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ELECTRONICALLY

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Commissioner of Food and Drugs
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

PETITION FOR RECONSIDERATION

Docket No. FDA-2019-P-4830

Ipsen SA (Ipsen) respectfully submits this petition for reconsideration pursuant to 21 CFR 10.33, among other provisions of law, to request the Commissioner of Food and Drugs to reconsider the May 21, 2024, decision in Docket No. FDA-2019-P-4830 denying Ipsen's citizen petition requesting the Food and Drug Administration (FDA) require *in vivo* bioequivalence studies for proposed generic versions of Somatuline® Depot (lanreotide acetate), a designated reference listed drug (RLD) for abbreviated new drug applications (ANDAs).

In denying Ipsen's petition, FDA did not adequately consider several critical issues, underscored by the generic product approved concurrent with FDA's denial. FDA's approach to bioequivalence for generic versions of Somatuline® Depot emphasized the importance of matching the formulation of the RLD and demonstrating similarity with respect to physicochemical characteristics. FDA concluded that it is "reasonable to expect" that similarly formulated lanreotide acetate products will perform the same inside the body. In so finding, the agency failed to consider the complexity of the formulation, and mischaracterized the transformation of the product *in vivo* as merely physical. Most critically, FDA's conclusion rests on the generic product being compositionally the same as the RLD in terms of the concentration of its active and inactive ingredients. The ANDA that FDA approved concurrent with the petition response is not compositionally the same as the RLD. This is evident from the product labeling. Under those conditions, the assumptions underlying FDA's approach to bioequivalence as relied on in the petition response, do not apply.

The grounds for reconsideration are particularly strong given the potential risk to patients. Somatuline® Depot is approved for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option, and for improving progression-free survival in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that have spread or cannot be removed by surgery and treatment of

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carcinoid syndrome. The safety and efficacy findings for Somatuline® Depot are based on its demonstrated ability to maintain sustained lanreotide serum levels over a multi-week dosing interval. FDA must ensure that a proposed generic has the same rate and extent of release over the course of the dosing interval. A single intramuscular injection of Somatuline® Depot will reside at the site of deposition for weeks, releasing lanreotide in a controlled manner over the entire course. An ANDA product that has not been shown to release lanreotide into systemic circulation at the same rate and to the same extent as the Somatuline® Depot over the course of the dosing interval is not therapeutically equivalent, and presents an unnecessary risk to patients. This impacts not only new patients initiating therapy, but also patients who are switched from Somatuline® Depot to a generic version after achieving an optimal maintenance dose. These patients are unlikely to recognize when a generic product fails to maintain therapeutic levels and may be at risk of their condition deteriorating irreversibly.

DECISION INVOLVED

On October 15, 2019, Ipsen submitted a citizen petition, pursuant to 21 CFR 10.30, requesting that FDA require an *in vivo* bioequivalence study to ensure that a proposed generic to Somatuline® Depot provides the same rate of release of lanreotide, to the same extent, over the entirety of the Somatuline® Depot dosing interval, which extends to four weeks or longer for a single administration.[1] Ipsen also requested that FDA take several steps to build into the bioequivalence study the necessary rigor to ensure that a proposed generic, in fact, maintains therapeutic levels of lanreotide to the end of the multi-week dosing interval. FDA denied the petition on May 21, 2024. Concurrent with the denial of the petition, FDA approved an ANDA for a generic lanreotide acetate product.

ACTION REQUESTED

Ipsen respectfully requests that the Commissioner reconsider its May 21, 2024, decision denying the request for the following actions to be taken:

(1) Require ANDAs that reference Somatuline® Depot to demonstrate bioequivalence by conducting an appropriate comparative *in vivo* study capable of demonstrating that a proposed generic drug product causes lanreotide acetate to release into

[1] Ipsen, Citizen Petition, Docket No. ID FDA-2019-P-4830-0001 (Oct. 15, 2019) ("petition" or "citizen petition").

systemic circulation at the same rate and to the same extent as the RLD over the course of the dosing interval.[2,3]

STATEMENT OF GROUNDS

I. BACKGROUND

A. Somatuline® Depot

Somatuline® Depot (lanreotide acetate) is approved for extended-release dosing (4-weeks or longer) for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.[4] It is also approved for improving progression-free survival in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that have spread or cannot be removed by surgery and treatment of carcinoid syndrome.[5]

Somatuline® Depot is administered as a viscous, gel-like injectable formulation that contains a supersaturated solution of lanreotide acetate and water in a semisolid phase. The final supersaturated solution contains 24.6% w/w of lanreotide, which is more than 10 times the normal solubility of lanreotide in water. This degree of lanreotide density is a function of the highly complex supramolecular liquid-crystalline structure, composed of proteinaceous assemblies of nanotubes.

After it is administered through deep subcutaneous injection, Somatuline® Depot forms a depot under the skin. The subsequently formed depot is the entity that is responsible for controlling the release of lanreotide over a multi-week interval. The depot that forms when Somatuline® Depot is administered differs structurally from the form of the drug as it exists outside the body. This is because, upon injection, the drug undergoes transformation from a gel-like substance to a solid or semisolid precipitate, forming an *in situ* slow-releasing structure that interfaces with the surrounding tissue. The properties of the supramolecular structure that can be measured outside the body and that correlate to or that influence the

[2] Because FDA denied the petition in part on the basis that *in vivo* bioequivalence testing was unnecessary for a proposed generic that qualified for a "biowaiver," Ipsen is asking in a concurrently submitted petition for stay of action that FDA reconsider the approval of InvaGen's ANDA 21719 for failing to demonstrate bioequivalence. The InvaGen products have different formulations than Somatuline® Depot and do not appear to be quantitatively the same as Somatuline® Depot in formulation – a presumption built into FDA's decision to waive *in vivo* bioequivalence. Among other things, InvaGen's products contain a different concentration of active ingredient and, therefore, should not be considered bioequivalent to Somatuline® Depot.

[3] Ipsen's citizen petition included additional requests, including requiring ANDA sponsors to conduct partial Area Under the Curve (pAUC) analysis as part of the *in vivo* bioequivalence study to ensure the generic is bioequivalent to the RLD over the required dosing interval; and for FDA to re-issue the *Lanreotide Draft Bioequivalence Guidance* based on the actions taken in response to the petition. Upon FDA granting this petition for reconsideration, Ipsen reserves its right to comment on any reissued guidance to the extent further comment may be required.

[4] *See* Somatuline® Depot Package Insert (PI) at Section 1.1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022074s024lbl.pdf (Tab A).

[5] *Id.* at Section 1.2 (Tab A).

dynamics of precipitation and *in situ* development of the depot are not known. The nanotube structure, solid-state chemistry, shape, and surface area of the depot each may influence the rate and extent of bioavailability of lanreotide *in vivo*.

B. InvaGen ANDA

Ipsen's citizen petition requested, among other things, that FDA require ANDAs to demonstrate bioequivalence by conducting an appropriate comparative *in vivo* study capable of demonstrating that a proposed generic drug product causes lanreotide acetate to release into systemic circulation at the same rate and to the same extent as the Somatuline® Depot over the course of the dosing interval. FDA denied the petition and on the same day, approved InvaGen's ANDA No. 217193 for lanreotide acetate. To the best of Ipsen's knowledge, InvaGen did not conduct an *in vivo* bioequivalence study in support of its ANDA.[6] The ANDA is for EQ 60 mg base / 0.2 mL, EQ 90 mg base / 0.3 mL, EQ 120 mg base / 0.5 mL lanreotide injection for subcutaneous use, packaged in single-dose, prefilled syringes, referencing Somatuline® Depot as the RLD.

C. Legal and Regulatory Framework

The Federal Food, Drug and Cosmetic Act (FDCA) requires proposed generic drug products to be "bioequivalent" to a drug product previously approved under section 505(b) (the RLD).[7] A drug product is considered bioequivalent to the RLD if "the rate and extent of absorption of the drug do[es] not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .."[8] For a drug product that is intended to deliver the active ingredient systemically within the body, those parameters can be measured directly in the bloodstream.[9]

By regulation, FDA has established that pharmacokinetic studies are preferred as the most accurate and dependable method of establishing bioequivalence for a systemically acting drug.[10] As FDA has

[6] InvaGen received approval for the same formulations of lanreotide acetate under a 505(b)(2) application based on a waiver of *in vivo* bioequivalence requirements, and it seems likely that FDA used the same approach with respect to the ANDA. *See* NDA 215395 (approved on Dec.17, 2021). A 505(b)(2) application was submitted instead of an ANDA because of differences in delivery device between the InvaGen products and Somatuline® Depot. Ipsen raised objections to the 505(b)(2) application in response to a citizen petition by InvaGen seeking a therapeutic equivalence rating. *See* Docket No. FDA-2022-P-0329. InvaGen ultimately withdrew the petition.

[7] 21 USC 355(j)(2)(A).

[8] 21 USC 355(j)(8)(B)(i).

[9] *See* 21 CFR 320.24(b)(1)(i).

[10] Under governing regulations, "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." 21 CFR 320.24(a). The regulation instructs applicants to use "the most accurate, sensitive, and reproducible approach available" among those listed by FDA. These methods include, in "descending order of accuracy, sensitivity, and reproducibility," *in vivo* pharmacokinetic studies, *in vivo* pharmacodynamic effect studies, clinical endpoint studies, and *in vitro* studies. 21 CFR 320.24(a), (b).

observed, "the statutory definition of BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety, emphasizes the use of pharmacokinetic endpoints in an accessible biological matrix, such as blood, plasma, and/or serum, to indicate release of the drug substance from the drug product into the systemic circulation."[11] Indeed, FDA has expressly observed that it "does not recommend *in vitro* approaches for drug products that are intended to be systemically absorbed." [12]

For certain drug products, FDA regulations permit a biowaiver where the "*in vivo* bioavailability or bioequivalence of the drug product may be self-evident."[13] For example, if the drug product "[i]s a parenteral solution intended solely for administration by injection [and] [c]ontains the same active and inactive ingredients in the same concentration" as an approved reference drug, FDA may waive the usual requirement for *in vivo* bioequivalence.[14]

Although lanreotide acetate is a systemically absorbed, extended release product, FDA's 2014 draft product-specific bioequivalence guidance for lanreotide acetate (injectable; subcutaneous) (*Lanreotide Draft Bioequivalence Guidance*) would allow an ANDA sponsor to seek a "biowaiver" in lieu of performing an *in vivo* study to show bioequivalence. For proposed products that are quantitatively (Q1) and qualitatively (Q2) the same as Somatuline® Depot and present satisfactory dissolution data, this *in vitro*-only option requires a demonstration of "equivalent molecular, structural, and thermodynamic properties," including an examination of conformation, nanotube structure, stability at different temperature and dilution. It also requires a comparative study based on an "*in vitro* drug-release rate test" in at least three lots of test and reference product.

D. Ipsen's Citizen Petition

The citizen petition focused on four main points. First, unlike typical immediate-release solutions for parenteral administration (for which FDA routinely waives the need for *in vivo* bioequivalence studies), Somatuline® Depot is an extended-release product with a high degree of structural organization and thermodynamic complexity.[15] Lanreotide is an octapeptide that forms macromolecular nanotubes (protein fibrils) in the finished dosage form.[16] The finished dosage form, manufactured under highly

[11] Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Dec. 2013) at 3, https://www.fda.gov/media/87219/download.

[12] *Id.* at 8. *See also* 21 CFR 320.24(b)(1)(i).

[13] 21 CFR 320.22(b).

[14] *Id.*

[15] *See generally* Petition at Section II.A.1 (citing Somatuline® Depot PI at Section 2 (describing the drug in the final dosage form as semisolid)); *see generally* NDA Module 3.2.P.2 2.3 (on file at FDA).

[16] *See* Valéry, C., *et al.*, Self-Association Process of a Peptide in Solution: From *β*-Sheet Filaments to Large Embedded Nanotubes. BIOPHYS J (Apr. 2004) 86(4):2484-501 (Docket No. ID FDA-2019-P-4830-0010, Tab 8 in original submission). The structural organization of lanreotide into nanotubes begins with the primary folding of the lanreotide peptide into β-hairpin structures formed by intramolecular disulfide bridging and hydrogen bonds. The monomeric components then form noncovalent antiparallel dimers, stabilized by hydrophobic effects and electrostatic repulsion between the β-hairpins. The

controlled conditions, is a supersaturated solution with dense networks of nanotubes in a highly structured liquid crystal. The structure and complexity of the nanotube is comparable to biological tubular assemblies such as the capsid of the tobacco mosaic virus.[17] The structure of the final, gel-like, semisolid drug product is complex, as are the sequence of steps in the peptide self-assembly process that generate this structure.

Second, when injected, this complex substance transforms into a solid or semisolid depot *in situ*.[18] The *in situ* depot determines the rate and extent of release of lanreotide slowly from the depot over multi-week intervals. Thus, the depot is the relevant form of the drug for purposes of assessing the rate and extent of drug release. While the *Lanreotide Draft Bioequivalence Guidance* proposed that a generic version of Somatuline® Depot should have "equivalent molecular, structural, and thermodynamic properties," including an examination of conformation, nanotube structure, stability at different temperature and dilution, and comparative *in vitro* release tests, Ipsen remains unaware of any scientific effort that has shown how these factors specifically correlate or relate to *in vivo* release. It is assumed and stated in the package insert for Somatuline®Depot that the most likely mechanism of release is diffusion from the precipitated drug. However, the structure of the solid depot itself, and how it evolves and decays over time, has not been characterized and remains, to Ipsen's understanding, largely unknown. Physiochemical comparability between two lanreotide depot products that are Q1/Q2 the same may be shown, but there remains a substantial gap – in terms of evidence and scientific understanding – between identification of the *in vitro* physicochemical properties of Somatuline® Depot and the extent to which each property determines (if at all) the rate and extent of release of lanreotide from the depot *in situ*.

Third, there are no known "acceptable comparative *in vitro* drug release-rate tests"[19] of the finished product that would correlate with rate and extent of *in vivo* drug release (IVIVC).[20] Design of a biorelevant *in vitro* release test (IVRT) for Somatuline® Depot poses significant technical challenges. The composition of the aqueous medium into which Somatuline® Depot is placed, in an *in vitro* test, would be expected to have a strong influence on maintenance of high order structure and, consequentially, the observed duration of the release profile. Complete dissolution in pure water occurs extremely rapidly. The rate of dissolution can be slowed by different buffer compositions, but it remains difficult to model

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dimers in turn are assembled into β-sheet filaments, formed by the stacking of dimers and consolidated by hydrogen bond networks. When a critical concentration is reached, the filaments gather together into bundles and begin to form long, flat ribbons. The ribbons then curl into open helical structures that eventually close to form a hollow nanotube. As the concentration is further increased, the nanotubes undergo additional structural transformation. It has been hypothesized that when the reaction volume is entirely occupied by the hexagonal packing of the hollow nanotubes, a further increase in peptide concentration causes the formation of new nanotubes from the filaments dissolved in the water either inside or outside the existing nanotubes. The embedded nanotubes exhibit the same molecular and supramolecular organizations as the individual monodisperse nanotubes that form at lower peptide concentration, but with higher thermodynamic stability.

[17] *See* Valéry, C., *et al.*, Biomimetic organization: Octapeptide self-assembly into nanotubes of viral capsid-like dimension. PROC NATL ACAD SCI USA (Sept. 2003) 100(18):10258-62 (Docket No. ID FDA-2019-P-4830-0009, Tab 7 in original submission).

[18] *See generally* Citizen Petition at Section II.A.2.

[19] *Lanreotide Draft Bioequivalence Guidance* at 1.

[20] *See generally* Citizen Petition at Section II.A.3.

the physiological conditions that give rise to the depot. Without a demonstrated IVIVC, or 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* drug release over the entire dosing interval.

Finally, the petition presented pharmacokinetic data showing that size, shape and surface area of the depot are important factors. The shape of the depot is a product both of the physicochemical properties of Somatuline® Depot – *i.e.*, the complex supramolecular structure and its physiological transformation *in situ* – as well as intrinsic variables that can influence disposition, such as the design of the delivery device, the force and duration of injection, and the progressive disruption and transformation of the liquid crystal superstructure and reformation as a solid or semisolid depot. The effects of these variables manifest themselves post-administration and support the need for *in vivo* bioequivalence studies.

E. FDA's Petition Response

FDA agreed with the petition that Somatuline® Depot is not a conventional parenteral product, that the nanotube structure in the finished dosage form is complex, and that bioequivalence is not self-evident.[21] However, FDA stated that "[a]lthough 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 . . . ."[22] According to FDA, this allowed it to conclude as a matter of "fact that the rate and extent of lanreotide acetate bioavailability is governed by the fundamental physicochemical properties of the drug product."[23] Thus, "because the formulation of Somatuline Depot is thermodynamically driven . . . two products similarly formulated will result in the same final physiochemical state."[24]

FDA similarly agreed with the petition that Somatuline® Depot undergoes a transformation *in situ*.[25] However, the agency found that "only the physical state of the lanreotide acetate changes after injection . . . ."[26] According to the agency, this is "a result of the spontaneous, thermodynamically-driven non-covalent self-assembly" of the nanotubes.[27] According to the agency, because only the physical form changes, "it is reasonable to expect that the drug product performance in vivo is determined by the

[21] FDA, Response Letter from FDA CDER to Ipsen, Docket No. ID FDA-2019-P-4830-0016 (May 21, 2024) (posted May 23, 2024) at 7.

[22] *Id.*

[23] *Id.*

[24] *Id.* at 8.

[25] *Id.* ("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.").

[26] Petition Response at 8.

[27] *Id.*

composition and properties of the as-supplied product."[28] FDA also found that because "the drug release process is mainly governed by physicochemical characteristics of the lanreotide acetate product, it is reasonable to expect that the in vitro physicochemical properties of the test product reflect in vivo behavior . . . ."[29]

FDA disagreed that IVIVC or a biorelevant IVRT were necessary, concluding it was not necessary that the IVRT correlate to clinical outcomes or model *in vivo* condition.[30] According to FDA, the purpose of the IVRT was merely to compare physical performance as part of the overall *in vitro* characterization.[31] FDA agreed that the size, shape and surface area of the depot are potentially important, but found that these factors were generally a function of the delivery device and properties of the formulation, including viscosity.[32] FDA agreed that most solid implants and depots require *in vivo* bioequivalence, but distinguishes these products as "generally formulated with excipients that control drug release, which is not the case with Somatuline Depot."[33]

F. Standard for Reconsideration

The Commissioner may grant a petition for reconsideration if the Commissioner determines the petition to be in the public interest and in the interest of justice.[34] In addition, the Commissioner will grant a petition for reconsideration if the Commissioner determines that the following apply:

- The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
- The petitioner's position is not frivolous and is being pursued in good faith.
- The petitioner has demonstrated sound public policy grounds supporting reconsideration.
- Reconsideration is not outweighed by public health or other public interests.[35]

[28] *Id.*

[29] *Id.*

[30] *Id.* at 9.

[31] Petition Response at 9.

[32] *Id.* at 10.

[33] *Id.* at 11.

[34] 21 CFR 10.33(d).

[35] *Id.*

II. ARGUMENT

The agency agreed that "lanreotide acetate is not a conventional injectable solution"[36] and that "the supersaturated solution before injection is not the final physical form of the depot after injection."[37] The agency also acknowledged that "the size, shape, and surface area of the depot following subcutaneous administration are potential factors that can affect the PK of lanreotide."[38] The agency nonetheless concluded that its *in vitro*-only approach was adequate for demonstrating bioequivalence. Despite acknowledging these points and generally finding that the nanotube structure is highly complex and undergoes further physical changes inside the body, the agency failed to adequately consider whether a generic version of Somatuline® Depot may show a difference in either the rate or extent of lanreotide release *in vivo* over the course of the month-long dosing interval.

To reach this position, FDA relied on speculation, assumptions, and a misapplied theoretical construct that fails to adequately describe the complexity of Somatuline® Depot. FDA recognized but failed to adequately consider the complexity and role of the nanotubes themselves, the extent that they may act as functional polymers, and the degree to which different manufacturers' products may vary. The agency assumes that Somatuline® Depot is a fundamentally uncomplex, closed system that may be described using simple textbook physics. This enabled FDA to set aside substantial uncertainties and to conclude that on the balance of probabilities, taken "as a whole," it is "reasonable to expect" that the proposed generic product will perform the same as Somatuline® Depot inside the body.[39]

The agency's reliance on fundamental laws of thermodynamics as the basis for concluding that two lanreotide acetate products will behave the same is wholly dependent on those two products being identical in all parameters relevant to the operation of thermodynamic principles. The physicochemical structural comparison FDA relies on to support the *in vitro* option in the *Lanreotide Draft Bioequivalence Guidance* allows the agency to conclude only that the two products are *similar*.[40] According to the agency, "the recommended in vitro tests . . . are to confirm that the generic product reaches a *similar* self-assembled thermodynamically stable structure."[41] It assumes that a generic product exhibiting a similar structure outside the body will transform similarly inside the body to form a depot with the same structure, consistency, shape – and that this structure will evolve and erode inside the body to maintain therapeutic levels for the entire month-long dosing interval. The agency did not support this supposition with any data. Instead, it posits that two similar systems will behave similarly because they are thermodynamically-driven. But this is not so. Ipsen agrees that nanotube formation is thermodynamically-driven, but thermodynamics is not a synonym for simplicity or predictability. Moreover, the premise of FDA's

[36] Petition Response at 7.

[37] *Id.* at 8.

[38] *Id.* at 10.

[39] *Id.* at 7.

[40] *Id.* at 9 (emphasis added).

[41] Petition Response at 8.

approach – and its reliance on thermodynamics as a predictive tool – is that the test product and the RLD are compositionally the same. FDA's reasoning breaks down entirely when the generic product is compositionally different.

A. FDA Failed to Adequately Consider the Complexity of Somatuline® Depot, Relying on Speculation to Fit the Agency's Preconceived *In Vitro* Standard of Bioequivalence

The agency must reconsider its decision denying the petition on the grounds that the agency failed to adequately consider the manufacturer-specific complexity of the nanotubes, and the variables governing formation and functional evolution of the depot inside the body. These variables may include the concentration and viscosity of the supersaturated solution as well as the shape and surface area of the depot as it forms and as it develops. These phenomena are not well understood, and are barely considered by the agency.

Instead, at key analytical junctions in the petition response, FDA relies on speculation. First, FDA agreed that the nanotubes themselves are complex, but concluded that the process of nanotube formation is a simple physical process. Second, again without data, FDA concludes that depot formation is governed solely by straightforward physical transition. In each instance, FDA invokes a selective concept of thermodynamics that fails to describe the potential contingent behavior of the lanreotide product's system. FDA forces Somatuline® Depot into an overly simple, abstract framework, in order to facilitate the *in vitro* option in the *Lanreotide Draft Bioequivalence Guidance*.

1) FDA Failed to Adequately Consider Potential Variation in Nanotube Structure and Function

While FDA agreed with the petition that Somatuline® Depot is not a conventional parenteral product, that the nanotube structure in the finished dosage form is complex, and that bioequivalence is not self-evident, it failed to consider the complexity and potential variability that may occur in nanotube manufacture. FDA erroneously concluded that because the process of nanotube formation is a "thermodynamically controlled process," two different manufacturer's products will necessarily result in the same physicochemical state.

As shown in the petition, the process of nanotube formation involves complex chemistry and principles of protein folding.[42] The process can be contingent on manufacturing conditions.[43] FDA does not present any data to show why it follows that merely because the process of nanotube formation involves "thermodynamics," the system is necessarily impervious to variation. FDA's only support is conclusory speculation, stating "it is reasonable to expect that the drug product performance in vivo is

[42] *See* Citizen Petition at 11-12.

[43] *See id.* at 11.

determined by the composition and properties of the as-supplied product."[44] Precisely why such an expectation is reasonable is unclear from FDA's response, as FDA does not even attempt to address potential sources of variation.

Even if FDA was correct that *in vivo* performance is entirely dictated by the as-supplied product, that conclusion does not mean that *in vivo* behavior is unaffected by variation in the manufacturing process that may influence nanotube structure and depot development, or that the agency's posited *in vitro* tests necessarily capture this variation. The agency concedes that the physicochemical characterization tests prescribed in the *Lanreotide Draft Bioequivalence Guidance* can result only in a finding of similarity, not sameness. FDA does not set forth any standards to ascertain when a proposed generic meets the threshold of similarity or comparability that the agency will accept.[45] Nor does FDA's response provide further assurances that it's biowaiver approach is sufficiently rigorous as applied to establish bioequivalence. Accordingly, the agency simply asserts, without data, that it is "reasonable to expect" that similarly formulated products with similar physiochemical properties will perform the same inside the body.[46]

2) *FDA Failed to Adequately Consider the Process of Depot Formation and Development*

The agency recognizes that the drug product in the finished dosage form undergoes *in situ* transformation, and that the altered state that exists *in vivo* is responsible for bioavailability, but asserts that processes and measurements outside allow an inference that products with similar structure will perform similarly inside the body. Although the mechanism of depot formation and erosion inside the body are not understood, as Ipsen argued in the petition, the agency simply asserts – again without data – that "depot properties are the result of a thermodynamic controlled process."[47] According to the agency, "[b]ecause the depot properties are the result of a thermodynamic controlled process, [in vitro] tests are sufficient to assess critical formulation characteristics that govern the performance of the product without the need for conducting in vivo BE studies."[48]

The structure of the product in the finished dosage form, and the factors that determine formation and release from the depot *in vivo*, are neither clear nor straightforward matters of physics as FDA's response makes them out to be. FDA mischaracterizes the transformation that occurs *in vivo* as simply a physical change. The change that occurs *in vivo* is much more than a simple transformation from solution

[44] *See* Petition Response at 8-9.

[45] The biowaiver option in the *Lanreotide Draft Bioequivalence Guidance* relies in part on "*equivalent* molecular, structural, and thermodynamic properties," but FDA's response shows it expects only that the generic product achieve "similar" results for drug release testing and physiochemical property characteristics, seriously calling into question FDA's meaning of "equivalent" in the draft guidance and whether the *in vitro* approach is sufficient to "provide reasonable assurance that a proposed generic product's performance will be similar to that of the RLD." *Id.* at 9.

[46] *Id. at* 8.

[47] *Id.*

[48] *Id.*

to solid. It involves progressive disruption of the nanotube structure at the surface of the depot. It is assumed and stated in the package insert for Somatuline® Depot that the most likely mechanism of release is diffusion from the precipitated drug at the surface of the depot. However, the structure of the solid depot itself, and how it evolves and decays over time, has not been characterized and remains, to Ipsen's understanding, largely unknown.

In sum, the agency assumes that a generic product exhibiting similarity in structure outside the body will form a similar structure inside the body, although the process of depot formation inside the body is largely unknown. The agency views lanreotide depot formation as a purely physical process based on precipitation, and concludes, without evidence, that the nanotube structures play no role in the body. While the agency agrees that there are other important variables that will govern the rate of release inside the body,[49] it assumes that a generic product with a similar structure outside the body, will similarly transform inside the body to form a depot with the same structure, consistency, shape – and that this structure will evolve and erode inside the body to maintain therapeutic levels for the entire month-long (or longer) dosing interval.[50] This is speculation, not reason.

The fragility of this chain of conjecture is apparent in the agency's own language. By the agency's own terms, the *in vitro* tests allow only an "expectation" of "comparable" release.[51] And this is for products that are "the same," and not merely "similarly formulated" with "similar" structure.[52] Because drug release is "mainly" governed by the physicochemical characteristics, it is "reasonable to expect" that *in vitro* properties reflect *in vivo* behavior,[53] and to therefore conclude that the *in vitro* tests taken "as a whole" are "appropriate and adequate to demonstrate BE."[54] Such speculative and qualified language reflects a significant divergence from the statutory standard, which requires that "the rate and extent of

[49] *See* Petition Response at 10 ("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.").

[50] FDA rejects comparison with other long acting depots with complex polymer formulations, adhering to a doctrinaire view that bioavailability can be a function of rate-controlling excipients only: "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." Petition Response at 15. FDA ignores the possibility that the nanotubes themselves are functional polymers, and are themselves poorly understood in terms of variation and effect on depot formation and controlling release. The nanotube formulation is complex and allows the depot to form and evolve. FDA recognizes but largely ignores the complexity of the nanotubes. It sidesteps the issue, using "thermodynamics" as a talisman.

[51] Petition Response at 7.

[52] *Id.* at 7-8.

[53] *Id.* at 8.

[54] *Id.* at 7-8.

absorption of the drug do not show a significant difference when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions."[55]

B. FDA's Reasoning and Reliance on the Laws of Thermodynamics Do Not Provide Assurance that Lanreotide Acetate Depot Systems Will Perform Equivalently

At key moments in its petition response, FDA invokes "thermodynamics" to explain Somatuline® Depot and justify the *in vitro* approach to bioequivalence. According to FDA, *in vitro* testing "is appropriate and adequate to demonstrate BE of a proposed generic product to Somatuline Depot . . . *because* the formulation of Somatuline Depot is thermodynamically driven."[56] According to FDA, the property of being thermodynamically driven necessarily means "that two products similarly formulated will result in the same final physicochemical state."[57] On this basis, FDA concluded that *because* the process and the product are thermodynamically driven, *in vitro* tests are sufficient to demonstrate bioequivalence. FDA explicitly states: "*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."[58]

Ipsen agrees that the system is thermodynamically driven. There is no question that lanreotide nanotubes are a highly organized complex system that can be described thermodynamically.[59] It is also clear that this system can display high thermodynamic stability depending on the conditions of the system.[60] However, folding and misfolding within this system can be driven by entropic factors.[61] Interactions between large assemblies of molecules operating dynamically in open, non-equilibrium, active, energy-dependent systems can exhibit stochastic and difficult to predict properties.[62]

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[55] 21 USC 355(j)(8)(B).

[56] Petition Response at 7-8 (emphasis added).

[57] *Id.* at 8.

[58] *Id.* (emphasis added).

[59] *See* Valéry, C., *et al.*, Biomimetic organization: Octapeptide self-assembly into nanotubes of viral capsid-like dimension. Proc Natl Acad Sci USA (Sept. 2003) 100(18):10258-62 (Docket No. ID FDA-2019-P-4830-0009, Tab 7 in original submission).

[60] *Id.* Folding of the nanotubes proceeds through a delicate balance of hydration and hydrophilic forces, hydrogen bonds, and other non-covalent forces. FDA agrees that this process is synergistic. On the basis of hydrogen bond lengths, alignment, and conditions, lanreotide may form β-hairpins, β-sheets, bundles, ribbons, open helices, hollow nanotubes, and hexagonal lattices. The hydrogen bonds may be distorted or well-aligned resulting in varying stability. Under the right conditions, a highly organized embedded nanotube structure forms.

[61] Davtyan, A., *et al.*, Stochastic Resonance in Protein Folding Dynamics. CHEMPHYSCHEM (Mar. 2016). 10.1002/cphc.201501125, https://doi.org/10.1002/cphc.201501125 (Tab B); Haque, M.M., *et al.*, Protein Misfolding Thermodynamics. J. PHYS. CHEM. LETT. (May 2019) 10, 10, 2506-2507, https://doi.org/10.1021/acs.jpclett.9b00852 (Tab C).; Sorokina, I., *et al.*, Is Protein Folding a Thermodynamically Unfavorable, Active, Energy-Dependent Process? INT. J. MOL. SCI. (Jan. 2022) 23(1): 521, https://doi.org/10.3390/ijms23010521 (Tab D).

[62] *Id.*

To the extent the predictability of the system, and the predictability of its transformation *in vivo*, is reasonable for products that are truly the same, FDA concedes that the *in vitro* tests are capable only of demonstrating similarity. FDA states plainly that *in vitro* tests are capable only of confirming "that the generic product reaches a *similar* self-assembled thermodynamically stable structure as the reference listed product."[63] The lanreotide nanotubes may vary, the distribution of diameters of the embedded tubes and the resulting viscosity of the formulation may not be the same. FDA's prescribed testing approach does not capture this variation and cannot ensure bioequivalent performance inside the body. Under these conditions, the predictability that FDA relies on breaks down. FDA simply assumes that the "generic product's in vivo performance will be similar . . . ."[64] Even assuming the predictability of the system *in vivo* is reasonable, its key premise is that the test product and the RLD are compositionally the same. As described below, FDA's reasoning must be abandoned entirely when the generic product is compositionally different.

C. FDA's Concurrent Approval of the InvaGen ANDA Product Demonstrates Flaws in Key Assumptions in FDA's Response and the *Lanreotide Draft Bioequivalence Guidance*

In its response, FDA acknowledges that the formulation of lanreotide acetate is critical to depot formation, drug release, and clinical performance. As FDA explained:

> 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…. [W]hile 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.[65]

Accordingly, FDA concludes that the standard described in its response is appropriate because a generic product must, among other things, have a formulation that is qualitatively (Q1) and quantitatively (Q2) the same as Somatuline® Depot. However, FDA does not interpret Q2 sameness to mean that a generic product must have the same ingredient quantities as the RLD. Rather, "OGD interprets [Q2] quantitative sameness to mean a concentration that is within 95-105% of the reference listed drug concentration. That is, sameness . . . does not suggest an exact value, but rather a ***range of values***."[66]

Ipsen respectfully requests that FDA reconsider its decision because FDA has implemented the standard in a manner that allows for the approval of generic products that have significant formulation differences from Somatuline® Depot without supporting *in vivo* bioequivalence studies. On the same day that FDA issued its response, FDA approved InvaGen ANDA No. 217193 for lanreotide

[63] Petition Response at 8.

[64] *Id.* at 9.

[65] *Id.* at 10.

[66] Draft Guidance for Industry: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use at 1 & n. 3 (Apr. 2022), https://www.fda.gov/media/157655/download.

acetate, which used Somatuline® Depot as the RLD.[67] The InvaGen ANDA received approval for the same strengths as Somatuline® Depot.[68] To our knowledge, InvaGen did not conduct an *in vivo* bioequivalence study, but rather received a biowaiver based, in part, on FDA's determination that the InvaGen formulation is Q1/Q2 the same as Somatuline® Depot.

Although the InvaGen ANDA products nominally contain the same ingredients as the Somatuline® Depot products, the InvaGen products do not contain the same amounts of those ingredients.[69] For example, based on information for the 120 mg/0.5 mL product contained in the labeling for Somatuline® Depot and the InvaGen ANDA product, the differences based purely on the weight of an ingredient in each syringe are as follows:[70]

EACH SYRINGE OF THE 120 mg/0.5 mL			
	Somatuline® Depot	**InvaGen**	**InvaGen Difference Compared to Somatuline® Depot**
Lanreotide Acetate	149.4 mg	156.6 mg	+7.2 mg (+4.8%)
Acetic Acid (to adjust pH)	*q.s*	*q.s.*	
Water for Injection	357.8 mg	411.6 mg	+53.8 mg (+15.0%)
Total Weight	510 mg	572.8 mg	+62.8 mg (+12.3%)

These are striking differences in ingredient amounts. The InvaGen product is 12.3% heavier than Somatuline® Depot and contains 15.0% more water and 4.8% more lanreotide acetate. The increased water almost certainly affects viscosity of the InvaGen product, which FDA noted in its response is a critical factor for depot formation and clinical performance. Despite these formulation differences, the *Lanreotide Draft Bioequivalence Guidance* does not even recommend a comparable viscosity test to ensure equivalent depot formation *in vivo* and clinical performance.

[67] FDA's approval of the InvaGen ANDA is not new information under 21 CFR 10.33(b). FDA reviewed the ANDA while the agency was considering the citizen petition and used the framework established in the response to approve the ANDA on the same day the response issued. FDA clearly considered the ANDA as part of its review of the citizen petition issues.

[68] The strengths are EQ 60 mg Base/0.2 mL (EQ 60 mg Base/0.2 mL); EQ 90 mg Base/0.3 mL (EQ 90 mg Base/0.3 mL); and EQ 120 mg Base/0.5 mL (EQ 120 mg Base/0.5 mL).

[69] *See* Lanreotide Acetate Injection (ANDA 217193) Package Insert at Section 11 (available through DailyMed, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2892b4c3-0329-4d29-97ff-3b45283bbab1) (Tab E).

[70] The 120 mg/0.5 mL product is used as an example, but the other InvaGen ANDA products have similar formulation differences compared to the corresponding Somatuline® Depot product.

The differences in weight result in other critical formulation differences. The labeling for Somatuline® Depot and the InvaGen ANDA product state that the syringes contain lanreotide acetate supersaturated bulk solution of 24.6% w/w lanreotide base. Using that percentage, the 120 mg/0.5 mL Somatuline® Depot contains 125.5 mg lanreotide base (.246 x 510 mg) while the comparable InvaGen ANDA product contains 140.9 mg lanreotide base (.246 x 572.8 mg). That is a 12.3% difference in weight of lanreotide base per syringe.

In addition, based on these results, the percent of lanreotide base compared to lanreotide acetate can be determined:

EACH SYRINGE OF THE 120 mg/0.5 mL		
	Somatuline® Depot	**InvaGen**
Lanreotide Base	125.5 mg	140.9 mg
Lanreotide Acetate	149.4 mg	156.6 mg
Base to Acetate %	84.0%	90.0%

Based on the labeling information, the InvaGen product has a 6% higher lanreotide base to acetate percentage, which is significant. Ipsen has over 17 years of experience working with lanreotide acetate manufacturing processes. Based on its experience, 90% base to acetate percentage is extremely difficult to obtain at industrial scale, potentially indicating that the % w/w lanreotide base for the InvaGen products actually may be lower than the 24.6% stated on the InvaGen labeling.

As FDA based its decision on the premise that ANDAs will have the same formulation as Somatuline® Depot, Ipsen requests that FDA reconsider its decision in light of how FDA has implemented the sameness standards in the petition to approve an ANDA with significant formulation differences.

Furthermore, the formulation differences raise the issue of whether the InvaGen products even are Q1/Q2 the same as the Somatuline® Depot products or have the same strengths as the Somatuline® Depot products. FDA has stated that Q2 is the difference (%) of an ingredient in the Test (T) and Reference (R) product (*i.e.*, [(T-R)/Rx100]).[71] Generally, FDA interprets Q2 sameness to mean a concentration that is within 95-105% of the RLD concentration.[72] Under FDA regulations, a generic parenteral solution may qualify for a biowaiver when the generic product "[c]ontains the ***same active and inactive ingredients in the same concentration*** as a drug product that is the subject of an approved full new drug application or abbreviated new drug application."[73] Similarly, strength is defined to include concentration of the drug

[71] *See, e.g.*, Navigating Formulation Assessments: From General Q1/Q2 Inquiries to Supporting Complex Excipient Sameness at slide 5 (Sept. 29, 2020), Formulation Assessments: General Q1/Q2 Inquiries to Supporting Complex Excipient Sameness.

[72] *See* Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards at 8-9 (Rev. 2) (Dec. 2016), https://www.fda.gov/media/86660/download.

[73] 21 CFR 320.22(b)(1) (emphasis added).

substance in mass or units of activity per unit volume or mass (*e.g.*, weight/weight, weight/volume, or units/volume), and drug substance is defined as an active ingredient.[74]

Somatuline® Depot is filled by weight and not volume. Also, the labeling expresses the concentration of lanreotide base in the supersaturated bulk solution as % w/w. Thus, an appropriate comparison for Q2 purposes is concentration difference % w/w. The InvaGen concentration (% w/w) of the active ingredient, lanreotide acetate, is significantly different – ***almost 7% lower*** – than Somatuline® Depot, which likely results in a more dilute and less viscous product. Specifically, Somatuline® Depot products have a concentration of 29.3% (w/w) and the InvaGen products have a lanreotide acetate concentration of 27.3% (w/w), which means the InvaGen concentration is 6.8% lower than Somatuline® Depot. For example, the calculation for the 120 mg/0.5 mL product is as follows:

	Lanreotide Acetate	**Total Weight**	**Concentration (% w/w)***	**Difference (compared to Somatuline® Depot)**
Somatuline® Depot	149.4 mg	510 mg	29.3%	---
InvaGen Lanreotide Injection	156.6 mg	572.8 mg	27.3%	-6.8%

*The w/w % concentration is derived by dividing the amount of lanreotide acetate in a given product by the product's total weight. Based on formulation information in the labeling, calculations for the 60 mg/0.2 mL and 90 mg/0.3 mL products also show that the InvaGen products have the same difference in lanreotide acetate concentration compared to Somatuline® Depot as the 120 mg/0.5 mL product (-6.8%).

Similarly, the InvaGen ANDA product does not seem to meet Q2 standards when % w/v differences are measured. Ipsen does not have insight into the total fill volume of the InvaGen products. However, using the stated volume of 0.5 mL, the InvaGen 120 mg product contains 411.6 mg of water, while Somatuline® Depot contains 357.8 mg. The difference is 53.8 mg of water per each 0.5 mL syringe. That is a 15% mg/mL difference, which significantly exceeds the ± 5% allowable difference for Q2 sameness. If volume is calculated based on water content, then it indicates that the InvaGen products have a larger volume than Somatuline® Depot. For example, if the 120 mg Somatuline® Depot product contains 357.8 mg of water equaling 0.5 mL, then 411.6 mg of water for the InvaGen product equals about 0.6 mL. The larger volume for InvaGen also would mean that its concentration of lanreotide acetate per 0.5 mL would be significantly lower than Somatuline® Depot (-13% w/v).

[74] 21 CFR 314.3; s*ee also* FDA Response to Citizen Petition Docket No. FDA-2020-P-2247 at 4, 12 (Feb. 23, 2024) (confirming that the strength of parenteral products includes concentration and noting that differences in drug substance concentration can affect the quality profile of a drug product, as well as introduce risks for incorrect dosing and medication errors).

Regardless of how the formulation differences are analyzed (amount in mg; % w/w; or % w/v), they are not consistent with the scientific basis of FDA's petition response. That FDA could accommodate such differences within the ANDA framework is highly concerning. It undercuts the conclusion that *in vitro* studies are sufficient to establish bioequivalence. Accordingly, FDA should reconsider its petition response.

CONCLUSION

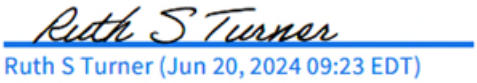
For the reasons described above, FDA's action in denying Ipsen's citizen petition is inconsistent with statutory and regulatory standards governing bioequivalence. Accordingly, Ipsen respectfully requests that FDA grant the action requested in this petition for reconsideration. Specifically, in accordance with 21 CFR 10.33(d), we have demonstrated that important aspects of the administrative record have not been adequately considered, nor has the law been faithfully applied in this case. We have pursued our request for a determination that any generic product under section 505(j) must be tested in human subjects based on sound scientific and statutory grounds, and have done so in good faith, repeatedly expressing our concern via comment on the *Lanreotide Draft Bioequivalence Guidance* and citizen petition about a generic applicant's ability to demonstrate bioequivalence without an *in vivo* study. Public policy is advanced by ensuring that only safe and effective generic drugs are approved for marketing and that agencies abide by their enabling statutes.[75] Given the importance of controlling the rate and extent of lanreotide release in a long-acting injectable, it is critical that generic products form the same *in situ* depot and demonstrate the same *in vivo* drug release profile.

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

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 21, 2024. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of Ipsen. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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