June 20, 2024

ELECTRONICALLY

Robert M. Califf, M.D.
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 STAY OF ACTION

Ipsen SA (Ipsen) respectfully submits this petition pursuant to 21 CFR 10.35, among other provisions of law, to request the Commissioner of Food and Drugs (the Commissioner) stay the May 21, 2024 approval of abbreviated new drug application (ANDA) No. 217193 submitted by InvaGen Pharmaceuticals, Inc. (InvaGen), which references Ipsen's new drug application (NDA) No. 022074 for Somatuline® Depot (lanreotide acetate) parenteral solution as the Reference Listed Drug (RLD).

As described in the InvaGen labeling, InvaGen uses a very different formulation than Somatuline® Depot, particularly with respect to quantities of ingredients. Despite the differences, FDA apparently approved the InvaGen ANDA without requiring *in vivo* bioequivalence data. FDA's approach may be acceptable for the typical parenteral solution where the drug already is uniformly dispersed and ready for absorption. However, as FDA has acknowledged, Somatuline® Depot is not the typical solution.[1] Rather, it is a unique and complex product. The finished product presents the drug in a viscous, gel-like form 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 extremely complex supramolecular nanotube structure in the finished dosage form.

The finished product does not, by any usual metric or paradigm, behave like a typical drug in solution. After administration, the product is designed to form a depot inside a patient's body, and to release lanreotide slowly from the depot over multi-week intervals. Unlike a typical parenteral solution –

[1] 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 ("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") (Tab 1).

IPSEN BIOPHARMACEUTICALS, INC.
One Main Street, 7th Floor
Cambridge, MA 02142
www.ipsenus.com

and indeed unlike most depot products – the depot that forms when Somatuline® Depot is administered is structurally different from the form of the drug as it exists outside the body. This is because, upon injection, the drug undergoes transformation from a semisolid to a solid or partially solid precipitate, forming an *in situ* slow-releasing structure that interfaces with the surrounding tissue. Dissolution and diffusion from the solid surface are thought to govern the rate and extent of drug release prior to systemic absorption, but the structure of the depot inside the body is not well understood.

Ipsen submitted a citizen petition raising the complexities associated with Somatuline® Depot and requesting, among other things, that generic versions of Somatuline® Depot be supported with *in vivo* bioequivalence data to ensure *in vivo* performance equivalent to Somatuline® Depot.[2] *In vivo* data is needed in this situation because the product transforms *in vivo* to form a depot, which is the form of the product critical for drug release, safety, and effectiveness. FDA recently denied the citizen petition.[3] FDA concluded that bioequivalence can be established for a generic product having a formulation that is Q1/Q2 the same as Somatuline® Depot with acceptable *in vitro* release-rate testing and *in vitro* characterization of lanreotide conformation, nanotube structure, and thermostability at different temperature and dilution.

On the same day that FDA denied the citizen petition, FDA also approved InvaGen ANDA No. 217193 applying the framework established in the petition response. FDA apparently concluded that the InvaGen ANDA formulations satisfy Q1/Q2 sameness standards and that supporting *in vitro* data were sufficient to demonstrate bioequivalence.

However, the formulation information contained in the InvaGen labeling shows that the InvaGen ANDA products have very different formulations than Somatuline® Depot, particularly with respect to the quantities of ingredients. These are not nominal differences, but rather significant changes that:

- undercut the scientific basis for allowing the InvaGen ANDA to rely on formulation sameness and *in vitro* data for approval;

- indicate that a waiver of an *in vivo* bioequivalence study (*i.e.*, biowaiver) was not appropriate because the InvaGen ANDA products do not meet the Q2 sameness standard; and

- raise a significant issue as to whether the InvaGen ANDA products are the same strengths as the Somatuline® Depot products.

The public interest in ensuring the InvaGen ANDA product is clinically equivalent to Somatuline® Depot is 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

[2] Ipsen, Citizen Petition, Docket No. ID FDA-2019-P-4830-0001 (Oct. 15, 2019) ("petition" or "citizen petition") (Tab 2) (an unredacted copy is on file with FDA).

[3] *See generally* Petition Response (Tab 1).

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 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.

Accordingly, Ipsen submits this petition for stay to ensure that the InvaGen ANDA products are clinically equivalent to the Somatuline® Depot products.

DECISION INVOLVED

The decision involved is FDA's approval of InvaGen ANDA No. 217193 for lanreotide acetate injection on May 21, 2024.

ACTION REQUESTED

Ipsen respectfully requests that the Commissioner stay the effective date of approval of InvaGen ANDA No. 217193 until the following:

1. The ANDA is supported with *in vivo* bioequivalence data showing that the ANDA products are bioequivalent to the corresponding Somatuline® Depot products;

2. FDA confirms that the different active ingredient quantities contained in the ANDA products and the corresponding Somatuline® Depot products do not result in different strengths for the ANDA products; and

3. FDA responds to the issues raised in Ipsen's petition for reconsideration (Docket No. FDA-2019-P-4830), which is being filed concurrently with this petition for stay.

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]

As described above, 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 extremely complex supramolecular nanotube structure in the finished dosage form. 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 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. Ipsen's Citizen Petition and Petition for Reconsideration

Ipsen submitted a citizen petition on October 15, 2019, requesting, 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 citizen petition on May 21, 2024.

FDA stated that the size, shape and surface area of the depot are potentially important factors affecting drug release, but found that these factors were generally a function of the delivery device and

[4] *See* Somatuline Package Insert (PI) at Section 1.1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022074s024lbl.pdf (Tab 3).

[5] *Id.* at Section 1.2 (Tab 3).

properties of the formulation, such as viscosity.[6] FDA also noted that most solid implants and depots require *in vivo* bioequivalence, but determined that those products are "generally formulated with excipients that control drug release, which is not the case with Somatuline Depot."[7]

FDA concluded that the rate and extent of lanreotide acetate bioavailability is governed by the fundamental physicochemical properties of the drug product.[8] Specifically, FDA stated that "peptide assembly is a spontaneous thermodynamic driven process, based on the synergistic effect of various intermolecular non-covalent interactions . . . ."[9] Thus, "because the formulation of Somatuline Depot is thermodynamically driven . . . two products similarly formulated will result in the same final physiochemical state."[10] Ultimately, FDA concluded that bioequivalence can be demonstrated by showing formulation Q1/Q2 sameness with supporting *in vitro* release-rate and characterization testing.[11]

Ipsen submitted a petition for reconsideration on June 20, 2024, concurrent with submission of this petition for stay.

C. InvaGen ANDA

On the same day that FDA issued its response to the citizen petition, FDA approved InvaGen ANDA No. 217193.[12] The InvaGen ANDA referenced Somatuline® Depot as the RLD and received approval for the same strengths as Somatuline® Depot. The InvaGen labeling shows that the InvaGen products have different quantities of ingredients compared to the corresponding Somatuline® Depot products.[13] Despite the differences, the InvaGen ANDA apparently was not supported with an *in vivo* bioequivalence study. Rather, the ANDA received approval based on formulation sameness to Somatuline® Depot and *in vitro* release-rate and characterization testing, including regarding lanreotide conformation, nanotube structure, and thermostability at different temperature and dilution.[14]

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[6] Petition Response at 10 (Tab 1).

[7] *Id.* at 11 (Tab 1).

[8] *Id.* at 7 (Tab 1).

[9] *Id*. (Tab 1).

[10] *Id.* at 8 (Tab 1).

[11] Petition Response at 7-8 (Tab 1).

[12] *See* Drugs@FDA: ANDA No. 217193, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217193.

[13] The PI for lanreotide acetate injection is available through DailyMed. *See* https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2892b4c3-0329-4d29-97ff-3b45283bbab1 (Tab 4).

[14] 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 December 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.

D. Standard for Petition for Stay

"The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice."[15] Within that context, the Commissioner must grant a stay if the following apply:

- The petitioner will suffer irreparable injury in the absence of a stay.
- The petitioner's case is not frivolous and is being pursued in good faith.
- The petitioner has demonstrated sound public policy grounds supporting the stay.
- Any delay resulting from the stay is not outweighed by public health or other public interests.[16]

II. ARGUMENT

A. Ipsen's Position is not Frivolous and is Being Pursued in Good Faith

The arguments advanced by Ipsen are not frivolous. As described in detail below, the InvaGen ANDA products contain significant formulation differences compared to the corresponding Somatuline® Depot strengths. The formulation differences raise issues related to FDA's scientific basis for granting a biowaiver and also indicate that the InvaGen ANDA should not have received a biowaiver. Furthermore, the different amounts of active ingredient indicate that the InvaGen ANDA products do not have the same strengths as the corresponding Somatuline® Depot products.

Ipsen is pursuing its position in good faith. Ipsen has repeatedly expressed its concern *via* its comment on the product specific bioequivalence guidance (*Lanreotide Draft Bioequivalence Guidance*) and 2019 citizen petition about a generic applicant's ability to demonstrate bioequivalence without conducting an *in vivo* study.

1. 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 . . .

[15] 21 CFR 10.35(e).

[16] *See id.*

because the formulation of Somatuline Depot is thermodynamically driven."[17] According to FDA, the property of being thermodynamically driven necessarily means "that two products similarly formulated will result in the same final physicochemical state."[18] 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."[19]

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.[20] It is also clear that this system can display high thermodynamic stability depending on the conditions of the system.[21] However, folding and misfolding within this system can be driven by entropic factors.[22] Interactions between large assemblies of molecules operating dynamically in open, non-equilibrium, active, energy-dependent systems can exhibit stochastic and difficult to predict properties.[23]

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 in the *Lanreotide Draft Bioequivalence Guidance* 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."[24] 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 . . .

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[17] Petition Response at 7-8 (emphasis added) (Tab 1).

[18] *Id.* at 8 (Tab 1).

[19] *Id.* (emphasis added) (Tab 1).

[20] *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 (Tab 5).

[21] *Id.* (Tab 5). 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.

[22] 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 6); 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 7) 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 8).

[23] *Id.* (Tabs 6-8).

[24] Petition Response at 8 (Tab 1).

."[25] 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.

2. The Formulation Differences Between the InvaGen ANDA Products and Somatuline® Depot Products Preclude a Waiver of *In Vivo* Bioequivalence Requirements

Based on available public information, it is Ipsen's understanding that InvaGen received a biowaiver even though the InvaGen products contain significantly different ingredient amounts than Somatuline® Depot. 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 the syringe are as follows:[26]

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 content almost certainly affects viscosity of the InvaGen product, which FDA noted in its response is a critical factor for depot formation and clinical performance.[27] 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.[28]

[25] *Id.* at 9 (Tab 1).

[26] 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.

[27] *See* Petition Response at 10 (Tab 1).

[28] Draft Product-Specific Bioequivalence Guidance on Lanreotide Acetate (July 2014).

Based on the different ingredient amounts, it does not seem that the InvaGen products meet the Q2 sameness standard needed for a biowaiver. 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."[29] FDA has stated that Q2 is the difference (%) of an ingredient in the Test (T) and Reference (R) product (*i.e.*, [(T-R)/Rx100]).[30] Generally, FDA interprets Q2 sameness to mean a concentration that is within 95-105% of the RLD concentration.[31]

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 by % 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 products do 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

[29] 21 CFR 320.22(b)(1) (emphasis added).

[30] *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.

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

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).

These changes are not merely cosmetic, but rather affect key product parameters. 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 S 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.

3. The Different Amounts of Active Ingredient Indicate that the InvaGen ANDA Products Do Not Have the Same Strengths as Somatuline® Depot

FDA regulations define "strength" in relevant part as "the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes . . . [t]he total quantity of drug substance in mass or units of activity in a dosage unit or container closure . . . and/or, as applicable . . . [t]he concentration of the drug substance in mass or units of activity per unit volume or mass."[32] Further, FDA has explained that "the strength of a parenteral drug product is determined by both . . . the total quantity

[32] 21 CFR 314.3(b).

of drug substance in a container closure and the concentration of the drug substance."[33] FDA confirmed its approach in a recent petition response, in which FDA noted that differences in either the concentration or the total drug content of a liquid parenteral drug product can introduce risks for incorrect dosing and medication errors.[34] FDA also stated that "differences in drug substance concentration also can affect the quality profile of a drug product."[35]

Furthermore, although the *Orange Book* expresses the strength of lanreotide acetate products in terms of lanreotide base, the relevant comparison is the amount and concentration of active ingredient, which is lanreotide acetate.[36] As FDA explained, "[i]t should be emphasized that the proposed definition of strength refers to the amount of the drug substance (active ingredient), and not the amount of the active moiety, in the drug product."[37]

i. The InvaGen Products have a Lower Concentration of Active Ingredient than Somatuline® Depot

The InvaGen products and Somatuline® Depot are identified as having the same strengths for purposes of the way strength is expressed in the *Orange Book*. However, as explained above, the ingredient information provided in the InvaGen labeling indicates that the InvaGen products have a significantly lower concentration of lanreotide acetate (the active ingredient) and therefore different strengths than the corresponding Somatuline® Depot products. Specifically, the labeling discloses that the InvaGen products have nearly a 7% lower concentration of active ingredient than Somatuline® Depot.

[33] 80 FR 6802, 6816 (Feb. 6, 2015) (Tab 9) (excerpt); *see also Orange Book* Preface at xvii (explaining that the strength of a parenteral drug product generally includes "both the total drug content and the concentration of drug substance in a container approved by FDA").

[34] Final Response Letter from FDA CDER to Boehringer Ingelheim USA Corporation, Docket No. FDA-2020-P-2247 at 4 (Feb. 23, 2024) (Tab 10).

[35] *Id*. at 12 (Tab 10).

[36] *See, e.g.*, 21 CFR 314.3(b) (defining "pharmaceutical equivalents" by reference to "the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety" and defining "strength" by reference to quantity or concentration of the "drug substance," which is itself defined as the active ingredient). Although the products' strengths are expressed as EQ mg base/mL, this does not negate that the active ingredient is lanreotide acetate. *Orange Book* Preface at viii ("[C]ertain drug products included in the Orange Book include a designation of "EQ" next to their expression of strength. This "EQ" designation generally is used in connection with salt drug products to indicate that the strength of such drug product is being expressed in terms of the equivalent strength of the active moiety (e.g., "EQ 200MG BASE"), rather than in terms of the strength of the active ingredient.").

[37] 80 FR 6802, 6816 (Feb. 6, 2015) (Tab 9) (excerpt).

ii. Similarly, Based on the Labeling of the Products, the InvaGen Products Do Not Seem to Contain or Deliver Identical Amounts of Lanreotide Acetate

For prefilled syringes, "where residual volume may vary," pharmaceutical equivalence is determined in part by whether the products "deliver identical amounts of the active drug ingredient."[38] Here, too, the labeling provides the relevant information. As the previous discussion shows, the InvaGen products have been formulated to have a different concentration of lanreotide acetate than Somatuline® Depot (27.3% v. 29.3%). At the same time, the InvaGen products and Somatuline® Depot are labeled as containing the same concentration of lanreotide base, 24.6%. Per the labeling, both products deliver the same total amount of lanreotide base.[39] If, as the labeling indicates, the concentrations of lanreotide base are the same for the InvaGen products and Somatuline® Depot but the concentrations of lanreotide acetate are different, then delivering the same amount of lanreotide base will necessarily require delivering a different amount of lanreotide acetate. Based on this information, it does not seem that the InvaGen products deliver the identical amount of active ingredient, lanreotide acetate, as the corresponding presentations of Somatuline® Depot.

B. Ipsen Will Suffer Irreparable Injury in the Absence of a Stay

The launch and/or continued marketing of a generic lanreotide acetate product by InvaGen will cause irreparable injury to Ipsen. The launch of a first generic is known to significantly diminish both the revenue and market share of the reference listed drug.[40] Courts have recognized that financial loss caused by price erosion and diminished market due to generic entry can constitute irreparable harm.[41] If InvaGen's lanreotide acetate product is allowed to enter and/or remain in the market, Ipsen will undoubtedly suffer irreparable injury.

C. Public Policy Supports a Stay Until the ANDA Product is Shown to be Bioequivalent to Somatuline® Depot

Sound public policy requires that the approval be stayed unless and until bioequivalence for the ANDA product is demonstrated *via* an *in vivo* bioequivalence study. There is a public interest in agency compliance with its governing statute. Equally critical is the public interest in ensuring that generic products have the same therapeutic effect as the RLD. The public interest is particularly strong for diseases where the demonstrated treatment effect relies on sustained drug exposure, as is the case with Somatuline® Depot.

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[38] 21 CFR 314.3(b).

[39] *Id.*

[40] *See, e.g.,* Balto DA, *Pharmaceutical Patent Settlements: The Antitrust Risks*, 55 FOOD & DRUG L.J. 321, 325-326 (2000) (Tab 11).

[41] *See, e.g.,* Memorandum Opinion, *Bayer Healthcare LLC v. FDA*, No. 13-487, at *13 (D.D.C. April 26, 2013) (collecting cases).

As explained in Ipsen's citizen petition, Somatuline® Depot is approved for the long-term treatment of acromegaly patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option, for the treatment of adult patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and for the treatment of carcinoid syndrome.[42]

Acromegaly is a rare hormonal disorder that results from a production of excess growth hormone (GH) by the pituitary gland.[43] Increased serum concentrations of GH cause the pathology of acromegaly by acting directly on target tissues and indirectly stimulating excess secretion of insulin-like growth factor (IGF-1). Specifically, GH binds to the GH receptor expressed primarily in the liver and cartilage, and induces the synthesis of IGF-1 from the liver, which mediates GH effects and stimulates the growth of bones and other tissues. GH and IGF-1 receptor are also located on cardiac myocytes. The clinical signs and symptoms of the disease include enlargement of acral bones, soft-tissue swelling, arthralgia, prognathism, organomegaly, sleep apnea, glucose intolerance or diabetes, hypertension and cardiac failure.[44]

The precise mechanism of action of lanreotide in treating GEP-NETs and carcinoid syndrome is less established. GEP-NETs are a rare type of tumor that form in the pancreas or in other parts of the gastrointestinal tract, including the stomach, small intestine, colon, rectum, and appendix. These tumors usually form in cells that secrete hormones, and the tumors produce extra amounts of hormones and other substances believed to cause symptoms of disease, including carcinoid syndrome. Carcinoid syndrome is associated with increased endogenous secretion of serotonin and kallikrein. In most patients, there is an increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a degradation product of serotonin. Patients with carcinoid syndrome treated with Somatuline® Depot 120 mg every 4 weeks had reduced levels of urinary 5-HIAA compared with placebo.[45]

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. An ANDA product that has not been shown to release lanreotide into systemic circulation at the same rate and to the same extent as Somatuline® Depot over the course of the dosing interval, cannot be guaranteed to be clinically equivalent to Somatuline® Depot, and presents an unnecessary risk to patients.

The InvaGen product may pose a risk to acromegalic patients of insufficient hormonal control and thus disease complications. The primary pharmacodynamic effect of lanreotide is a reduction of GH levels

[42] We note that carcinoid syndrome was carved out of the labeling for the InvaGen product.

[43] *See* NDA 22-074, Medical Review (October 27, 2006) at 1, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022074s000_MedR_P1.pdf (Tab 12) (excerpt).

[44] *Id.* (Tab 12).

[45] Somatuline PI at Section 12 (Tab 3).

enabling normalization of levels in acromegalic patients.[46] By producing a reduction of GH, IGF-1 levels are also decreased, which permits the normalization of levels in acromegalic patients and can lead to reversal of disease complications.[47] The response to achieve this effect is dose-dependent.[48] Titration to a stable maintenance dose with Somatuline® Depot is a long and careful process. The dose, dosing interval and dosage regimen were designed to ensure that serum concentrations of lanreotide approach and are maintained within the median values sufficient to provide hormonal control of acromegaly based on clinical data and modeling.[49] As explained in Ipsen's citizen petition, the minimum concentration at day 28 of the dosing interval is a key parameter to ensure hormonal control of acromegaly.[50] There is a serious question whether the InvaGen product is able to achieve hormonal control of acromegaly, because, as explained above, there is a serious question whether InvaGen is bioequivalent to Somatuline® Depot based on the information available for the InvaGen product and its material differences from Somatuline® Depot. Even if patients are monitored, and treatment of acromegaly can be adjusted according to GH and/or IGF-1 levels, titration to a stable maintenance dose is a long process, and once stabilized, hormonal control can be sensitive to fluctuations. A generic drug that exhibits different *in vivo* rate and extent of release not only impacts whether the initial dose selected would reach lanreotide serum levels sufficient to approach hormonal control after the first injection, but also, more importantly, could impact patients who would be switched from Somatuline® Depot to a generic version after achieving an optimal maintenance dose.

Similarly, the InvaGen product may pose a risk to patients with GEP-NETs if the product fails to achieve comparable levels of lanreotide serum levels to Somatuline® Depot. GEP-NETs are a serious form of cancer, and patients being treated with lanreotide have either failed treatment with surgery and/or radiotherapy, or for whom such options are unavailable. Achieving the same lanreotide release to the same extent over the course of the dosing interval is critical to ensure that the InvaGen product achieves the same level of tumor suppression as was shown for Somatuline® Depot. That disease progression due to ineffective dosing with the InvaGen product may not be readily apparent to patients and healthcare providers poses an unacceptable risk.

D. The Delay Resulting From a Stay is not Outweighed by Public Health or Other Public Interests

As noted above, the public interest in ensuring that generic products have the same therapeutic effect as the RLD supports a stay in this situation. There are no countervailing public health or other public interests sufficient to outweigh those issues. Ipsen recognizes that there is a public interest in the availability of lower cost generics. That general public interest in the widespread availability of generics, however, is premised on the generic having satisfied the statutory and regulatory requirements intended

[46] *See* NDA 22-074, Medical Review at 39 (Tab 13) (excerpt).

[47] Petition at 25 (Tab 2).

[48] *See* NDA 22-074, Medical Review at 39 (Tab 13) (excerpt).

[49] To correlate lanreotide levels with GH reductions, Ipsen developed a maximum effect on GH concentration model to describe the relationship between lanreotide and GH concentrations. *Id.* at 40 (Tab 13) (excerpt).

[50] Petition at 25 (Tab 2).

to ensure it can be expected to have the same clinical effect and safety profile as the listed drug. Here, where InvaGen's lanreotide product has not been shown to be bioequivalent to Somatuline® Depot – a fundamental feature of an ANDA product – the interests of patients who may be dispensed a generic lanreotide product weigh in favor of a stay.

Accordingly, any delay necessary for InvaGen to conduct *in vivo* testing or for FDA to address the concerns raised in this stay of action is not outweighed by any public health or other public interests.

CONCLUSION

For all these reasons, the Commissioner should stay the effective date of approval of InvaGen ANDA No. 217193 as described in this petition for stay.

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,

Ruth S Turner
Ruth S Turner (Jun 20, 2024 09:20 EDT)

Ruth Turner
Vice President, Regulatory Affairs, North America
Ipsen Biopharmaceuticals, Inc
One Main Street (Unit 700)
Cambridge, MA 02142
+1 908-616-7228

Enclosures

Cc: David Fox, Hogan Lovells, David.fox@hoganlovells.com
Jason Conaty, Hogan Lovells, Jason.conaty@hoganlovells.com