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May 21, 2024

Re: Docket No. FDA-2019-P-4830

Dear Mr. Sansone:

This letter responds to your citizen petition dated October 15, 2019 (Petition).[1] In the Petition, you request that the Food and Drug Administration (FDA or Agency) take several actions with respect to any abbreviated new drug application (ANDA) pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that references Ipsen Biopharmaceuticals, Inc.'s (Ipsen) product Somatuline Depot (lanreotide acetate) subcutaneous solution (new drug application (NDA) 022074). In the Petition, you request that FDA take the following actions:

1. Require ANDA applicants that reference Somatuline Depot to demonstrate bioequivalence (BE) by conducting an *in vivo* study capable of demonstrating that a proposed generic drug product[2] causes lanreotide acetate to release into systemic circulation at the same rate and to the same extent as the reference listed drug (RLD) over the course of the dosing interval;

2. Require that ANDAs include comparative impurity analysis on samples of finished drug product (post sterilization) and control for peptide-related impurities to the same extent and same level as the RLD;

3. Require that ANDAs include comparative performance testing of the delivery device to ensure it is equivalently functional and useable;

4. Require ANDA sponsors to conduct a partial Area Under the Curve (pAUC) analysis as part of the in vivo BE study to ensure the generic is bioequivalent to the RLD over the required dosing interval; and

[1] On October 17, 2019, Ipsen submitted a version of the Petition that was redacted and accompanied by publicly-available references only as well as a version of the Petition that was unredacted and accompanied by a full set of references. In determining what information to include in this response, we have independently evaluated whether the information in the Petition is confidential. For additional information on the Agency's disclosure policy, see 21 CFR Part 20.

[2] For the purpose of this response, the term generic drug refers to a new drug product for which approval is sought in an abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

5. Re-issue the Agency's July 2014 product specific BE draft guidance entitled "Draft Guidance on Lanreotide Acetate" (Draft PSG) based on the actions taken in response to the Petition.[3]

We have carefully considered the information in the Petition. For the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Somatuline Depot (Lanreotide Acetate)

On August 30, 2007, Ipsen obtained approval for NDA 022074 for Somatuline Depot, a prolonged-release formulation containing lanreotide acetate and given by deep subcutaneous injection by a healthcare provider. Somatuline Depot is available in three strengths: Equivalent (EQ) 60 milligrams (mg) base/0.2 milliliter (mL); EQ 90 mg base/0.3mL; and EQ 120 mg base/0.5mL. It is indicated for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy, the treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival, and the treatment of adults with carcinoid syndrome (when used, it reduces the frequency of short-acting somatostatin analog rescue therapy).[4]

B. Applicable Statutory and Regulatory Framework

1. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to, among other things, add section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence to establish the safety and effectiveness of the proposed drug product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[5] To rely on this finding, an ANDA applicant must provide sufficient information to show that its drug product is bioequivalent to the RLD.[6] An ANDA applicant generally must also demonstrate, among other things, that its drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength,

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[3] Petition at 4.

[4] Somatuline Depot labeling (Feb. 2023), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022074s026lbl.pdf.

[5] A *reference listed drug* or RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)). RLDs are identified in FDA's list of *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the Orange Book, available at https://www.accessdata.fda.gov/scripts/cder/ob/.

[6] *See* section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

and (with certain permissible differences) labeling as the RLD.[7] FDA must approve an ANDA unless it finds that, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.[8] The scientific premise underlying the Hatch-Waxman Amendments is that drug products that meet the ANDA approval requirements are therapeutically equivalent and may be substituted for each other.[9]

These general principles apply to products submitted in ANDAs, including drug-device combination products.[10] A generic drug-device combination product classified as therapeutically equivalent to the RLD can be expected to have the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. This does not mean, however, that the proposed generic drug-device combination product and its RLD need to be identical in all aspects. FDA recognizes that an identical design may not always be feasible and, in certain instances, differences in the design of the user interface for a generic drug-device combination product as compared to the RLD may exist without precluding approval of the generic drug-device combination product under an ANDA. In some instances in which differences exist, certain additional information and/or data relating to the user interface of the proposed generic drug-device combination product, such as data from comparative use human factors studies, may be appropriate to support approval of the proposed generic drug-device combination product in an ANDA. The extent to which differences between the proposed product and the RLD affect the approvability of the proposed ANDA product will be evaluated on a case-by-case basis.

2. The Bioequivalence Requirement

Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is considered bioequivalent to the listed drug if:

> . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses..... [11]

In 21 CFR 314.3(b), FDA defines bioequivalence (in pertinent part) as:

> . . . the absence of a significant difference in the rate and extent to which the active ingredient or active moiety..... becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

[7] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).
[8] Section 505(j)(4) of the FD&C Act.
[9] *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which BE has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. 21 CFR 314.3(b).
[10] *See*, *e.g.*, sections 505(j(2)(A), 505(j)(4), and 503(g)(1) of the FD&C Act.
[11] *See also* 21 CFR 320.1(e) and 320.23(b).

A showing that the active ingredient or active moiety in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. BE testing determines whether differences in formulation (e.g., differences in inactive ingredients or manufacturing processes) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

As discussed further below, the statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.[12] This flexibility is reflected in FDA's regulations, which describe the types of evidence that may be used to establish bioequivalence:

> FDA may require *in vivo or in vitro testing, or both,* to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products..... The selection of the method used to meet an *in vivo or in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[13]

Section 320.24(b) of FDA regulations describes acceptable BE methods in general descending order of accuracy, sensitivity, and reproducibility. The BE methods include: (1) in vivo pharmacokinetic (PK) studies of the active ingredient, or when appropriate its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid, or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolite(s) are measured as a function of time; (3) in vivo studies measuring acute pharmacodynamic effect; (4) comparative clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo bioavailability. In addition, section 320.24(b)(6) of the regulations states that FDA has the flexibility to accept "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." The Agency's authority to make BE determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human

[12] *See* section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with discretion to determine whether *in vitro* or *in vivo* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

[13] § 320.24(a) (emphasis added). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis: "Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . *is determined on a case-by-case basis*, depending on the drug under study." Abbreviated New Drug Application Regulations, Final Rule (57 FR 17950, 17972, April 28, 1992) (emphasis added).

research when other methods of demonstrating BE meet the statutory and regulatory standards for approval;[14] (2) permitting the Agency to use the latest scientific advances in approving drug products;[15] (3) protecting the public health by ensuring only safe and effective generic drugs are approved for marketing;[16] and (4) making more safe and effective generic drugs available.[17]

Congress intended to grant FDA wide discretion to establish BE standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments, and courts have recognized FDA's discretion to determine how the BE requirement should be met for a product or class of products, as long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[18]

C. FDA's Bioequivalence Recommendations and Draft Product-Specific Guidance on Lanreotide Acetate

FDA's draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) describes our general recommendations for demonstrating BE for products submitted under an ANDA. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited.

In addition to our general recommendations, we often provide product-specific recommendations for demonstrating BE. These product-specific recommendations are made to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.[19] Our process for making product-specific guidances

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[14] *See* 21 CFR 320.25(a) (stating that a "guiding principle" for the conduct of an in vivo bioavailability study is "that no unnecessary human research should be done"); *Abbreviated New Drug Application Regulations, Proposed Rule,* 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, stating that "the agency does not believe that Congress intended that unnecessary human research be conducted ... if the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies.").

[15] *See Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement,* 42 FR 1624, 1629 (Jan. 7, 1977) ("As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement.").

[16] *See Schering Corp. v. Sullivan,* 782 F. Supp. 645, 650 (D.D.C. 1992) (noting that one underlying policy of the Hatch-Waxman Amendments is to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

[17] *See* id. (finding that the purposes of Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala,* 860 F. Supp. 859, 866-67 (D.D.C. 1994) (finding that the BE waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act," including making safe and affordable generic drugs available).

[18] *Fisons*, 860 F. Supp. at 865 (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot*, 955 F.2d 1103, 1106 (D.C. Cir. 1993)); *see also Fisons,* 860 F. Supp. at 866-67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995).

[19] *See* FDA's web page on Product-Specific Guidances for Generic Drug Development, available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

available to the public is explaind in the guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010).

FDA announced the availability of a product specific BE draft guidance entitled "Draft Guidance on Lanreotide Acetate" (Draft PSG) on July 23, 2014.[20] The Draft PSG recommends two options – in vitro or in vivo studies – for demonstrating BE for lanreotide acetate injection. Under Option 1, a waiver of in vivo BE study will be granted if the test product demonstrates equivalent molecular, structural, and thermodynamic properties as the reference listed product.[21] Option 1 further recommends that lanreotide conformation, nanotube structure, and thermo stability at different temperature and dilution should be characterized. In addition, acceptable comparative in vitro drug release-rate tests of lanreotide acetate from the proposed generic and reference product should be demonstrated. The comparative study should be conducted with at least three lots of both reference and test products. Option 2 is a single-dose, randomized, parallel *in vivo* PK study with the highest strength of lanreotide acetate (EQ 120 mg base) in healthy subjects (males and females, general population). The analyte to measure is lanreotide in plasma and BE is based on the 90% confidence interval (CI) of the geometric mean ratio of the PK profile parameters, C_{max} and area under the curve (AUC).

II. DISCUSSION

In the Petition, you request that FDA take several actions with respect to ANDAs that reference Somatuline Depot. First, you assert that an in vitro approach is insufficient to determine BE and that FDA must require applicants to conduct an in vivo BE study.[22] Second, you assert that FDA must require ANDAs to include comparative impurity analysis on samples of the finished drug product (post sterilization) and control for peptide-related impurities to the same extent and level as the RLD. Third, you request that FDA require ANDAs to include comparative performance testing of the drug delivery device to ensure it is equivalently functional and useable as the RLD. Fourth, you request that FDA require ANDA applicants to conduct a partial Area Under the Curve (pAUC) analysis as part of the in vivo BE study to ensure the generic is bioequivalent to the RLD over the required dosing interval. Finally, you request that FDA reissue the Draft PSG based on the actions taken in response to the Petition. We address each of these requests below.

A. The Petition Fails to Show That In Vivo Evidence of BE Is Required

1. *A Generic Lanreotide Acetate for Subcutaneous Injection Product May Demonstrate BE Without In Vivo Testing*

[20] 79 FR 42800 (July 23, 2014). The Draft PSG is available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Lanreotide%20Acetate_draft_Subcutaneous%20injection_RLD%2022074_RC07-14.pdf.

[21] *See* Draft PSG. FDA reviews the adequacy of the evidence submitted in support of a waiver when reviewing a specific ANDA. This is because the significance and variation of each property/measurement is product-, attribute-, and technique-specific. We have not limited the Draft PSG to particular studies or acceptance criteria because knowledge, techniques, and analyses may evolve or improve. Moreover, by not setting specific acceptance criteria, we encourage ANDA applicants to match the physicochemical properties of the reference product as closely as possible and provide detailed scientific justification supporting their proposed product.

[22] Petition at 2, 3, 8-19.

The Petition states that in vitro testing is insufficient to establish BE for a proposed generic lanreotide acetate injection product referencing Somatuline Depot. To support your request that FDA require applicants to conduct an in vivo BE study, you state that in vivo bioavailability is not self-evident because "Somatuline Depot is not a normal solution and is not an immediate-release drug product" and that "unlike typical solutions for parenteral administration, [Somatuline Depot] exhibits a high structural organization and thermodynamic complexity."[23] You also state that bioavailability is not self-evident based on the drug product itself and the physical and chemical parameters described in the Draft PSG are insufficient to reach a conclusion on bioequivalence.[24]

We disagree that in vitro testing is insufficient to establish BE for a proposed generic lanreotide acetate injection product referencing Somatuline Depot. FDA has wide discretion to determine the type of evidence required to demonstrate BE, which may include in vivo or in vitro testing, or both.[25] For the reasons explained below, FDA believes that the in vitro approach recommended as Option 1 in the Draft PSG is adequate to establish BE for this product.

Option 1 recommended in the Draft PSG does not assume that BE of a generic product is self-evident based solely on formulation sameness. Instead, Option 1 is based on the fact that the rate and extent of lanreotide acetate bioavailability is governed by the fundamental physicochemical properties of the drug product. Although the lanreotide peptide nanotube structure is complex, the peptide assembly is a spontaneous thermodynamic driven process, based on the synergistic effect of various intermolecular non-covalent interactions, which can take place and be maintained in water. Lanreotide acetate spontaneously self-assembles in water through the association of beta sheets driven by amphiphilicity and a systematic aromatic-aliphatic side chain segregation, which leads to the formation of nanotubular assembly with 2D hexagonal packing. In vitro experiments have shown that the nanotube assembly is completely reversible.[26,27,28] Accordingly, Option 1 recommends comparative in vitro studies to show a proposed generic product with the same composition (Qualitatively - Q1 and Quantitatively - Q2 the same) has the same self-assembled thermodynamically stable structure and thus can be expected to have comparable drug release as the reference listed product. To that end, Option 1 recommends characterization of lanreotide conformation, nanotube structure, and thermostability at different temperature and dilution. Results of all comparative in vitro studies are then evaluated, as a whole, to support the conclusion that the proposed generic product is BE to the RLD product.

Thus, while we generally agree lanreotide acetate is not a conventional injectable solution for immediate release for which BE may be self-evident based on Q1/Q2 sameness alone, the in vitro approach described under Option 1 in the Draft PSG is appropriate and adequate to

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[23] Petition at 11.
[24] Petition at 11-13.
[25] *See* 21 CFR 320.24(a); see also section I.B.2 above (discussing FDA's discretion to determine how the BE requirement is met).
[26] Biomimetic organization: Octapeptide self-assembly into nanotubes of viral capsid-like dimension, C. Valery, etc., 2003. www.pnas.org_cgi_doi_10.1073_pnas.1730609100..
[27] Self-Association Process of a Peptide in Solution: From b-Sheet Filaments to Large Embedded Nanotubes. C. Valery, etc., Biophysical Journal, 2004, Volume 86: 2484-2501.
[28] Lanreotide Depot: An antineoplastic treatment of carcinoid or neuroendocrine tumors, EM Wolin, etc, J Gastrointest Canc (2016) 47: 366-374, DOI 10.1007/s12029-016-9866-9.

demonstrate BE of a proposed generic product to Somatuline Depot. This is because the formulation of Somatuline Depot is thermodynamically driven such that two products similarly formulated will result in the same final physicochemical state. Therefore, the recommended in vitro tests in Option 1 of the Draft PSG (e.g., characterization of the nanotube structure and thermo stability at different temperatures and dilutions) are to confirm that the generic product reaches a similar self-assembled thermodynamically stable structure as the reference listed product. Because the depot properties are the result of a thermodynamic controlled process, these tests are sufficient to assess critical formulation characteristics that govern the performance of the product without the need for conducting in vivo BE studies.

2. Lanreotide Release Is a Function of the Composition and Properties of the As-Supplied Product

The Petition claims that because "the physical form of the drug product that governs the rate and extent of release of lanreotide into systemic circulation is different from the structure that exists in vitro," a waiver of in vivo bioequivalence cannot be applied to proposed generics of Somatuline Depot.[29] According to the Petition, because the "properties that ultimately regulate drug release do not arise until after the depot has been formed in vivo" and "in vitro testing has not been shown to be predictive of in vivo drug release from the depot," generic versions of Somatuline Depot require an in vivo study to demonstrate BE and that a biowaiver for such a product is inappropriate.[30]

We agree with your description of Somatuline Depot as a supersaturated solution of lanreotide acetate, water for injection, and acetic acid (for pH adjustment) that forms a depot in vivo. However, assessing the depot formed in vivo is not the only approach for demonstrating BE of this product. While we agree that the supersaturated solution before injection is not the final physical form of the depot after injection, only the physical state of the lanreotide acetate changes after injection, as a result of the spontaneous, thermodynamically-driven non-covalent self-assembly process described above. The depot is formed from the interaction of lanreotide acetate with the local physiological environment, and there are no other inactive ingredients that control drug release; instead, the mechanism of drug release is, as recognized by the Petition, "most likely passive diffusion of lanreotide from the solid surface of the depot."[31] That is, although the drug product as supplied is not in the same physical form as the final depot that is responsible for drug release in vivo, it is reasonable to expect that the drug product performance in vivo is determined by the composition and properties of the as-supplied product. Indeed, the Petition does not provide evidence that the depot would form differently for products demonstrating the same physicochemical properties. As a result, bioequivalence of this product is supported if a proposed generic product has the same formulation composition, demonstrates a comparable thermodynamically stable structure, and has a comparable in vitro peptide release as the reference listed product. Given the drug release process is mainly governed by the physicochemical characteristics of the lanreotide acetate in the product, it is reasonable to expect that the in vitro physicochemical properties of the test product reflect in vivo behavior, and thus that a test product with equivalent molecular, structural, and thermodynamic properties as the

[29] Petition at 14, 15.
[30] Petition at 2, 8-13.
[31] Petition at 25; *see also* id. at 9.

reference product can be expected to exhibit equivalent in vivo drug release. Additionally, the recommended in vitro drug release testing involves a phase inversion (precipitation) similar to the depot forming process that occurs upon subcutaneous administration.

3. Demonstrated IVIVC or a Predictive IVRT Is Not Required to Support a BE Determination

The Petition asserts that a demonstrated in vitro in vivo correlation (IVIVC) or validation of a biorelevant in vitro release test (IVRT) is an "essential step before it would be appropriate to recommend a biowaiver" for a proposed generic referencing Somatuline Depot, and that BE must therefore be demonstrated by conducting an appropriate comparative in vivo study.[32] The Petition further states that "Ipsen lacks biorelevant IVRT or IVIVC," and without "an otherwise validated biorelevant IVRT, it would be a matter of speculation as to whether a proposed generic with seemingly equivalent parameters to Somatuline Depot would result in equivalent in vivo release over the entire dosing interval."[33]

An IVIVC is not required for the Agency to recommend an in vitro approach to establish BE to Somatuline Depot. IVIVCs are generally used when an applicant seeks to establish the in vitro drug release test (i.e., dissolution test) – and only the in vitro drug release test – as a surrogate for human BE studies in situations where such studies are normally required (e.g., post-approval changes in the manufacturing of a drug product).[34] Here, the in vitro testing option is not intended to reflect a clinical correlation between the in vitro test identified in the Draft PSG and an in vivo BE test. In the case of lanreotide acetate injection, the in vitro drug release test is not the only evidence the Agency proposes to rely on for evidence of BE. Additionally, as discussed above, under Option 1 of the Draft PSG the proposed in vitro testing is combined with a requirement of formulation and end-product sameness such that the bioavailability of the proposed generic product and the RLD are expected to be the same. Taken together, we believe that the results of the drug release test and the physicochemical property characterization, when similar to the results for the reference listed product, provide a reasonable assurance that a proposed generic product's in vivo performance will be similar to that of the RLD, even if there is no established IVIVC for the individual in vitro criteria.

Based on the mechanism of drug release, which the Petition recognizes is most likely a passive diffusion process mainly governed by characteristics of the lanreotide acetate,[35] confirming that a proposed generic product has a comparable in vitro lanreotide release rate to that of the reference listed product can help ensure that the proposed generic product will perform in a comparable manner. IVRT, in the absence of an established IVIVC, is still a useful in vitro performance test to support BE and to be included as part of a quality control strategy. Based on the mechanism of drug release (passive diffusion), it is possible to develop an IVRT method that can assess potential formulation or product differences based on the same fundamental

[32] Petition at 15-17.
[33] Petition at 17.
[34] *See* guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (Sept. 1997), available at http://www.fda.gov/downloads/ucm070239.pdf.
[35] Petition at 25.

mechanism of release. This, along with the other recommended tests in the Draft PSG, can support a BE determination without the need to establish an IVIVC.

4. The Petition Fails to Show That An In Vivo Study with PK Endpoints Is Required

The Petition states that in vivo BE studies for generic versions of Somatuline Depot are needed because the "intrinsic variables that determine formation of the depot and the properties of the depot that ultimately determine drug release are evident only after the product has been administered."[36] The Petition further states that Ipsen's studies (nonclinical findings and clinical PK data) indicate that the size, shape, and surface area of the depot are factors that influence the rate and extent of release.[37] Additionally, the Petition notes that "FDA's bioequivalence recommendations for implants and pellets all call for *in vivo* testing."[38]

The Petition includes a comparison of $C_{min,ss}$ (minimum concentration at the steady-state) ratios that it asserts "show that the shape of the depot is a factor governing the rate and extent and release."[39] However, the Petition does not adequately establish that $C_{min,ss}$ is a surrogate to estimate the size, shape, and surface area of the depot formed following injection of lanreotide acetate, and thus we do not find the $C_{min,ss}$ data persuasive as to the Petition's assertion that an in vivo study is required to establish BE of lanreotide acetate products.

We acknowledge that in theory, the size, shape, and surface area of the depot following subcutaneous administration are potential factors that can affect the PK of lanreotide. However, we do not agree that a generic product with the same formulation composition, and comparable thermodynamically stable structure and delivery device properties could nonetheless exhibit significant differences in formed depot size, shape, and surface area to the reference product. Regarding your claims regarding the impact of the shape and surface area of the depot on drug release in vivo, while we generally agree that these properties of the depot affect drug release, we note that they largely depend on the injection process which can be affected by formulation properties, including viscosity, and the injection device and process. As detailed in section II.C below, review of a ANDA referencing Somatuline Depot would include assessment of the device constituent.

Additionally, your investigation through analysis of human PK data is insufficient to determine the impact of these factors. As cited in the Petition, a study of three formulations with different lanreotide concentrations produced similar PK lanreotide exposure in vivo.[40] That is, the cited study suggests the in vivo PK study was not able to distinguish the three formulations despite their different lanreotide content, a difference that can be reliably detected by in vitro studies. Thus, the PK study cited in the Petition does not support the Petition's claim that in vivo PK is the most appropriate approach for establishing BE. Given the high inter-subject PK variability, as noted in the Somatuline Depot labeling,[41] an in vivo parallel study with PK endpoints would

[36] Petition at 17-19.
[37] Petition at 17, 18.
[38] Petition at 19.
[39] Petition at 18.
[40] *See* Petition at 16, n. 56.
[41] Somatuline Depot labeling (Feb. 2023), Section 12.3 Pharmacokinetics, "Single-dose linearity was demonstrated with respect to AUC and Cmax, and showed high inter-subject variability."

likely require a large number of subjects to sufficiently power a study to be sensitive to small differences in product formulation. Therefore, although also a viable BE approach, Option 2 recommended in the Draft PSG (an in vivo study with PK endpoints) is not considered to be a necessarily more accurate, sensitive, and reproducible method than the tests recommended in Option 1 for detecting potential difference(s) between a Q1/Q2 formulated generic product and the reference product.

We acknowledge that FDA typically recommends that the bioequivalence of most implants and pellets be assessed using in vivo studies. However, the references you cite[42] are not pertinent to Somatuline Depot because the cited products are generally formulated with excipients that control drug release, which is not the case with Somatuline Depot. Therefore, different scientific considerations apply to these other products and FDA's recommendations for them do not apply to Somatuline Depot.

In summary, based on the Agency's current knowledge and understanding of Somatuline Depot, we believe that the recommended Q1/Q2 and other formulation considerations and in vitro testing recommended under Option 1 are adequate to establish BE for proposed generic lanreotide acetate injection drug products that reference Somatuline Depot (NDA 022074) as an RLD. Thus, we disagree that FDA must require ANDAs referencing Somatuline Depot to conduct an in vivo BE study. The adequacy of the data and information submitted to establish BE in a particular ANDA submission is an issue to be determined during review of the submission.

B. Qualification of the Impurity Profile

You request that FDA require ANDA applicants of Somatuline Depot to conduct comparative impurity analysis on the finished drug product subsequent to sterilization and control for peptide-related impurities to the same extent and same level as the RLD.[43] You state that Somatuline Depot "is a peptide-based product that is assembled into a complex supramolecular structure known to generate degradation products as an impurity" and that the structures you've identified "pose potential aggregation and immunogenicity risk and therefore must be controlled and limited."[44] You state that the "impurity issue for Somatuline Depot is exacerbated by the terminal sterilization process."[45] Thus, you assert that "comparative physicochemical analysis must be based on the finished dosage form subsequent to sterilization and extrusion from the delivery device."[46]

In general, we agree that the testing and control of drug product impurities should be done on the finished drug product, which would generally mean post-sterilization for a product whose

[42] Petition at 9. The Petition references the Draft Guidance on Goserelin Acetate (Zoladex), Draft Guidance on Leuprolide Acetate (Viadur), Draft Guidance on Testosterone (Testopel), and Draft Guidance on Octreotide Acetate (Sandostatin LAR) in notes 28-29 of the Petition.
[43] Petition at 3, 4, 19, 20.
[44] Petition at 19.
[45] Petition at 20.
[46] Id.

manufacturing process includes a terminal sterilization step.[47] Generally, an applicant needs to assess and qualify impurities and specifications should be set by the applicant to ensure product safety.[48] ANDA applicants may propose their unique combinations of manufacturing process, formulation, and container closure system. This may result in an impurity profile which may differ from that of the RLD based on the applicant's own development studies.[49] Additional data may be requested in situations where the impurity profile indicates the presence of a new impurity, or a higher level of an impurity in the proposed generic product relative to the RLD. FDA will assess the impurity profile of a proposed generic and determine whether it is acceptable at the time the application is reviewed.

C. Comparative Performance Testing of Delivery Device System

The Petition requests that FDA require ANDA applicants to conduct comparative performance testing on the delivery device system to ensure equivalent performance and usability.[50] The Petition also states that "[f]or purposes of generic drug-device combination products, the ANDA applicant must demonstrate that its proposed device components are functionally equivalent to the innovator's device in all relevant aspects, including its design, performance, labeling, use and handling."[51] The Petition further states that "at a minimum, FDA must require a comparative assessment of the critical design and performance attributes of a proposed generic to Somatuline Depot."[52]

In general, as detailed in the draft guidance entitled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Draft Comparative Analyses Guidance),[53] FDA recommends that ANDA applicants conduct comparative analyses of the user interface[54] between a generic combination product and its RLD.

As discussed above in section I.B.1, a drug-device combination product classified as therapeutically equivalent to the RLD can be expected to have the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.[55] To inform its evaluation of therapeutic equivalence for a generic drug-device combination product, FDA recommends ANDA applicants provide an analysis of the user interface for the generic drug-device combination product when compared to the

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[47] Additionally, you request that an impurity assessment of a proposed generic of Somatuline Depot must be conducted post-extrusion from the delivery device (Petition at 20). While we agree that an impurities assessment generally should be performed on the finished drug product, you have not provided data in the Petition to show new impurities are formed during extrusion from the delivery device.

[48] *See* guidance for industry *ANDAs: Impurities in Drug Products* (Nov. 2010) available at https://www.fda.gov/files/drugs/published/ANDAs--Impurities-in-Drug-Products.pdf.

[49] *See MAPP 5017.2 Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance* available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp; see also guidance for industry *ANDAs: Impurities in Drug Products* (Nov. 2010) at 4 available at https://www.fda.gov/files/drugs/published/ANDAs--Impurities-in-Drug-Products.pdf.

[50] Petition at 20-23.

[51] Petition at 21.

[52] Petition at 23.

[53] Draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (recommended Jan. 2017) (Draft Comparative Analyses Guidance) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[54] User interface refers to all components of the combination product with which a user interacts. This includes the delivery device constituent part of the combination product and any associated controls, displays, as well as product labeling and packaging. *See* Draft Comparative Analyses Guidance.

[55] 21 CFR 314.3.

RLD to identify any potential differences.[56] The focus of the comparative analyses is to examine the overall external operating principles of the delivery device and the features that the users (in this case, healthcare providers) rely on to safely and effectively perform tasks that are critical to the use of the product. The three types of comparative analyses described in the Draft Comparative Analyses Guidance are a physical comparison of the delivery device constituent parts, a labeling comparison, and a comparative task analysis. These analyses aid in determining whether the generic product can be substituted for the RLD under the conditions specified in the labeling without additional training prior to the use of the generic combination product. However, this does not mean that a generic must be identical to the RLD in all design aspects. As noted in the Draft Comparative Analyses Guidance, FDA may accept differences in design if they are adequately analyzed, are scientifically justified, and do not preclude approval in an ANDA.[57] The Draft Comparative Analyses Guidance states that, in some instances in which differences exist, certain additional information and/or data relating to the user interface of the proposed generic combination product, such as data from a comparative use human factors study, may be appropriate to evaluate the proposed generic combination product in an ANDA.[58] Generally, an evaluation of such information is intended to confirm that the differences in device and labeling between the generic combination product and the RLD are acceptable and that the proposed generic combination product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in labeling.[59]

The Petition states that generic versions of Somatuline Depot "must include an assessment of the device constituent of the drug-device combination product to ensure equivalent performance and usability" because of the "extreme viscosity of the formulation and the difficulty of injecting the drug product."[60] The Petition also states that numerous human factor studies and extensive performance testing were conducted to ensure that the delivery device maintained its critical design attributes and essential performance characteristics.[61] Based on Ipsen's work on the drug delivery system, the Petition requests that "at a minimum, FDA must require a comparative assessment of the critical design and performance attributes of a proposed generic to Somatuline Depot" and that "FDA must refrain from approving any ANDA that does not include data, including human factors data, demonstrating that the proposed delivery device is equivalent to the RLD."[62]

As noted above, we generally agree that "an assessment of the device constituent" must be included. In the case of drug-device combination products, FDA generally requires applicants to submit data on device design and performance compared against that of RLD. This may include comparative in vitro performance testing data to support the drug delivery device performance, human factors data, and combination product quality.

It is recommended that ANDA applicants referencing Somatuline Depot, like other ANDA applicants for drug-device combination products, adhere to the recommendations outlined in Draft Comparative Analyses Guidance as described above. We do not agree, however, that

[56] *See* Draft Comparative Analyses Guidance at 5-8.
[57] *See* Draft Comparative Analyses Guidance at 5.
[58] Id. at 3.
[59] Id.
[60] Petition at 20.
[61] Petition at 22, 23.
[62] Petition at 23.

comparative use human factors data must be required in any ANDA referencing Somatuline Depot to demonstrate the proposed delivery device and its user interface is equivalent to the RLD. As described in the Draft Comparative Analyses Guidance, FDA recommends that ANDA applicants conduct comparative analyses of the user interface between a generic drug-device combination product and its RLD. The comparative analyses aid in the identification and assessment of design differences in the user interface of the generic drug-device combination product when compared to its RLD. Some differences identified in the comparative analyses may be acceptable if they do not significantly impact a critical task or result in impermissible differences in labeling and in these situations, no additional data would be requested for these differences. For design differences that may impact a critical task, FDA may request additional data, such as comparative use human factors data, from an ANDA applicant. [63] Based on the additional data, FDA may or may not determine that the design difference(s) between the user interface of the proposed generic drug-device combination product and the RLD is acceptable for a proposed generic drug-device combination product. However, whether this type of comparative use human factors data would be requested depends on the differences identified and the potential risk any difference has on the clinical effect or safety profile of the generic product when compared to the RLD under the conditions specified in labeling, and is thus evaluated on a case-by-case basis. Accordingly, while we agree to the extent that ANDAs referencing Somatuline Depot should include analyses of the proposed product user interface, as compared to that of Somatuline Depot, we disagree that all ANDAs referencing Somatuline Depot should be required to include comparative use human factors data.

D. Partial Area Under the Curve Analysis

In addition to requesting that FDA require in vivo BE evidence generally, the Petition asserts that a pAUC analysis must be required as part of an in vivo BE study to ensure that a proposed generic has the same rate and extent of release as Somatuline Depot over the course of the dosing interval.[64] As discussed above, we believe that an in vivo study is not required to demonstrate BE; an ANDA applicant can choose to demonstrate BE by following the in vitro approach recommended as Option 1 in the Draft PSG. We also disagree that an ANDA applicant opting to demonstrate BE by following Option 2 in the Draft PSG, the in vivo approach, should be required to conduct a pAUC analysis. In general, pAUC may be used for certain modified-release products in which the different phases of release correspond to a clinical effect. The beginning and ending times for the pAUC should relate to a clinically relevant measure.[65] In the case of Somatuline Depot, a pAUC would not provide additional information compared to our

[63] The comparative use human factors data referenced here are intended to confirm that the differences in device and labeling between the generic combination product and RLD are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. FDA does not consider the comparative use human factors data to be the results of clinical investigations intended to demonstrate the safety or effectiveness of the proposed generic combination product. *See* draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (recommended Jan 2017).

[64] Petition at 23.

[65] *See* draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

current recommendation and as explained below, our evaluation of the information you provided in support of your request to require pAUC analysis as part of an in vivo BE study does not change our current thinking.

In asserting that an analysis of pAUC metrics must be required as part of an in vivo BE study, the Petition points to draft PSGs for Leuprolide Acetate/Norethindrone acetate (Lupaneta pack), Triptorelin pamoate (Trelstar), Leuprolide acetate (Leupron Depot), Octreotide acetate (Sandostatin LAR) and Naltrexone (Vivitrol) as examples of depot products for which FDA recommended single-dose in vivo BE studies with pAUC.[66] We acknowledge that a pAUC measurement is recommended in the PSGs you have cited. As aforementioned, pAUC is recommended when the selected pAUC would provide additional information on assessing potential formulation difference to make sure the relevant clinical outcomes are met. It is noted that the products in the PSGs cited by the Petition are polymer-based formulations whose sustained release feature for maintaining effective drug concentration towards the end of dosing interval can be significantly affected by formulation characteristics. Considering a proposed generic product can have different manufacturing process than the RLD which may lead to differences in formulation characteristics, pAUC is recommended for such products to ensure the drug release mechanism is comparable between a proposed test product and the reference product and help justify potential acceptable differences in formulation characteristics.

However, Somatuline Depot is fundamentally different in terms of drug release mechanisms and formulation composition from the products in the referenced draft PSGs. Unlike the examples you have cited, Somatuline Depot's formulation is thermodynamically stable and does not involve functional polymeric excipients or other inactive ingredients that may affect drug release from the depot. Additionally, lanreotide release from the depot is driven by passive diffusion throughout the dosing interval (28 days). The rate and extent of drug release from Somatuline Depot is driven by the solubility of lanreotide whereas drug release from the cited polymer-based long acting drugs is controlled by polymer degradation in combination with active ingredient diffusion. Accordingly, FDA's recommendations for establishing BE for these products you cited above are not pertinent to Somatuline Depot.

The Petition states that the "release of lanreotide from Somatuline Depot is both multiphasic and sustained," and that there is a "limited burst release on the first day … followed by a sustained release to give a long terminal half-life of 23-30 days."[67] As discussed above, although release of lanreotide from Somatuline Depot is sustained in vivo, this feature is a result of lanreotide solubility, as reflected in the drug product's labeling.[68] Sustained in vivo release behavior driven by passive diffusion does not by itself require pAUC without appropriate justification from either the formulation aspect or the clinical aspect. The Petition does not provide persuasive evidence to describe what additional information a pAUC analysis could provide in the case of Somatuline Depot.

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[66] Id.

[67] Petition at 24.

[68] Somatuline Depot labeling, 12.3 Pharmacokinetics which states that"[t]he most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption to the bloodstream."

The Petition asserts "[f]or long-acting injectable depot products, *in vivo* PK studies with partial AUC analysis are increasingly recognized as the most accurate, sensitive, and reproducible form of study."[69] Based on this, the Petition states that "FDA must require that ANDAs include a single-dose PK study and demonstrate bioequivalence based upon the geometric mean of the rations of the test drug to the RLD for a partial AUC time point designed to ensure maintenance of release across the dosing interval"[70] Although we generally agree that a pAUC and the time point design are important when designing clinical bioequivalence studies for long-acting products that contain drug release-controlling inactive ingredient(s), such as the products you cited as examples, we do not agree that in this case an in vivo PK study with pAUC analysis would be the most accurate, sensitive, and reproducible study for a proposed generic as discussed in the paragraph above. You cited a study showing that three formulations with different lanreotide concentrations gave rise to similar PK lanreotide exposure in vivo.[71] While such differences in lanreotide concentrations and their impact on related formulation characteristics can be well characterized in vitro, the study cited failed to demonstrate the ability of in vivo PK study for detecting differences in lanreotide concentration. Thus, the information you provided does not support your statement that an in vivo PK study is the most accurate, sensitive, and reproducible form of BE study compared to an in vitro characterization and drug release studies. Additionally, the Petition does not adequately identify what additional information the requested pAUC could provide for evaluating a proposed Q1/Q2 generic lanreotide acetate formulation beyond what is provided by C_{max} and AUC.

In sum, for the reasons discussed above, we disagree that FDA must require ANDA sponsors to conduct a pAUC analysis as part of an in vivo BE study.

E. Draft PSG

The Petition requests that FDA reissue the Draft PSG "based on the actions taken in response to [the Petition]."[72] We note that, for the reasons described above, we deny the Petition requests to require in vivo BE evidence and to require pAUC analysis as part of an in vivo BE approach. To the extent you are requesting that FDA revise the Draft PSG in accordance with those or any other Petition requests, that request is denied. We note that the Draft PSG contains nonbinding recommendations and an ANDA applicant may use an alternative approach as long as it satisfies the requirements of the applicable statutory provisions and regulations.[73] If you have any additional comments about the recommendations in the Draft PSG, such comments should be submitted to the Draft PSG docket (Docket No. FDA-2007-D-0369-0547).

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[69] Petition at 26.

[70] Id. The Petition also states that, as an alternative to requiring a single-dose PK study with pAUC analysis, "a repeated dose would be required to demonstrate bioequivalence at steady state" "due to the importance of the minimum concentration at Day 28 and the accumulation ratio of 2.7 between single and repeated dose" (Petition at 27). We disagree that a multiple-dose BE study should be required in the absence of pAUC analysis, as single-dose studies in healthy subjects are generally more sensitive than steady-state studies conducted in a patient population in assessing differences in the release of the drug substance from the drug product into systemic circulation. *See* draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[71] Petition at 16 n.56.

[72] Petition at 4.

[73] *See* 21 CFR 10.115(d)(2). The acceptability of a given alternative approach will be evaluated during the review of a specific ANDA.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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