & Drug Administration. The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before The Subcommittee On Oversight And Investigations Of The Committee on Energy and Commerce House of Representatives One Hundred Twelfth Congress Second Session November 14, 2012 Serial No. 112–181.

refers to buccal or sublingual routes as ''[a] potential alternative,'' citing ''[a]ccessibility and easy administration'' as the ''main advantages connected to these types of routes.'' However, the authors also note that these routes of administration present challenges. The article ''describes the current state of the art with respect to the creation of nanoparticles containing peptides such as insulin, glucagon-like peptide 1 (GLP–1), and their agonists, and theorizes the production of mucoadhesive unidirectional release buccal tablets or films.'' The paper identifies potential ''challenges'' that could emerge with the development of new formulations of peptide drugs that could be administered via non-parenteral routes of administration for the treatment of diabetes mellitus (*e.g.,* insulin, GLP–1 receptor agonists).

The authors did not design their study to assess, and, accordingly, do not identify, any medical unsuitability of FDA-approved GLP–1 receptor agonists for treatment of diabetes mellitus. Further, the article refers only to general concerns associated with injectable routes of administration (*e.g.,* patient discomfort), which does not support the nominator's position that the FDA-approved products are medically unsuitable for patients. We also note that the paper discusses GLP–1 drugs generally, and not the approved semaglutide drug products (Ref. 2).

Injectable Products

The nominators refer to ''[r]anges depending on medical provider requests'' and list examples of such strengths. For products proposed for the SC route of administration, the nominators provide example concentrations of 0.00067 g/mL (0.67 mg/mL), 2 mg/3 mL (0.68 mg/mL), 4 mg/3 mL (1.34 mg/mL), 0.00167 g/mL (1.67 mg/mL), 0.0025 g/mL (2.5 mg/mL), 8 mg/3 mL (2.68 mg/mL), 8 mg/2 mL (4 mg/mL), 5 mg/mL, 8 mg/mL, and 16 mg/mL injections. As these are identified as examples, the nominations do not identify each of the concentrations—and therefore the drug products—proposed to be compounded for the SC route of administration.

Several of the concentrations identified differ from the approved products. At the time the nominations were submitted, the proposed concentrations of 8 mg/2 mL (4 mg/mL), 5 mg/mL, and 8 mg/mL exceeded the concentrations of the approved semaglutide products. In addition, the nominators proposed to compound a 16 mg/mL solution for SC injection. However, semaglutide is also now approved as a 7.2 mg/0.75 mL (9.6 mg/mL) solution for SC injection. Therefore, the proposed concentrations of 8 mg/2 mL (4 mg/mL), 5 mg/mL, and 8 mg/mL no longer exceed the concentrations of the approved semaglutide products. The nominations did not provide supporting data or information for the use of products with a higher concentration.[25] [26] FDA is also not aware of data or information that identifies patients for whom the concentrations of the FDA-approved SC injections are medically unsuitable.

The nominators state that some patients are ''hyper-responders'' and that they may ''need a lower dose than what is commercially available.'' One nominator states that ''[i]t has been estimated that 5–15% of the population are hyper-responders to this medication (and 15% have been estimated to be non-responders).'' The nominator provides no reference that supports its statement about what ''has been estimated.'' The nominator cites Wilding et al. (2021), which does not mention ''hyper-responders'' or the 5–15% statistic (Ref. 3). As the nominator notes, the study showed that more patients in the semaglutide group than the placebo group discontinued treatment after gastrointestinal events, and that nausea occurred ''primarily during the dose-escalation period'' (Wilding et al. 2021). However, the article also states that ''[m]ost gastrointestinal events were mild-to-moderate in severity, were transient, and resolved without permanent discontinuation of the regimen.'' One nominator states that ''[i]t is believed with alternative maintenance doses and/or a slower titration schedule, more patients will remain on the treatment and have clinically meaningful outcomes as a result.'' The nominator again provides no support for its statement that this is ''believed'' to be the case, and the results of a study describing mild-to-moderate, transient gastrointestinal events primarily during a dose escalation period do not support the proposition that there are ''hyper-responders'' for whom the strength of the approved product makes it medically unsuitable.

One nominator states that ''hyper-responders'' are those who are ''sensitive'' to the drug and thus may need either a slower titration or a lower maintenance dose, noting that only the 1.7 mg and 2.4 mg weekly doses are approved for maintenance.[27] Noting that semaglutide is only FDA-approved in single patient use pens, one of the nominators states that ''[i]t is impossible to achieve lower or higher doses with an auto-injector pen.'' However, the nominations do not explain why, if a patient requires a lower maintenance dose, one of the FDA-approved products that contain a lower concentration (*i.e.,* 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL) could not be used.[28] The nominations also do not explain why a slower titration using the FDA-approved products could not be used in patients who do not tolerate dose escalation every 4 weeks.[29]

[25] For example, one nomination states that patients may benefit from higher doses but does not identify higher doses to be delivered from the proposed compounded drug product. The nominations also do not identify patients for whom the concentrations of the FDA-approved SC injections that were approved at the time are medically unsuitable such that a higher concentration is needed. The nominations advance a general hypothesis that higher doses have a ''superior effect'' relative to approved oral products, and ''potentially'' to injectable formulations. With respect to the assertion that ''[c]ertain patients benefit from higher doses than are commercially available,'' even if accurate, any improved outcomes from the higher strength, or the fact that a higher strength is being studied, would not mean that the approved product does not achieve the intended clinical benefit or that it is otherwise medically unsuitable for patients. The nominators did not provide a basis to conclude that patients need the specific concentrations proposed. As noted, FDA has now approved a concentration that is higher than those of the products approved at the time the nominations were submitted.

[26] In addition, since submission of the nominations, the results of the study a nominator cited from clinicaltrials.gov, NCT05486065, have been published (Aroda et al. 2025). The results do not support the nominator's argument. In this phase 2 clinical trial, 8 mg and 16 mg doses of semaglutide were compared to 2 mg doses of semaglutide and placebo. The study did not demonstrate a statistically significant improvement in glycemic control (as measured by hemoglobin A1c) in subjects treated with the 8 mg or 16 mg dose compared to the 2 mg dose using the treatment policy estimand. There was a statistically significant decrease in body weight when the semaglutide 16 mg dose was compared to the 2 mg dose using the treatment policy estimand, but the study did not demonstrate a statistically significant decrease in body weight when the 8 mg dose was compared to the 2 mg dose. We note that adverse events and treatment discontinuations due to adverse events were more frequent in the 8 mg and 16 mg groups than in the 2 mg dose group.

[27] While not specified in the nomination, we assume the nominator is referencing semaglutide approved by FDA under the brand name Wegovy, NDA 215256. Additionally, we note that with the approval of Wegovy HD 7.2 mg/0.75 mL, the approved maintenance doses are now 1.7 mg, 2.4 mg, and 7.2 mg weekly.

[28] While the ''Dosage and Administration'' section of the FDA-approved labeling for NDA 215256 states that the maintenance dose is 1.7 mg, 2.4 mg, and 7.2 mg, the section also states to ''[c]onsider treatment response and tolerability when selecting the maintenance dosage.'' See *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s029lbl.pdf.* Accessed 3/31/26.

[29] According to the ''Dosage and Administration'' section of the FDA-approved labeling for NDA 215256, ''[i]f patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.'' See *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s029lbl.pdf.* Accessed 3/31/26.

In its nomination, BPI Labs, LLC refers to ''[i]njectable dosing, or microdosing,'' for use in controlling side effects. In its nomination, the Outsourcing Facilities Association (OFA) states that a different dose may be ''more suitable for their patient in order to manage side effects and increase adherence''—but does not identify alternative doses to be delivered from the proposed compounded drug product. Further, the general statement that a different dose may be ''more suitable'' does not mean that the concentration of the approved product is *not* suitable. In addition, OFA included in its comment that ''[m]icrodosing trends have been widely reported and allow patients otherwise intolerant to standard doses to continue treatment,'' citing an article published in The New York Times (Ref. 4). However, the New York Times article does not include any data or information to support the proposition that the FDA-approved product could not be used to obtain lower doses or that it is otherwise medically unsuitable. In assessing clinical need, we consider, in part, whether there is a basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable—not whether the approved product in fact meets medical needs. Nor does the clinical need analysis turn on information about general ''trends'' without identifying patients for whom the approved drug would be medically unsuitable.

Oral Products

The nominators also propose to compound semaglutide as oral tablets and capsules.[30] The nominations refer to ''[r]anges depending on medical provider requests'' and list examples of such strengths. For products proposed for the oral route of administration, the nominators provide strengths of 25 mg and 50 mg oral tablets and capsules. As these are listed as examples, the nominations do not identify each of the strengths—and therefore the drug products—proposed to be compounded for the oral route of administration. Semaglutide is FDA-approved as 1.5 mg, 3 mg, 4 mg, 7 mg, 9 mg, 14 mg, and 25 mg oral tablets; there are no FDA-approved oral capsules. The nominators do not explain why capsules would be needed.

One nominator states that the current FDA-approved oral tablets ''are inadequate to treat all cases of obesity in patients with inadequately controlled type 2 diabetes.'' The other nominator states that ''[o]ral dosages, other than commercially avaialble [*sic*] strenghts [*sic*], are required for those requiring side effect based minimum or maximum dosing regimens'' and that ''according to published data, up to 10% [of] the current population deals with Trypanophobia (fear of needles) and up to 33% in children.'' This nominator further states that ''[t]he current oral offerings of commercial Rybelsus do not fit all patient populations and often need to be individualized.'' The nominators also assert that ''[t]here is evidence that higher doses than are currently commercially available show a superior effect as compared to the commercially available doses for oral formulations.''

The nominations do not identify, and FDA is not otherwise aware of, data or information that identifies patients for whom the strengths of the FDA-approved oral tablets are medically unsuitable. In addition, semaglutide was approved as a 25 mg tablet after the nominators submitted their nomination. The nominators did not supplement their nominations after the approval to provide any data or information bearing on medical suitability. The nominators have not provided a basis to conclude that the FDA-approved 25 mg oral tablet is medically unsuitable for any patients who would need the 25 mg strength. Thus, we address here the proposal for 50 mg oral tablets.

One nominator submitted two articles, Aroda et al. (2023) and Knop et al. (2023), in which patients received oral semaglutide at doses of 25 mg and 50 mg. Aroda et al. 2023 (PIONEER PLUS) was a multi-center, randomized, double-blind, phase 3b trial that studied the use of 25 mg and 50 mg once-daily oral doses of semaglutide in adults with type 2 diabetes compared to the approved once-daily 14 mg dose. The 25 mg and 50 mg tablets ''were a new formulation developed to enhance bioavailability compared with the 14 mg dose'' (Ref. 5). Knop et al. (2023) (OASIS 1) was a randomized, double-blind, placebo-controlled, phase 3 superiority trial that studied the use of semaglutide 50 mg once daily compared to placebo in adults with overweight or obesity without type 2 diabetes (Ref. 6). The formulation used for the 25 mg and 50 mg doses was developed to enhance bioavailability. First, while Aroda et al. (2023) found that the 25 mg and 50 mg doses ''were superior to 14 mg in reducing $HbA_{1c}$ and bodyweight,'' the authors noted that ''dosing might not reflect clinical practice since participants were escalated to higher doses according to randomisation and irrespective of clinical need.'' Additionally, the study developed a new formulation of semaglutide in order to enhance the bioavailability compared to the approved 14 mg tablet.[31] The authors of the article noted the following study limitation: ''it was not possible to assess whether the efficacy and tolerability of oral semaglutide were directly affected specifically by the new formulation. It is therefore possible that the additional benefit of the 25 mg and 50 mg doses was not only dose-related, but also reflected the higher bioavailability of this formulation.'' The nomination does not provide any information regarding the formulation of the compounded product, and the nomination does not explain, or even assert, that the compounded product would overcome the poor bioavailability of oral semaglutide. As noted, FDA has

[30] One nomination states that 3 mg, 7 mg, and 14 mg are the currently available dosages. We note that semaglutide is also approved as 1.5 mg, 4 mg, 9 mg, and 25 mg oral tablets. The nomination was received prior to the approval of these strengths, but there is no information in the nomination, and the nominator did not supplement its nomination after the approval, to show that these approved products would be medically unsuitable for any patient who would need a higher strength.

[31] There are three formulations of semaglutide for oral administration that are approved. One is approved under the brand name Rybelsus, one under the brand name Ozempic, and one under the brand name Wegovy. According to the Prescribing Information for Rybelsus and Ozempic, the population pharmacokinetics estimated absolute bioavailability of semaglutide is approximately 0.4–1% following oral administration of 3 mg, 7 mg, and 14 mg of Rybelsus (formulation R1) and 1–2% following oral administration of 1.5 mg, 4 mg, and 9 mg of Ozempic (formulation R2); both drug products are co-formulated with salcaprozate sodium (SNAC), which facilitates the absorption of semaglutide after oral administration. Refer to the ''Clinical Pharmacology—Pharmacokinetics'' section of the FDA-approved labeling for NDA 213051 available at *https://www.accessdata.fda.gov/spl/data/d66c588c-f975-45de-819e-f879c453385d/d66c588c-f975-45de-819e-f879c453385d.xml* and *https://www.accessdata.fda.gov/spl/data/dfe441cd-c20f-452b-a8a5-3a6017b6b006/dfe441cd-c20f-452b-a8a5-3a6017b6b006.xml*. Accessed 3/25/26. According to the Prescribing Information for Wegovy, the population pharmacokinetics estimated absolute bioavailability of semaglutide is approximately 1–2% following oral administration of Wegovy and is co-formulated with salcaprozate sodium, which facilitates the absorption of semaglutide after oral administration. Refer to the ''Clinical Pharmacology—Pharmacokinetics'' section of the FDA-approved labeling for NDA 218316 available at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/218316s005lbl.pdf*. Accessed 3/31/26. As described in the Supplementary Appendix of the PIONEER PLUS article (Aroda et al. 2023), the oral semaglutide 25 mg and 50 mg tablets used in the study consisted of a new formulation developed to enhance bioavailability compared with the 14 mg dose. The Supplementary Appendix is available online at *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01127-3/abstract*. Two excipients (microcrystalline cellulose [filler] and povidone K 90 [binder]) were omitted, with magnesium stearate remaining as the only excipient besides the active drug substance and the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC).

approved a 25 mg semaglutide oral tablet. With respect to the 50 mg tablet proposed in the nomination, improved outcomes from the higher strength, or the fact that a higher strength is being studied, does not mean that the approved product does not achieve the intended clinical benefit or is otherwise medically unsuitable for patients.

The Knop et al. study was a placebo-controlled trial that determined that oral semaglutide 50 mg is superior to placebo in decreasing bodyweight. Similar to the Aroda et al. (2023) study, this study utilized a new formulation of semaglutide to enhance the bioavailability.[32] While the study found, and the nominator cited, that oral semaglutide 50 mg daily ''led to a superior and clinically meaningful decrease in bodyweight compared with placebo,'' this does not support a conclusion that an attribute of the approved semaglutide makes it medically unsuitable. Obtaining a better response with a higher dose does not mean that the strengths of the currently approved products are not effective or that they are otherwise medically unsuitable.

The nominators' statements that the strengths of the approved tablets ''are inadequate'' or ''do not fit all patient populations'' do not explain why the approved products are inadequate or identify patients for whom they are inadequate. To the extent the nominators are referring to the arguments discussed above about obtaining a better response with a higher dose, as discussed, that does not mean that the approved product is medically unsuitable for patients.

Proposals for Formulations Without Certain Excipients

One nominator states that ''[a]n individual patient may have intolerances or sensitivities to inactive ingredients in the commercially available drug product,'' but does not identify which inactive ingredients they are referring to. Therefore, the nominator does not identify an attribute of the approved drugs that makes them medically unsuitable or a compounded drug intended to address that attribute.

Some of the proposed concentrations are the same as the FDA-approved product (*i.e.,* 2 mg/3 mL (0.68 mg/mL), 4 mg/3 mL (1.34 mg/mL), 8 mg/3 mL (2.68 mg/mL)). One nominator states that the ''FDA-approved semaglutide injections indicated for type 2 diabetes contain propylene glycol, which has caused an increase in irritation at the injection site.'' The nominator claims that ''type 2 diabetic patients that require doses not offered in the non-propylene glycol formulations can benefit [from] compounded semaglutide'' and included one article, Snitker et al. (2022), that evaluated the injection-site experience of two formulations of semaglutide, semaglutide C and semaglutide D, compared to semaglutide multidose pen injector (MPI) (Ref. 7).[33] The article does not appear to support the nominator's position. The article does not, as the nominator claims, find that ''95% of patients preferred the formulation without propylene glycol.'' When comparing semaglutide D, the formulation that did not contain propylene glycol, with semaglutide MPI, a formulation that contains propylene glycol, the authors concluded that ''[t]he injection-site experience with semaglutide D was almost indistinguishable from semaglutide MPI . . . with either product associated with no or very mild injection-site pain.'' Additionally, what the nomination describes as ''patient preference'' for a different formulation than the approved drug does not mean that the formulation of the approved drug is medically unsuitable.

Semaglutide for SC injection is approved by FDA under the brand names Ozempic, Wegovy, and Wegovy HD. Ozempic is approved in three concentrations as a multidose pen injector, each of which contains propylene glycol 14 mg/mL; Wegovy is approved in five concentrations as a single-dose pen injector, none of which contain propylene glycol; and Wegovy HD is approved in one concentration as a single-dose pen injector, which does not contain propylene glycol. One nominator observes that ''type 2 diabetic patients that require doses not offered in the non-propylene glycol formulations can benefit [from] compounded semaglutide.''

A search of the FDA Adverse Event Reporting System (FAERS) database identified numerous reports associated with semaglutide and injection site reactions and, despite the presence or absence of propylene glycol in the FDA-approved formulation, injection site reactions occurred in both Ozempic and Wegovy users. Of the reports identified, one case referenced propylene glycol. The report described a patient with a history of severe allergy to propylene glycol who, after treatment with Ozempic for 2 months for type 2 diabetes mellitus, developed a ''red, swollen bubble at the injection site the size of a quarter'' that resolved after discontinuing Ozempic. It is unclear whether the reaction experienced can be attributed to propylene glycol.[34]

FDA has not identified any data or information to suggest that propylene glycol would cause a drug product containing semaglutide to be medically unsuitable. Injection site reaction is an adverse event reported in trials with various injectable therapeutic products, including other anti-hyperglycemic products not formulated with propylene glycol (*e.g.,* insulin products, other GLP–1 receptor agonists, tirzepatide). Additionally, all FDA-approved semaglutide injections, including the propylene glycol-free formulations of Wegovy and Wegovy HD, are labeled for injection site reactions.[35] The data and information do not suggest that a formulation without propylene glycol would mitigate the skin irritation that can be associated with subcutaneously injected therapies such as semaglutide.[36] Even if the formulations containing propylene glycol were medically unsuitable for certain patients, the nominator has provided no basis to conclude that those patients could not use the FDA-approved products that are not formulated with propylene glycol.[37] Additionally, the

[32] As described in the Methods section of the OASIS–1 article (Knop et al. 2023), two excipients (microcrystalline cellulose and povidone K 90) included in the oral formulation currently approved at the time of publication for the treatment of type 2 diabetes were omitted in order to enhance bioavailability.

[33] Semaglutide C is a single-dose pen injector that does not contain phenol and contained a higher concentration (1.9%) of propylene glycol than the semaglutide MPI. This formulation is not similar to any formulation approved in the United States. Semaglutide D is a single-dose pen injector that does not contain phenol and contained sodium chloride instead of propylene glycol. This formulation is similar to the formulation of FDA-approved Wegovy. Semaglutide MPI contains phenol and propylene glycol. This formulation is similar to the formulation of FDA-approved Ozempic. The authors stated that this formulation is ''a benchmark for low injection-site pain.''

[34] It is important to note that FAERS data have limitations. First, there is no certainty that the reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event.

[35] Refer to the ''Adverse Reactions'' section of the FDA-approved labeling for NDA 209637 and NDA 215256 available at *https://www.accessdata.fda.gov/spl/data/341dc8b9-9576-48a7-b8d8-c583c67b7007/341dc8b9-9576-48a7-b8d8-c583c67b7007.xml* and *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s029lbl.pdf.* Accessed 3/31/26.

[36] The presence of propylene glycol in Ozempic and the absence of this excipient in Wegovy suggests that determinants of injection site reactions are likely more complex than the inclusion or exclusion of propylene glycol in the formulation.

[37] We note that the semaglutide drug products approved for use as an SC injection (*i.e.,* Ozempic, Wegovy, Wegovy HD) have differing concentrations

notion that a patient ''can benefit'' from a compounded formulation does not mean that the approved formulation is medically unsuitable.

Multi-ingredient Products

The nominators also propose to compound semaglutide as ''combination injectables including those doses above combined with [p]yridoxine or an antiemetic medication.'' However, the nominations provide no other information about the proposed compounded products, or why they think patients would use these combinations. For example, the nominations do not identify the drug products containing semaglutide and pyridoxine, or semaglutide and ''an antiemetic,'' proposed to be compounded.[38] Without identifying an attribute of the approved drugs that make them medically unsuitable (*e.g.,* why a patient could not receive an FDA-approved semaglutide product and separately an FDA-approved pyridoxine product or antiemetic) or the product proposed to be compounded to address that attribute, we do not have a basis to conclude that there is a clinical need for an outsourcing facility to compound semaglutide to make this multi-ingredient product.

Whether for convenience or for some other purpose, as noted, the nominators provide no information (*e.g.,* proposed use, active ingredients, strength) about the drug product that would be compounded as a multi-active pharmaceutical ingredient (API) product. The nominators do not identify an attribute of the approved product that makes the product medically unsuitable or explain why the addition of a second active ingredient would address any such attribute.

Other Issues

One nomination also states that ''a medical professional may determine that a different dose than is commercially available is more suitable for their patient in order to manage side effects and increase adherence,'' and that ''[a]n administration device, such as an auto-injector, that only provides a fixed dose does not allow for these more tailored doses''; it is, according to the nomination, ''impossible to achieve lower or higher doses with an auto-injector pen.'' The nomination further states that ''an administration device, such as an auto-injector, may not be suitable for a specific patient'' and that ''an alternative container/closure [system] or administration device may improve patient compliance and safety.'' We have addressed above the arguments about a need for different strengths than the approved products; we explained that FDA has not identified a basis to conclude that the strengths of such products cause them to be medically unsuitable for certain patients. To the extent the nominator is arguing that a different container-closure device would necessitate compounding from a bulk drug substance rather than an approved drug, that question is inapplicable to this Part 1(a) analysis. Thus, we need not reach the argument about use of a different container-closure to achieve different strengths.

The nominators also state that semaglutide should be added to the 503B Bulks List because FDA-approved products containing semaglutide are in or could be subject to shortage, drugs produced by outsourcing facilities are produced in accordance with CGMP, and there are also potential concerns related to growth demand and access to these products. However, FDA does not interpret such issues, such as shortages and backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance. As noted above, section 503B contains a separate provision for compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing.

For these reasons, FDA tentatively finds no basis to conclude that there is an attribute of the FDA-approved drug products containing semaglutide that makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that the proposed compounded products are intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because there is no basis to conclude that there is an attribute of the FDA-approved drug products containing semaglutide which makes them medically unsuitable to treat certain patients, FDA does not need to evaluate whether the proposed drug products containing semaglutide must be compounded from a bulk drug substance rather than using an FDA-approved drug product.

3. Docket Comments

To the extent relevant to the clinical need analysis, FDA has considered the following submissions to the docket regarding the nomination of semaglutide for the 503B Bulks List (FDA–2015–N–3469):

Covington & Burling LLP on behalf of Novo Nordisk, Inc. (NNI) submitted a comment dated October 21, 2024 (FDA–2015–N–3469–0402),[39] opposing the nomination of semaglutide to the 503B Bulks List.[40] [41] OFA submitted comments dated October 24, 2024 (FDA–2024–P–4937–0003),[42] and dated February 13, 2025 (FDA–2024–P–4937–0004),[43] regarding the arguments made in the citizen petition. NNI submitted a supplement to its earlier comment dated April 15, 2025 (FDA–2015–N–3469–

and labeled indications. Wegovy and Wegovy HD, the approved formulations that do not contain propylene glycol, have not been shown to be safe and effective for the treatment of type 2 diabetes. For the Part 1(a) analysis, we ask a limited, threshold question to determine whether there might be clinical need for a compounded drug product, by asking what attributes of the approved drug the proposed compounded drug would change, and why. Because this nomination did not pass through Part 1(a), we did not reach Part 2 and therefore did not consider the Part 2 factors, including the available evidence of effectiveness or lack of effectiveness of a drug product compounded with semaglutide.

[38] Even if the nominations had provided sufficient information to ascertain the drug product proposed to be compounded, we note that, in general, we do not expect to find clinical need for a bulk drug substance to compound drug products containing two or more bulk drug substances unless: (1) combining the substances is intended to address the medical unsuitability of the FDA-approved drug products for certain patients and (2) the combination is likely to address a clinical need that could not be addressed by delivering each component of the drug product alone. Not including drug products with two or more active ingredients on the 503B Bulks List unless these conditions are met helps to ensure that patients are not exposed to a drug product containing an unnecessary active ingredient, helps avoid risks of unwanted interactions or complications in formulation, and protects the integrity of the drug approval process.

[39] Available at *https://www.regulations.gov/comment/FDA-2015-N-3469-0402.*

[40] The comment enclosed a citizen petition submitted by Covington & Burling LLP on behalf of NNI (FDA–2024–P–4937–0001).

[41] For purposes of this clinical need evaluation, we address the arguments from the petition that are directly relevant to the clinical need analysis, including those that engage with arguments in the nominations. We also note that this preliminary **Federal Register** notice does not reflect a final Agency decision on any of the arguments raised in the petition. FDA is issuing the preliminary **Federal Register** notice to seek public comment on the issues raised in the nominations and comments to the docket, including relevant portions of the petition that was enclosed in NNI's comment. FDA's final decision on those issues will be reflected in the final **Federal Register** notice and response to the petition. FDA intends to issue the response to the petition concurrently with the **Federal Register** notice setting forth FDA's final decision about whether semaglutide will be added to the 503B Bulks List.

[42] Available at *https://www.regulations.gov/comment/FDA-2024-P-4937-0003.*

[43] Available at *https://www.regulations.gov/comment/FDA-2024-P-4937-0004.*

0413 and FDA–2024–P–4937–0005),[44] responding to OFA's comments.

*B. Tirzepatide*

Tirzepatide has been nominated [45] for use in compounded drug products for ''Type 2 diabetes mellitus,'' [46] ''as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus''; ''[t]o reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight''; ''[t]o reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 12 years and older with obesity [and] adults with overweight in the presence of at least one weight-related comorbid condition''; ''to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity''; and ''related health conditions as determined appropriate by medical provider.''

Tirzepatide is an active ingredient,[47] as both a single-dose pen and a single-dose vial, in FDA-approved drug products: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL solutions for SC injection (Mounjaro, NDA 215866; Zepbound, NDA 217806). Tirzepatide is also an active ingredient, as both a multi-dose vial and a single-patient-use KwikPen, in FDA-approved drug products: 10 mg/2.4 mL (4.17 mg/mL) for four 2.5 mg/0.6 mL doses, 20 mg/2.4 mL (8.33 mg/mL) for four 5 mg/0.6 mL doses, 30 mg/2.4 mL (12.5 mg/mL) for four 7.5 mg/0.6 mL doses, 40 mg/2.4 mL (16.7 mg/mL) for four 10 mg/0.6 mL doses, 50 mg/2.4 mL (20.8 mg/mL) for four 12.5 mg/0.6 mL doses; and 60 mg/2.4 mL (25 mg/mL) for four 15 mg/0.6 mL doses solutions for SC injection (Mounjaro, NDA 215866; Zepbound, NDA 217806).

Tirzepatide was nominated and evaluated for the SC injection, sublingual, buccal, and oral routes of administration in various strengths. The nominations provide examples of such strengths and state that different strengths may be compounded ''depending on medical provider requests.'' [48] In addition, the nominations propose to compound tirzepatide as ''combination injectables including those doses above combined with [p]yridoxine or an antiemetic medication'' (Ref. 8).

1. Suitability of FDA-Approved Drug Product(s)

The nominators propose to compound a ''subcutaneous injection, oral sublingual, buccal, and oral tablet or capsule'' in various strengths. The nominators propose to compound drug products in various routes of administration and provide examples of strengths associated with some of those routes. The nominators suggest that tirzepatide might also be used to compound other drug products, but the nominators do not identify those products. To assess clinical need, we consider whether the nomination identifies an attribute of the approved drug that makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation. With respect to the nominator's statement that the compounded products will be used for ''related health conditions as determined appropriate by medical provider,'' we cannot find that there is a clinical need for an outsourcing facility to compound tirzepatide for unidentified health conditions. With respect to the proposed use of ''to reduce the risk of major adverse cardiovascular events in adults with established cardiovascular disease and either obesity or overweight,'' the nominator did not provide any supporting data or information for this use. Additionally, the nominator does not identify an attribute of the FDA-approved drug containing tirzepatide that would make it medically unsuitable to treat this condition.

Oral, ''Oral Sublingual'' and Buccal Products

We address here the proposals for oral, ''oral sublingual,'' and buccal products because no tirzepatide drug product is approved in these routes of administration.

The nominators refer to ''[r]anges depending on medical provider requests'' and list examples of such strengths. For products proposed for the sublingual route of administration, the nominators provide example concentrations of 5 mg/mL and 7.5 mg/mL; the nominators do not provide any concentrations of products proposed to be compounded for oral and buccal administration. As the proposed concentrations for the sublingual route of administration are listed as examples, the nominations do not identify each of the strengths—and therefore the drug products—proposed to be compounded for the oral, sublingual, and buccal routes of administration.

One nominator states that the injection route of administration is ''linked to patient discomfort and is subject to refrigerated storage.'' The nominator further states that ''[a]n injectable only formulation causes unnecessary fears in these patients and may lead to adherence failure,'' and that ''an oral tablet, capsule, sublingual or buccal tablet in varying strengths would satisfy this clinical need.'' Regarding sublingual and buccal forms, the nominators state that ''there are certain patients who cannot swallow and an injectable may not be preferable . . . therefore there is a clinical need for sublingual dosage forms.'' One nominator claims that the buccal and sublingual routes ''are recognized as valid alternatives'' and that these routes ''in varying strengths would satisfy this clinical need.'' One nominator refers to an article, Pratap-Singh et al. (2023), that the authors characterize as ''a guideline for future investigators in creating buccal or sublingual tablets for the delivery of [peptide] drugs used to treat diabetes.'' For the reasons noted in our discussion of this article in the semaglutide section, addressing similar arguments from the nominators, we tentatively find that it provides no basis to conclude that the routes of administration of FDA-approved tirzepatide products make them medically unsuitable for certain patients.

FDA has not identified a basis to conclude that the injectable routes of administration of the FDA-approved tirzepatide products cause those products to be medically unsuitable for certain patients and that a compounded oral, buccal, or sublingual product would address such attribute. For example, with respect to the argument that ''an injectable may not be preferable'' for some patients, the

[44] Available at *https://www.regulations.gov/comment/FDA-2015-N-3469-0413* and *https://www.regulations.gov/document/FDA-2024-P-4937-0005*.

[45] See Docket No. FDA–2015–N–3469, document nos. FDA–2015–N–3469–0389 and FDA–2015–N–3469–0411.

[46] One nomination proposes to compound tirzepatide for ''type 2 diabetes mellitus.'' We understand the nomination to have intended this proposed use to be as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. We note that tirzepatide was approved on December 19, 2025, for pediatric patients 10 years of age and older (NDA 215866). The nomination was received prior to the approval of tirzepatide for this patient population, and the nominator did not supplement its nomination after the approval to show that these approved products would be medically unsuitable for such patients.

[47] Contains sodium chloride 4.1 mg, sodium phosphate dibasic heptahydrate 0.7 mg, and water for injection.

[48] Nominators included the following examples of strengths for injectable products: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL, 20mg/0.5 mL, and 30mg/0.5 mL. For the sublingual route of administration, nominators proposed 5 mg/mL and 7.5 mg/mL.

statutory standard for inclusion of a substance on the 503B Bulks List is clinical need—not ''preference.'' Similarly, the potential for a patient to experience ''discomfort'' after receiving an injection does not mean that injectable product is medically unsuitable for the patient.

Injectable Products

The nominators refer to ''[r]anges depending on medical provider requests'' and list examples of such strengths. For products proposed for the SC route of administration, the nominators provide example concentrations of 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL, 20 mg/0.5 mL, and 30 mg/0.5 mL injection. As these concentrations are listed as examples, the nominations do not identify each of the concentrations—and therefore the drug products—proposed to be compounded for the SC route of administration.

One nominator states that a different dose may be ''more suitable for their patient in order to manage side effects and increase adherence.'' However, the nominator does not identify alternative doses to be delivered from the proposed compounded drug. Further, the general statement that a different dose may be ''more suitable'' does not mean that the available strengths of the approved product are *not* suitable.

Regarding the proposals to compound tirzepatide for use as an SC injection in concentrations that exceed the concentrations of the approved tirzepatide products (proposed concentrations of 20 mg/0.5 mL and 30 mg/0.5 mL), the nominations do not provide supporting data or information for the use of compounded products with a higher concentration than the approved product. The nominations state that patients may benefit from higher doses but do not identify higher doses to be delivered from the proposed compounded drug product; nor do the nominations identify patients for whom the concentrations of the FDA-approved SC injections are medically unsuitable because a higher concentration is needed. With respect to the assertion that ''[c]ertain patients benefit from higher doses than are commercially available,'' even if accurate, obtaining a better response with a higher dose does not mean that the approved product does not achieve the intended clinical benefit or that it is otherwise medically unsuitable for patients. The nominators have not provided a basis to conclude that patients need the specific concentrations proposed. FDA is also not aware of data or information that identifies patients for whom the concentrations of the FDA-approved SC injections are medically unsuitable.[49]

The nominators state that some patients are ''hyper-responders'' and that they may ''need a lower dose than what is commercially available.'' One nominator states that ''hyper-responders'' are those who are ''very sensitive'' to the drug and thus may need either a slower titration or a lower maintenance dose, noting that only the 5 mg, 10 mg, and 15 mg weekly doses are approved for maintenance. One nominator states that ''an auto-injector that only provides a fixed dose does not allow for these more tailored doses.'' [50] However, the nominations do not explain why, if a patient requires a lower maintenance dose, the FDA-approved products that contain a lower concentration (*i.e.,* 2.5 mg/0.5 mL) or smaller volumes from the vials could not be used. The nominations also do not explain why a slower titration using the FDA-approved products could not be used in patients who do not tolerate dose escalation every 4 weeks.[51] In addition, the nominations do not provide specific lower maintenance dosages that are different from the FDA-approved products,[52] and they do not provide sufficient information about the products proposed to be compounded for FDA to assess whether the products would address the attribute, if there were one, that makes the approved drugs medically unsuitable.

Multi-ingredient Products

The nominators also propose to compound tirzepatide as ''combination injectables including those doses above combined with [p]yridoxine or an antiemetic medication.'' However, the nominations provide no other information about the proposed compounded products, or why they think patients would need these combinations. For example, the nominations do not identify the drug products containing tirzepatide and pyridoxine, or tirzepatide and ''an antiemetic,'' proposed to be compounded.[53] They do not even identify which antiemetic would be included in the compounded product. Without identifying an attribute of the approved drugs that makes them medically unsuitable (*e.g.,* why a patient could not receive an FDA-approved tirzepatide product and separately an FDA-approved pyridoxine product or antiemetic), or the product proposed to be compounded to address that attribute, we cannot find that there is a clinical need for an outsourcing facility to compound tirzepatide to make this multi-ingredient product.

Other Issues

Regarding excipients, one nominator states that patients may have intolerances or sensitivities to inactive ingredients in the commercially available drug product. However, the nomination does not identify which inactive ingredients they are referring to. Therefore, the nominator does not identify an attribute of the approved drugs that makes them medically unsuitable, or a compounded drug intended to address that attribute.

One nomination also states that ''a medical professional may determine that a different dose than is commercially available is more suitable for their patient in order to manage side effects and increase adherence,'' and that ''[a]n administration device, such as an auto-injector, that only provides a fixed dose does not allow for these more tailored doses.'' The nomination further states that ''an administration device, such as an auto-injector, may not be suitable for a specific patient'' and that ''an alternative container/closure system or administration device may improve patient compliance and safety.'' We

[49] We note that tirzepatide was approved as both a multi-dose vial and a single-patient-use KwikPen after the nominators submitted their nomination. There is no information in the nominations, and the nominators did not supplement their nominations after the approval, to show that this approved product would be medically unsuitable for any patient who would need a higher dose.

[50] We note that tirzepatide is approved by FDA as single-patient-use pens and vials.

[51] While the ''Dosage and Administration'' section of the FDA-approved labeling for NDA 217806 states that the recommended maintenance dose is 5 mg, 10 mg, or 15 mg, the section also directs prescribers to ''[c]onsider treatment response and tolerability when selecting the maintenance dosage.'' See *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215866s009lbl.pdf.* Accessed 4/15/26.

[52] According to the ''Dosage and Administration'' section of the FDA-approved labeling for NDA 217806, ''[i]f patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.'' See *https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215866s009lbl.pdf. Accessed 4/15/26.*

[53] Even if the nominations had provided sufficient information to ascertain the drug product proposed to be compounded, we note that, in general, we do not expect to find clinical need for a bulk drug substance to compound drug products containing two or more bulk drug substances unless: (1) combining the substances is intended to address the medical unsuitability of the FDA-approved drug products for certain patients and (2) the combination is likely to address a clinical need that could not be addressed by delivering each component of the drug product alone. Not including drug products with two or more active ingredients on the 503B Bulks List unless these conditions are met helps to ensure that patients are not exposed to a drug product containing an unnecessary active ingredient, helps avoid risks of unwanted interactions or complications in formulation, and protects the integrity of the drug approval process.

have addressed above the arguments about different strengths than the approved products; we explained that FDA has not identified a basis to conclude that the strengths of such products cause them to be medically unsuitable for certain patients. To the extent the nominator is arguing that a different container-closure device would necessitate compounding from a bulk drug substance rather than an approved drug, that question is inapplicable to this Part 1(a) analysis. Thus, we need not reach the argument about use of a different container-closure to achieve different strengths.[54]

The nominators also state that tirzepatide should be added to the 503B Bulks List because FDA-approved products containing tirzepatide are in shortage and drugs produced by outsourcing facilities are produced in accordance with CGMP. FDA does not interpret such issues, such as shortages and backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance. As noted above, section 503B contains a separate provision for compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list. We also note that as of the date of this notice, FDA-approved tirzepatide drug products are not on the FDA drug shortage list.[55]

For these reasons, FDA tentatively finds no basis to conclude that there is an attribute of the FDA-approved drug products containing tirzepatide that makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that the proposed compounded products are intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because there is no basis to conclude that there is an attribute of the FDA-approved drug products containing tirzepatide which makes them medically unsuitable to treat certain patients, FDA need not evaluate whether the proposed drug products containing tirzepatide must be compounded from a bulk drug substance rather than using an FDA-approved drug product.

3. Docket Comments

To the extent relevant to the clinical need analysis, FDA has considered the following submission to the docket regarding the nomination of tirzepatide for the 503B Bulks List (FDA–2015–N–3469):

Eli Lilly and Company submitted a comment to the docket dated November 4, 2024 (FDA–2015–N–3469–0404),[56] opposing the nomination of tirzepatide to the 503B Bulks List.

*C. Liraglutide*

Liraglutide has been nominated [57] for use in compounded drug products as ''[a]n adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus''; ''[t]o reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease''; ''[a]s an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in [a]dult patients with an initial body mass index (BMI) of 30 kg/m$^2$ or greater (obese), or 27 kg/m$^2$ or greater (overweight) in the presence of at least one weight-related comorbid condition (*e.g.,* hypertension, type 2 diabetes mellitus, or dyslipidemia)'' and ''[p]ediatric patients aged 12 years and older with body weight above 60 kg and initial BMI corresponding to 30 kg/m$^2$ for adults (obesity) by international cut-offs.''

Liraglutide is an active ingredient in FDA-approved drug products: 18 mg/3 mL (6 mg/mL) solution for SC injection (Saxenda, NDA 206321); 18 mg/3 mL (6 mg/mL) solution for SC injection (Victoza, NDA 022341); and 18 mg/3 mL (6 mg/mL) solution for SC injection (liraglutide 18 mg/3 mL, *e.g.,* ANDA 215503). Each FDA-approved liraglutide product contains propylene glycol.

Liraglutide was nominated and evaluated for the SC injection route of administration in strengths in ''[r]anges depending on medical provider requests'' (Ref. 9).[58] The nomination provides an example of one such strength.

1. Suitability of FDA-Approved Drug Product(s)

The nominator proposes to compound an SC injection containing liraglutide. The nominator suggests that liraglutide might also be used to compound other drug products, but the nominator does not identify those products. With respect to strengths to be compounded using the bulk drug substance, the nomination refers to ''[r]anges depending on medical provider requests.'' The nomination provides just one example concentration of ''18 mg/3mL or 6 mg/mL that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg, 2.4 mg or 3 mg.'' This proposed concentration is the same as that of the FDA-approved products (*i.e.,* Saxenda, Victoza, liraglutide 18 mg/3 mL), and the proposed doses to be delivered from the compounded product are the same as those listed in the product labeling for Saxenda (NDA 206321). With respect to compounded drugs generally, the nominator states that ''a medical professional may determine that a different dose than is commercially available is more suitable for their patient in order to manage side effects and increase adherence.'' However, the nominator does not state that this is the case for liraglutide specifically. Even if the statement had been specific to liraglutide, ''manag[ing] side effects'' and ''increas[ing] adherence'' do not reflect an unsuitability with the approved products. Nor did the nomination identify a product proposed to be compounded; the nomination does not identify the ''different dose[s]'' referenced in this statement.

After reviewing the nominations and comments to the docket, we tentatively find no basis to conclude that the strength of FDA-approved liraglutide products makes them medically unsuitable for certain patients. The nomination has not provided a basis to conclude that strength of the approved products is an attribute that makes them medically unsuitable to treat certain patients; the only proposed strength the nominator provides is the same as the FDA-approved drugs. Nor has the nominator identified the drug products proposed to be compounded; the nominator has provided only one example of a strength. Vague statements that a healthcare provider may determine that a different dose is needed for side effects and improved patient adherence, without identifying the dose, patients, or any attribute that makes the approved drugs unsuitable for such patients, do not establish clinical need.[59]

[54] We note that the nominators do not acknowledge that tirzepatide is approved not only in auto-injectors, but also in vials.

[55] FDA Drug Shortages Database available at *https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.*

[56] Available at *https://www.regulations.gov/comment/FDA-2015-N-3469-0404.*

[57] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0391.

[58] The nomination provided the following examples of strengths for injectable compounded products: 18 mg/3 mL or 6 mg/mL that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg.

[59] We acknowledge a nominator's comment (FDA–2024–P–5966–0003) stating that ''microdosing trends have been widely documented and allow for hypersensitive patients otherwise intolerant to standard doses to continue treatment,'' citing an article published in the New York Times. However, the New York Times article does not

The nominator also proposes to compound liraglutide products without certain excipients. The nominator states that ''[a]n individual patient may have intolerances or sensitivities to inactive ingredients in the commercially available drug product,'' but does not identify which inactive ingredients they are referring to. Therefore, the nominator does not identify an attribute of the approved drugs that makes them medically unsuitable, or a compounded drug intended to address that attribute.

The nominator notes that ''FDA-approved liraglutide injections indicated for type 2 diabetes contain propylene glycol, which has caused an increase in irritation at the injection site.'' The nomination further states that ''[s]ince there are no commercially available forms of liraglutide that do not contain propylene glycol, patients with sensitivities to propylene glycol will benefit from compounds formulated without it.'' Even if this were accurate, the notion that a patient ''will benefit'' from a compounded formulation does not mean that the approved formulation is medically unsuitable. The nominator submitted one article, Snitker et al. (2022), that evaluated the injection-site experience of two formulations of semaglutide, semaglutide C and semaglutide D, compared to semaglutide MPI [60] This article, which did not evaluate liraglutide, does not appear to support the nominator's position. The article does not, as the nominator claims, find that ''95% of patients preferred the formulation without propylene glycol.'' When comparing semaglutide D, the formulation that did not contain propylene glycol, with semaglutide MPI, a formulation that contains propylene glycol, the authors concluded that ''[t]he injection-site experience with semaglutide D was almost indistinguishable from semaglutide MPI . . . with either product associated with no or very mild injection-site pain.'' Additionally, as discussed above, ''patient preference'' for a different formulation than the approved drug does not mean that the formulation of the approved drug is medically unsuitable.

A search of the FAERS database identified numerous reports associated with liraglutide and injection site reactions occurring in both Victoza and Saxenda users. The search did not retrieve any reports of liraglutide and injection site reactions with a case narrative containing ''propylene.'' [61] FDA has not identified any data or information to suggest that propylene glycol would cause a drug product containing liraglutide to be medically unsuitable. Injection site reaction is an adverse event reported in trials with various injectable therapeutic products, including other anti-hyperglycemic products not formulated with propylene glycol (*e.g.,* insulin products, other GLP–1 receptor agonists, tirzepatide). Additionally, all FDA-approved liraglutide injections are labeled for injection site reactions.[62] The data and information do not suggest that a formulation without propylene glycol would mitigate the skin irritation that can be associated with subcutaneously injected therapies such as liraglutide. Additionally, the notion that a patient ''will benefit'' from a compounded formulation does not mean that the approved formulation is medically unsuitable. FDA has not identified any data or information discussing patients for whom propylene glycol would cause a drug product containing liraglutide to be medically unsuitable.[63]

The nomination also states that liraglutide might be used to compound drug products in different container-closure devices. The nomination states that use of an alternative container-closure system or administration device ''may improve patient compliance and safety.'' To the extent the nominator is arguing that a different container-closure device would necessitate compounding from a bulk drug substance rather than an approved drug, that question is inapplicable to this Part 1(a) analysis. With respect to the nominator's statement about ''improve[d] patient compliance and safety,'' the nominator does not identify an attribute of the approved products that makes them medically unsuitable.

For these reasons, FDA tentatively finds no basis to conclude that there is an attribute of the FDA-approved drug products containing liraglutide that makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that the proposed compounded products are intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because there is no basis to conclude that there is an attribute of the FDA-approved drug products containing liraglutide which makes them medically unsuitable to treat certain patients, FDA need not decide whether the proposed drug products containing liraglutide must be compounded from a bulk drug substance rather than using an FDA-approved drug product.

3. Docket Comments

To the extent relevant to the clinical need analysis, FDA has considered the following submissions to the docket regarding the nomination of liraglutide for the 503B Bulks List (FDA–2015–N–3469):

Covington & Burling LLP on behalf of NNI submitted a comment dated December 20, 2024 (FDA–2015–N–3469–0407),[64] opposing the nomination of liraglutide to the 503B Bulks List. The comment enclosed a citizen petition from Covington & Burling LLP on behalf of NNI (FDA–2024–P–5966–0001).[65] [66]

include any data or information to support the position that the FDA-approved product could not be used to obtain lower doses or that it is otherwise medically unsuitable. In assessing clinical need, we consider, in part, whether there is a basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable—not whether the approved product in fact meets medical needs. Nor does the clinical need analysis turn on information about general ''trends'' without identifying patients for whom the approved drug would be medically unsuitable.

[60] Semaglutide C is a single-dose pen injector that does not contain phenol and contained a higher concentration (1.9%) of propylene glycol than the semaglutide MPI. This formulation is not similar to any formulation approved in the United States. Semaglutide D is a single-dose pen injector that does not contain phenol and contained sodium chloride instead of propylene glycol. This formulation is similar to the formulation of FDA-approved Wegovy. Semaglutide MPI contains phenol and propylene glycol. This formulation is similar to the formulation of FDA-approved Ozempic. The authors stated that this formulation is ''a benchmark for low injection-site pain.''

[61] It is important to note that FAERS data have limitations. First, there is no certainty that the reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event.

[62] Refer to the ''Adverse Reactions'' section of the FDA-approved labeling for, *e.g.,* NDA 022341 and NDA 206321, available at *https://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/5a9ef4ea-c76a-4d34-a604-27c5b505f5a4/spl-doc* and *https://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/3946d389-0926-4f77-a708-0acb8153b143/spl-doc.* Accessed 3/23/26.

[63] We note that injection site reaction is an adverse event reported in trials with various injectable therapeutic products, including other anti-hyperglycemic products not formulated with propylene glycol (*e.g.,* insulin products, other GLP–1 receptor agonists, tirzepatide). These data and information do not suggest that a formulation without propylene glycol would mitigate the skin irritation that can be associated with subcutaneously injected therapies such as liraglutide.

[64] Available at *https://www.regulations.gov/comment/FDA-2015-N-3469-0407.*

[65] Available at *https://www.regulations.gov/document/FDA-2024-P-5966-0001.*

[66] For purposes of this clinical need evaluation, we address the arguments from the petition that are directly relevant to the clinical need analysis, including those that engage with arguments in the nomination. We also note that this preliminary **Federal Register** notice does not reflect a final Agency decision on any of the arguments raised in the petition. FDA is issuing the preliminary **Federal Register** notice to seek public comment on the

Continued

OFA submitted a comment on March 17, 2025 (FDA–2024–P–5966–0003),[67] responding to arguments made in the citizen petition. Covington & Burling LLP on behalf of NNI submitted a supplement to its earlier comment on June 17, 2025 (FDA–2024–P–5966–0005),[68] responding to OFA's comments.

## IV. Conclusion

For the reasons stated above, FDA tentatively finds no basis to conclude that there is a clinical need for an outsourcing facility to compound using the following bulk drug substances: semaglutide, tirzepatide, and liraglutide. Therefore, we propose not to include these bulk drug substances on the 503B Bulks List.

## V. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff **(SEE ADDRESSES)** and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.


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* 8. FDA Memorandum to File, ''Clinical Need Evaluation for Tirzepatide in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' April 2026.
* 9. FDA Memorandum to File, ''Clinical Need Evaluation for Liraglutide in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' April 2026.


**Grace R. Graham,**

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**BILLING CODE 4164–01–P**

issues raised in the nominations and comments to the docket, including relevant portions of the petition that was enclosed in NNI's comment. FDA's final decision on those issues will be reflected in the final **Federal Register** notice and response to the petition. FDA intends to issue the response to the petition concurrently with the **Federal Register** notice setting forth FDA's final decision about whether liraglutide will be added to the 503B Bulks List.

[67] Available at *https://www.regulations.gov/document/FDA-2024-P-5966-0003.*

[68] Available at *https://www.regulations.gov/document/FDA-2024-P-5966-0005.*

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Institutes of Health

### Office of the Director, National Institutes of Health; Notice of Meeting

Pursuant to section 1009 of the Federal Advisory Committee Act, as amended, notice is hereby given of a meeting of the Office of AIDS Research Advisory Council.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should inform the Contact Person listed below in advance of the meeting. The meeting can be accessed from the NIH Videocast at the following link: *https://videocast.nih.gov/.*

*Name of Committee:* Office of AIDS Research Advisory Council.

*Date:* June 25, 2026.

*Time:* 12:00 p.m. to 04:30 p.m.

*Agenda:* The 72nd Office of AIDS Research Advisory Council meeting will include a report from the Office of AIDS Research Director, and discussions with council members, guests, and NIH officials regarding NIH HIV research.

*Address:* Office of AIDS Research, Office of the Director, National Institutes of Health, 5601 Fishers Lane, Grand Hall, Rockville, MD 20892.

*Meeting Format:* Virtual Meeting.

*Contact Person:* Melissa Herrera, Office of AIDS Research, Office of the Director, National Institutes of Health, 5601 Fishers Lane, Room 2F18, Rockville, MD 20892, (301) 496–0357, *OARACinfo@nih.gov.*

Registration is not required to attend this meeting.

Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

In the interest of security, NIH has procedures at *https://www.nih.gov/about-nih/visitor-information/campus-access-security* for entrance into on-campus and off-campus facilities. All visitor vehicles, including taxicabs, hotel, and airport shuttles will be inspected before being allowed on campus. Visitors attending a meeting on campus or at an off-campus federal facility will be asked to show one form of identification (for example, a government-issued photo ID, driver's license, or passport) and to state the purpose of their visit.

(Catalogue of Federal Domestic Assistance Program Nos. 93.14, Intramural Research Training Award; 93.22, Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds; 93.232, Loan Repayment Program for Research Generally; 93.39, Academic Research Enhancement Award; 93.936, NIH Acquired Immunodeficiency Syndrome Research Loan Repayment Program; 93.187, Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds, National Institutes of Health, HHS)

Dated: April 28, 2026.

**Bruce A. George,**

*Program Analyst, Office of Federal Advisory Committee Policy.*

[FR Doc. 2026–08491 Filed 4–30–26; 8:45 am]

**BILLING CODE 4167–05–P**