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

CITIZEN PETITION

Ipsen SA (Ipsen) submits this citizen petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law.¹ Ipsen is the sponsor of Somatuline® Depot (lanreotide acetate) for subcutaneous injection, the reference listed drug (RLD) for generic versions of Somatuline Depot under section 505(j) of the Food, Drug, and Cosmetic Act (FDCA). By this petition, we respectfully request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application (ANDA) for a proposed generic version of Somatuline Depot. In particular, we request a determination that any proposed generic must be tested *in vivo* to assure that it is bioequivalent to Somatuline Depot. Based on Ipsen's many years of experience with the product, and our understanding of the variables that may impact the product, Ipsen does not believe patient safety and patient benefit can be assured if a generic version of Somatuline Depot were to be approved without testing in human subjects.

SUMMARY

Somatuline Depot is approved for extended-release dosing (4-weeks or longer) for several rare diseases, including 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.² It is also the first and only FDA-approved drug 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.³

¹ This citizen petition contains trade secrets and confidential commercial information, as defined by 21 CFR 20.61, that are protected from public disclosure under the Freedom of Information Act (FOIA) and the Trade Secrets Act. A redacted version of this petition has been submitted for public dissemination. The non-redacted version is for the agency's internal and confidential use. It is not for public dissemination either by posting on www.regulations.gov or through the Division of Dockets Management. Pursuant to 21 CFR 61(e), if FDA receives a request for further public disclosure and determines that disclosure may be required, Ipsen requests pre-disclosure notification and the opportunity to object to any disclosure.

² See Somatuline Package Insert, Section 1.1, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022074s024lbl.pdf (Package Insert).

³ *Id.* at Section 1.2.

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 258 mg/mL (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 liquid-crystalline structure. The finished product does not, by any usual metric or paradigm, behave like a typical drug in solution.

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 – 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 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.

Importantly, *in vitro* testing has not been shown to be predictive of *in vivo* drug release from the depot. The properties that ultimately regulate drug release do not arise until after the depot has been formed *in vivo*. This is unlike other drugs products in solution, where the bioavailability of the drug may be apparent in the solution itself. Despite years of research and Ipsen's experience with the product, the precise factors that determine formation of the depot and release of the drug from the depot have not been determined.

Accordingly, a potential generic to Somatuline Depot poses unique bioequivalence challenges. The form of the drug that controls and determines drug release is not the same as the form of the drug as it exists in the finished product. Moreover, the form of the drug that controls and determines drug release does not arise until after the product has been administered to the patient deep within the subcutaneous tissue. Ipsen's data also indicate that the size, shape and surface area of the depot formed *in vivo* may be relevant to the overall rate and extent of drug release. Thus, to assess the rate and extent of drug release from a lanreotide depot product, particularly one manufactured by a different sponsor using different materials and different techniques to achieve the supersaturated solution, and in light of the current state of scientific knowledge about lanreotide acetate and other similar drugs, one must conduct an *in vivo* study. Ipsen is unaware of any *in vitro* methods or models that can predict the rate and extent of *in vivo* drug release based on the pre-administration form of the drug.

In a July 2014 draft recommendation for demonstrating bioequivalence for lanreotide acetate (injectable; subcutaneous) (*Lanreotide Draft Guidance*), FDA offered two options: "Option 1" would allow generic sponsors to seek a "biowaiver" in lieu of conducting an *in vivo* study, provided certain physicochemical comparisons could be made and an "acceptable comparative *in vitro* drug release-rate" study could be conducted. "Option 2" recommends a single-dose *in vivo* pharmacokinetic study in normal healthy volunteers.

As discussed in Section II.A below, the extent to which the molecular structure and physical characteristics observed *in vitro* accurately predict formation of the depot, or accurately predict the rate and extent of drug release from the depot, has not been determined. Additionally, Ipsen's experience with the product shows that *in vitro* release-rate testing of the drug product (the supersaturated solution in the finished dosage form) is not predictive of *in vivo* drug release, which is dependent on a transformation of the product that occurs only after deep subcutaneous injection. Ipsen is also not aware of any "acceptable comparative *in vitro* drug release-rate tests"⁴ of the finished product that are either biorelevant, in terms of modeling the solid-state *in situ* depot, or that would correlate with rate and extent of *in vivo* drug release. Nor is Ipsen aware of evidence showing how the specific physical and chemical parameters described in the *Draft Guidance* might be used to safely and reliably predict *in vivo* drug release, particularly for a version of the product manufactured anew by a different sponsor, under different conditions, using different techniques, to arrive at the final supersaturated concentration.

Ipsen also notes that the supramolecular structure of the finished drug product is affected by the process of [REDACTED]. Lanreotide acetate is known to form peptide [REDACTED] impurities when exposed to [REDACTED]. For this reason, as discussed in Section II.B., comparative analyses of peptide-related impurities must be conducted on the finished drug product (test and reference) [REDACTED], with peptide-related impurities controlled to the same extent and same levels as found in the RLD.

In addition, and as discussed in Section II.C, separate from the need for an *in vivo* demonstration of bioequivalence, an ANDA referencing Somatuline Depot must include an assessment of the device constituent of the drug-device combination product to ensure equivalent performance and usability. While comparative usability may not typically be emphasized for generic versions of products administered by healthcare practitioners, in this case the performance and use of the device is critical given the extreme viscosity of the formulation and the difficulty of injecting the product.

Finally, in Section II.D Ipsen explains that while Ipsen believes "Option 2: *in vivo* bioequivalence study" in the *Lanreotide Draft Guidance* is the only viable method by which a proposed generic sponsor could establish bioequivalence to Somatuline Depot, the *Draft Guidance* does not include recommendations for analysis of partial Area Under the Curve (pAUC). Partial AUC must be included to ensure that bioequivalence for a proposed generic version of Somatuline Depot adequately tracks the 4-week dosing interval.

On August 28, 2019, Ipsen submitted comments to the *Lanreotide Draft Guidance* on the lack of scientific evidence to support the biowaiver option, and on the need for a more stringent *in vivo* study consistent with recommendations that have been made by FDA for other types of depot products. Given

⁴ Draft Guidance on Lanreotide Acetate (Jul. 2014) available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Lanreotide%20Acetate_draft_Subcutaneous%20injection_RLD%2022074_RC07-14.pdf (*Lanreotide Draft Guidance*).

the importance of these issues in light of emerging regulatory science and prevailing standards for approving generic versions of depot drug products – including, most recently, the agency’s September 25-26, 2019, public workshop on this issue⁵ – Ipsen is submitting this petition to request specific action as to any ANDAs that may be seeking approval, or may in the future seek approval, without an *in vivo* demonstration of bioequivalence and without the additional assurances of safety and effectiveness discussed below.

ACTIONS REQUESTED

Ipsen respectfully requests that the Commissioner take the following actions:

- (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 systemic circulation at the same rate and to the same extent as the RLD over the course of the dosing interval;
- (2) Require that ANDAs include comparative impurity analysis on samples of finished drug product (███████████) and control for peptide-related impurities to the same extent and same level as the RLD;
- (3) Require that ANDAs include comparative performance testing of the delivery device to ensure it is equivalently functional and useable;
- (4) Require ANDA sponsors to conduct 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
- (5) Re-issue the *Draft Guidance* based on the actions taken in response to this petition.

⁵ See generally FY2018 Generic Drug Regulatory Science Initiatives Public Workshop, FDA Research Updates on FY 2018 Initiatives (May 24, 2018), available at <https://www.fda.gov/media/113597/download>. See also Garner J., et al., Beyond Q1/Q2: the impact of manufacturing conditions and test methods on drug release from PLGA-based microparticle depot formulations. *J Pharm Sci* (Jan. 2018) 107(1):353-61 (Tab 1); Andhariya, J.V., et al., Development of *in vitro-in vivo* correlation of parenteral naltrexone loaded polymeric microspheres. *J Controlled Release* (Apr. 2017) 255:27-35 (Tab 2).

STATEMENT OF GROUNDS

I. BACKGROUND

A. Somatuline Depot

FDA approved Somatuline Depot on August 30, 2007, 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.⁶ Acromegaly is a rare hormonal disorder that results from a production of excess growth hormone (GH) by the pituitary gland.⁷ 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.⁸

On December 16, 2014, FDA approved lanreotide for the treatment of adult patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and on September 15, 2017, the agency approved an additional indication for treatment of carcinoid syndrome. The dosing regimens for the three approved indications are: (1) Acromegaly: 90 mg every 4 weeks for 3 months, followed by titration to maintenance, with possible extended 120 mg dosing every 6 or 8 weeks for patients already controlled using 60 or 90 mg dosing; (2) GEP-NETs: 120 mg every 4 weeks; and (3) carcinoid syndrome: 120 mg every 4 weeks. The product is approved in three strengths: 60 mg, 90 mg and 120 mg.⁹

The active pharmaceutical ingredient (API) in Somatuline Depot is lanreotide acetate, an octapeptide analog of natural somatostatin thought to exhibit similar biological activity as natural GH inhibiting hormone, somatostatin.¹⁰ Somatostatin is a naturally occurring peptide produced by cells in the central and peripheral nervous systems, the endocrine pancreas and gut, and other tissue. It is initially produced as a large 116 amino acid precursor that is processed to form the major 14- and 28-amino acid forms of somatostatin (SRIF-14 and SRIF-28), whose actions are mediated via 5 receptor

⁶ See Package Insert, Section 1.1.

⁷ See NDA 22-074, Division Director's Memo (October 27, 2006) at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022074s000_MedR_P1.pdf (Division Memo).

⁸ Id.

⁹ See Package Insert, Sections 1, 2.

¹⁰ Id. at Section 11.

subtypes, SST1 through SST5. Somatotrophs (cells that produce somatotropin and GH) express SST2 and SST5 and their activation results in suppression of GH secretion. Over 90% of GH-secreting tumors also express SST2 and SST5, making use of these receptors effective targets for treatment. However, because the circulating half-life of endogenous somatostatin is short, therapeutic use of the endogenous substance is severely limited. Somatostatin analogues (SSAs) such as lanreotide acetate have longer circulating half-lives and are able to achieve the same effect of suppressing pituitary GH release.¹¹

Lanreotide acetate has a high selectivity for human somatostatin receptors SST2 and SST5, and its activity at these receptor sites is thought to be the primary mechanism responsible for GH inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions.¹² The primary pharmacodynamic effect of lanreotide is a reduction of GH levels enabling normalization of levels in acromegalic patients. 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. The response to achieve this effect is dose-dependent.¹³

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.¹⁴

The precise mechanism of action of lanreotide in treating GEP-NETs and carcinoid syndrome is less well 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.¹⁵

¹¹ Division Memo at 2.

¹² See NDA 22-074, Clinical Review at 39, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022074s000_MedR_P1.pdf (NDA 22-074 Clinical Review).

¹³ *Id.*

¹⁴ 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.

¹⁵ Package Insert, Section 12.

B. Legal and Regulatory Background

Section 505(j) of the FDCA establishes an abbreviated approval pathway for a generic drug product that is “the same as” a drug product previously approved under section 505(b) (the RLD).¹⁶ An applicant seeking to market a generic version of the RLD submits an ANDA.¹⁷ The ANDA approval process allows a generic applicant to rely entirely on FDA’s previous finding of safety and effectiveness for the RLD rather than to independently demonstrate the safety and effectiveness of its proposed drug.¹⁸ A generic applicant must demonstrate that the proposed generic drug product is “the same as” the RLD in all relevant respects – including active ingredient, dosage form, strength, route of administration, and (with narrowly permitted exceptions) labeling – and that it is bioequivalent to the RLD.¹⁹

A generic drug is considered bioequivalent to the RLD if “the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .”²⁰ 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.²¹

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.²² As FDA has 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

¹⁶ 21 USC 355(j).

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ 21 USC 355(j)(2)(A)(ii)-(v). A principal benefit of approval under an ANDA is to receive an A-rating as therapeutically equivalent in the Orange Book. With an A-rating in the Orange Book, the generic drug product would be eligible in most states to be automatically substituted for the approved reference product at the pharmacy level. The underlying premise is that drug products sharing the characteristics that must be demonstrated for ANDA approval are therapeutically equivalent to each other and to the RLD, meaning one can be substituted for the other “with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product.” Orange Book, 2019, Preface viii.

²⁰ 21 USC 355(j)(8)(B)(i).

²¹ See 21 CFR 320.24(b)(1)(i).

²² 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).

the drug product into the systemic circulation.”²³ Indeed, FDA has expressly observed that it “does not recommend *in vitro* approaches for drug products that are intended to be systemically absorbed.”²⁴

For certain drug products, FDA regulations permit a biowaiver where the “*in vivo* bioavailability or bioequivalence of the drug product may be self-evident.”²⁵ 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.²⁶

C. FDA’s Draft Guidance for Lanreotide Acetate for ANDA Submissions

The *Lanreotide Draft Guidance* contains two options for establishing bioequivalence for proposed products that show Q1/Q2 sameness to Somatuline Depot and present satisfactory dissolution data. “Option 1” would allow an ANDA sponsor to seek a “biowaiver” in lieu of performing an *in vivo* study to show bioequivalence. 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. “Option 2” recommends a single-dose *in vivo* pharmacokinetic study using the 120 mg strength in normal healthy volunteers.²⁷

II. ARGUMENT

A. FDA Must Require Sponsors of Generic Versions of Somatuline Depot to Conduct an *In Vivo* Bioequivalence Study

Somatuline Depot is a complex, semisolid liquid-crystal in the finished dosage form that undergoes a transformation to form a solid, implant-like depot *in situ*. As with most drug products that deposit the formulation to a local site inside the body, and that remain in place and release drug over a prolonged interval, bioavailability of the drug product is not self-evident. This is in contrast to most orally or parenterally administered drug products in solution that are generally absorbed promptly and

²³ Draft Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Dec. 2013) at 3, available at <https://www.fda.gov/media/87219/download> (ANDA Bioequivalence Guidance).

²⁴ *Id.* at 8. See also 21 CFR 320.24(b)(1)(i).

²⁵ 21 CFR 320.22(b).

²⁶ *Id.*

²⁷ See *Lanreotide Draft Guidance*.

completely into the blood stream. The bioequivalence of such products may be considered self-evident when they are shown to be qualitatively and quantitatively the same.

The agency in the *Lanreotide Draft Guidance* indicated that *in vivo* drug release for Somatuline Depot can be treated more like that of a solution than a depot when it allowed for a biowaiver based on physicochemical comparison and *in vitro* drug-release rate testing. However, Somatuline Depot exists as a solution – a highly dense, semi-solid supersaturated solution – only for purposes of drug administration, and not for purposes of controlling drug release. Drug release into systemic circulation is controlled by the solid-form depot that resides in the body. To our knowledge, all other product-specific bioequivalence recommendations for parenteral, systemically-acting implants specify at least one *in vivo* BE study.²⁸ Likewise, all depots that rely on poly(lactic-co-glycolic acid) (PLGA) copolymer microspheres to attain prolonged release require *in vivo* bioequivalence testing.²⁹ Here, however, based on untested assumptions, the agency has concluded that the factors governing bioavailability for Somatuline Depot are relatively simple and therefore adequately investigated by *in vitro* methods. In fact, the factors that determine Somatuline Depot formation and release from the depot *in vivo* are neither straightforward nor self-evident. It would be erroneous and, worse, a serious risk to patient health and safety, to continue on the path of allowing a generic to be approved without *in vivo* bioequivalence testing.

As noted, Somatuline Depot is unlike a typical parenteral solution – and indeed unlike most depot drug products – in that the depot that forms inside the body at the body has a different structure than that which exists in the finished dosage form. The physicochemical properties of the solid depot, and the macroscopic factors that may govern the rate and extent of bioavailability *in vivo*, are not accessible to *in vitro* probing. While the agency set forth in the *Lanreotide Draft Guidance* that a proposed 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 is unaware of any scientific effort that has shown how these factors specifically correlate or relate to *in vivo* release. It is

²⁸ See, e.g., Draft Guidance on Goserelin Acetate (Zoladex), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Goserelin_Acetate_impSO_20578_19726_RC10-08.pdf; Draft Guidance on Leuprolide Acetate (Viadur), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Leuprolide%20Acetate_draft_Implantation%20implant_RLD%202108_8_RC07-08.pdf; Draft Guidance on Testosterone (Testopel), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Testosterone_pellet_80911_RC08-11.pdf. According to the compendial definition, “Implants are long-acting dosage forms that provide continuous release of the drug substance for periods of months to years. They are administered by the parenteral route and are sterile.” USP <1151> Pharmaceutical Dosage Forms (Tab 3, excerpt). Use of the term “pellet” for implantable dosage forms is no longer preferred. *Id.*

²⁹ See, e.g., Draft Guidance on Octreotide Acetate (Sandostatin LAR), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Octreotide%20acetate_inj_21008_RV02-14.pdf (*Octreotide Acetate Draft Guidance*); Draft Guidance on Leuprolide Acetate (Lupron Depot), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Leuprolide_acetate_inj_19732_20011_20263_RV02-14.pdf (*Leuprolide Acetate - Lupron Depot Draft Guidance*).

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.

Ipsen acknowledges that FDA has taken steps through its regulatory science program to study the factors governing the rate and extent of drug release from depot products and other complex dosage forms. These efforts have been directed towards developing *in vitro-in vivo* correlation (IVIVC) and biorelevant or predictive *in vitro* release test (IVRT) methods that may facilitate development of generic products for complex dosage forms.³⁰ FDA has emphasized that for long-acting parenteral products, including *in situ* forming implants, there are no standard or applicable compendial *in vitro* release assays and that the release mechanism (especially *in vivo*) is not fully understood.³¹ As FDA has noted, among the critical questions are how physicochemical characteristics correlate with *in vitro/in vivo* release, and how IVRT correlates with *in vivo* bioavailability.³² The goal of IVIVC and *in vitro-in vivo* relationship (IVIVR) investigation is to elucidate a test that is *biopredictive* or clinically relevant in order to potentially justify a biowaiver.³³

Ipsen appreciates that this FDA funded research has been directed in particular to PLGA-based products and the data are specific to that platform. Ipsen is supportive of FDA's advancement of regulatory science in the area of depot drug development and bioequivalence, and respects the complexities involved. However, Ipsen is unaware of any evidence yet developed under the agency's

³⁰ See Garner J., *et al.*, Beyond Q1/Q2: the impact of manufacturing conditions and test methods on drug release from PLGA-based microparticle depot formulations, *J Pharm Sci* (Jan. 2018) 107(1):353-361 (Tab 1). See also Draft Guidance on Leuprolide Acetate / Norethindrone Acetate (Feb. 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Leuprolide_acetate_Norethindrone_acetate_NDA_203696_%20RC11-17.pdf.

³¹ See, e.g., Wang, Y., "Bioequivalence Approaches for Long-Acting Drug Products: Regulatory and Scientific Considerations," at 3-4, Complex Generic Drug Product Development Workshop, Sep. 25-26, 2019 (2019 Workshop) (Tab 4).

³² *Id.* at 10.

³³ See Kolhatkar, V., "Considerations on In Vitro Drug Release Testing for Long Acting Drug Products for Quality Control," at 21-22, 2019 Workshop (Tab 5); see also Andhariya, J.V., *et al.*, Development of *in vitro-in vivo* correlation of parenteral naltrexone loaded polymeric microspheres. *J Controlled Release* (Apr. 2017) 255:27-35 ("*In vitro* drug release testing can provide extensive insight into the release rate as well as drug release mechanism(s). Therefore, it is an important tool to not only ensure consistent product performance and safety, but also assist in product development. When a correlation between *in vitro* and *in vivo* drug release is established, the *in vitro* release method may potentially be used as a surrogate for bioequivalence studies that would otherwise be required for any scale-up and post-approval changes.") (citations omitted) (Tab 2); Garner J., *et al.*, Beyond Q1/Q2: the impact of manufacturing conditions and test methods on drug release from PLGA-based microparticle depot formulations, *J Pharm Sci* (Jan. 2018) 107(1):353-361 ("*In vitro* drug release testing has been routinely used as a quality control tool. In addition to that, some *in vitro* drug release testing methods can also be used to predict *in vivo* performance of a product (*in vitro-in vivo* correlation).") (citations omitted) (Tab 1).

ongoing research program or elsewhere that would support reliance on IVRT in the case of Somatuline Depot.

Importantly, FDA has recognized, “[o]ne of the major reasons the *in vivo* release mechanisms of PLGA microspheres are not well understood is due to the difficulty of retrieving the particles following administration,” and that “[f]actors present in the subcutaneous administration environment that are not accurately represented by current *in vitro* release environments . . . but little work to date has been done in attempt to validate . . . hypotheses regarding how these factors influence drug release.”³⁴ Even more difficult, in the case of lanreotide depot, is that the ultimate structures and parameters responsible for controlling drug release for the depot do not form until the formulation precipitates inside the body. The FDA approved labeling infers this fact by stating that “SOMATULINE DEPOT is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids” and that it is “most likely . . . the precipitated drug” that is the ultimate form that determines bioavailability.³⁵

In sum, outside the body, Somatuline Depot exists as a complex, semisolid, liquid crystalline substance. Inside the body, the deposited mass precipitates and presents a solid surface to the surrounding tissue. The physicochemical characteristics of the drug product *in vitro* that correlate to *in vivo* release have not been determined, and Ipsen is unaware of any evidence that would support reliance on such properties, along with comparative IVRT, as a substitute for *in vivo* bioequivalence studies to support approval of a new sponsor’s drug product. [REDACTED]

[REDACTED] Therefore, at this time, Ipsen believes there is a lack of valid, coherent scientific evidence that would support reliance on biowaiver in lieu of an *in vivo* study.

1) *Because Somatuline Depot is Not a Normal Solution and is Not an Immediate-Release Product, In Vivo Bioavailability is not Self-Evident*

Somatuline Depot, unlike typical solutions for parenteral administration, exhibits a high structural organization and thermodynamic complexity.³⁶ The physicochemical structure of Somatuline Depot outside the body, in the dosage form, is a function both of the lanreotide acetate molecule and the

³⁴ Doty, A.C., et al., Mechanisms of *in vivo* release of triamcinolone acetonide from PLGA microspheres. J Controlled Release (2017) 256: 19-25 (“Biological factors that may influence the way drugs are released from PLGA matrices include the inflammatory response and the presence of enzymes, lipids, organic amines, and other endogenous compounds present in the administration environment. Physical-chemical factors that may alter mechanisms of release from PLGA microspheres *in vivo* as compared to *in vitro* include pH and buffering systems (e.g., bicarbonate buffer present *in vivo* vs. common phosphate buffers used *in vitro*), fluid volume, and convection. It is clear that the body’s reaction to the administration of PLGA microparticles is a complex process made up of a number of factors, which could potentially affect drug release in a variety of ways.”) (citations omitted) (Tab 6).

³⁵ See Package Insert, Section 12.3.

³⁶ See id. 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).

conditions of manufacture. Under appropriate conditions, at a concentration of around 5% (w/w) in water, lanreotide acetate salt begins to assemble into complex, highly ordered supramolecular structures. At around 10% w/w in pure water, lanreotide acetate forms monodisperse liquid crystalline nanotubes with a diameter of 244 Å.³⁷ The structure and complexity of the nanotube is comparable to biological tubular assemblies such as the capsid of the tobacco mosaic virus.³⁸ But, in contrast to the structures that occur in nature that are formed by polypeptides of high molecular weight, lanreotide is a small peptide composed of only eight amino acid residues.

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 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.³⁹

The nanotubes are organized into hexagonal assemblies, each composed of seven nanotubes. As concentration is further increased, the nanotubes undergo additional structural transformation. Specifically, the monodisperse nanotubes seen at 10% w/w become progressively disrupted, and above 20% w/w the hexagonal lattice is lost.⁴⁰ In its place, a polydisperse array of embedded nanotubes is formed, *i.e.*, tubes within tubes. 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.⁴¹

Accordingly, the structure of the final, gel-like, semisolid drug product (sometimes referred to in the regulatory documents as the “Autogel”) is complex, as are the sequence of steps in the peptide self-assembly mechanisms that generate this structure. It is thus unlike other parenteral solutions where *in*

³⁷ 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 7); see also NDA Module 3.2.P.2 2.3 (on file at FDA).

³⁸ 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 7).

³⁹ 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 (Tab 8).

⁴⁰ Id.

⁴¹ Id.

vivo bioavailability may be self-evident. Indeed, during the development of the product, FDA acknowledged that “[t]he Agency does not have any experience with a drug product like Autogel as an extended release formulation.”⁴² Most drug products that are solutions for parenteral injection allow bioequivalence to be inferred. The thermodynamics of drug release is relatively simple in such cases. The drug exists in a “released” form and is readily bioavailable in and directly from the drug product itself. Accordingly, for most solutions for parenteral injection, if a generic version of the product is Q1 and Q2 the same as the RLD, an *in vivo* bioequivalence study may be waived in most cases.⁴³

That is not the case for Somatuline Depot. First, Somatuline Depot is an extended release product that results in 4 weeks of prolonged exposure to lanreotide based on a single dose. Under the regulations, FDA has stated that a biowaiver is not intended for an extended release product.⁴⁴ Second, at a dense concentration of 24.6%, the drug substance exists in a semisolid, highly structured liquid crystal form within the finished product. After the formulation is injected, it undergoes a significant transformation before establishing an *in situ* depot. In forming the depot, the formulation begins to precipitate, to change from semisolid to solid, with the surface of the depot presenting a solid phase of the drug to the surrounding tissue. It is dissolution and diffusion from this solid surface that likely governs the rate and extent of release of drug from the drug product.⁴⁵

Thus, the depot is the relevant form of the drug for purposes of assessing the rate and extent of drug release. Bioavailability cannot be considered self-evident based on the drug product itself. Nor can reliance on the physical and chemical parameters described in the *Lanreotide Draft Guidance*, when applied to the drug product, be considered sufficient to reach a conclusion of equivalent drug release. Instead, it is the physical and chemical properties of the ultimately formed depot that controls drug release. Moreover, as discussed below, biorelevant correlation between the physicochemical characteristics of the drug product and the *in situ* depot has not been established.

⁴² See Minutes from Pre-NDA Meeting Jul. 6, 2004 at 8 (on file at FDA) (*Pre-NDA Meeting Minutes*).

⁴³ Ipsen is aware of one long-acting solution product with approved generic products that may have been approved in part based on a waiver of *in vivo* bioequivalence. See generally Faslodex (fulvestrant) 50 mg/mL, NDA 021344. Here, however, as with other parenteral products that are solutions for injection, the solubilized drug substance is released and absorbed directly from solution. More specifically, the active ingredient exists in a “released” form in a castor oil-based solution before and after injection, where there is no particular organizational architecture of fulvestrant in the formulation. The mechanism of slow release is governed by the disappearance of the oil containing the drug from the injection site that contributes to the overall rate of drug release from the local administration site. In this context, the generation of *in vitro* data for prediction of *in vivo* drug performance is reasonable considering that drug release from the lipophilic vehicle constitutes the rate limiting step *in vivo*. This is distinct from Somatuline Depot, which undergoes a transformation inside the body to a solid precipitant which itself is responsible for drug release and the bioavailability of the product.

⁴⁴ See 21 CFR 320.22(d)(iv).

⁴⁵ Package Insert, Section 12.3.

2) *The In Vitro Supramolecular Properties of Somatuline Depot That Determine In Vivo Drug Release Have Not Been Established*

The relationship between the *in vitro* physical and chemical properties of the product, and the rate and extent of release of lanreotide from the slow-releasing depot, has (to our knowledge) not been determined. While it is known that the embedded nanotube structure is thermodynamically more stable than the hexagonal arrays of hollow nanotubes, the physiological parameters that perturb the organization *in vivo* and contribute to the formation of the depot are not entirely understood.⁴⁶

In vitro and nonclinical data suggest that the depot is formed by precipitation of the peptide,

⁴⁷ For example, the

⁴⁸ This has an observable effect on the behavior of the [REDACTED]

[REDACTED] .⁴⁹ The depot

in situ therefore appears to experience a dynamic transition to the solid state. As a result, the physical form of the drug product that governs the rate and extent of release of lanreotide into systemic circulation is different from the structure that exists *in vitro*.⁵⁰

⁴⁶ The FDA-approved labeling acknowledged that Somatuline Depot “is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids.” *Id.* See also NDA 22-074, Clinical Pharmacology and Biopharmaceutics Review at 8, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022074s000_ClinPharmR_P1.pdf (noting that “changes in local physiological environment of the depot could result in changes in the release profile of lanreotide Autogel” and that factors such as “surface area and density of the depot” are important) (NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review).

⁴⁷ See NDA Module 3.2.P.2.2.3.2 (on file at FDA).

⁴⁸ *Id.*

⁴⁹ *Id.* [REDACTED]

[REDACTED] *Id.*

⁵⁰ The solid form of the *in situ* depot in patients, including its evolution and induration over the course of the dosing interval is supported by the Phase 1 study [REDACTED] (on file at FDA).

For this reason, the assumptions surrounding a waiver of *in vivo* bioequivalence cannot be applied to proposed generics of Somatuline Depot. Unlike conventional parenteral solutions, the drug exists in a different physical form from its *ex vivo* to its *in vivo* state, and drug release from the formulation is governed by the *in vivo* form of the drug. The precise relationship between the properties of the formulation in the final dosage form, and the formation of the solid phase at the interface of the depot and the surrounding tissue that would be expected to govern drug release, is not known. Based on our own research and experience, Ipsen is not aware of a valid scientific basis for characterizing and correlating the *in vitro* properties with *in vivo* bioavailability. Comparability between two lanreotide depot products (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*.⁵¹

3) *Ipsen* [REDACTED]

Ipsen is not aware of any “acceptable comparative *in vitro* drug release-rate tests”⁵² of the finished product that would correlate with rate and extent of *in vivo* drug release (IVIVC). Design of a biorelevant IVRT for Somatuline Depot poses significant technical challenges. The unique combination of hydrophilic and hydrophobic residues, and the presence of a disulfide bond in the sequence of lanreotide, gives rise to the molecule having an amphiphilic character. These factors play an important role in the formation of three dimensional ordered structures by means of non-covalent forces.⁵³ However, these complex structures, [REDACTED]

[REDACTED]. For this reason, 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. [REDACTED]

but it remains difficult to model the conditions that give rise to the depot in an *in vitro* system that will allow relevant measurements to be taken.

51 [REDACTED]

⁵² *Lanreotide Draft Guidance* at 1.

⁵³ 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 (Tab 8); NDA Module 3.2.P.2.2.3.1 (on file at FDA).

[REDACTED]

55

Ipsen also sought to demonstrate a correlation between *in vivo* and *in vitro* release to investigate the potential use of *in vitro* dissolution as a surrogate for *in vivo* behavior.

[REDACTED]

56

[REDACTED]

[REDACTED]

⁵⁴ See NDA Module 3.2.P.2.2.4 (on file at FDA).

⁵⁵ *Id.*

⁵⁶ [REDACTED]

[REDACTED] See Cherif-Cheikh, R., *et al.*, AutogelTM: A new lanreotide prolonged release formulation. Proceed Int'l Symp Control Rel Bioact Mater (1998) 25:798-99 (Tab 9).

⁵⁷ See Ipsen Pharma S.A., Autogel "in vitro" Release Test: Search of an *in vivo*-*in vitro* correlation using Phase I Clinical Data, SOMA-0199 (Aug. 9, 2000) (on file at FDA).

⁵⁸ See Pre-NDA Meeting Minutes, CMC Question 2 (on file at FDA).

A demonstrated IVIVC, or validation of a biorelevant IVRT, is an essential step before it would be appropriate to recommend a biowaiver for a generic lanreotide depot product.⁵⁹ This is particularly important in this case, where the drug is a semisolid and where it is further transformed during administration into a depot of specific shape, size, surface area and composition. As described in this petition, the relationship between the physical and chemical properties of the drug product as it exists outside the body and the corresponding properties of the *in situ* depot have not been established. Due to the design-constraints of the manufacturing process, and the structural complexity of the final drug product – and because Ipsen lacks biorelevant IVRT [REDACTED]

[REDACTED]
60 [REDACTED]

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.

4) *The Intrinsic Variables That Determine Formation of the Depot and the Properties of the Depot that Ultimately Determine Drug Release are Evident Only After the Product Has Been Administered*

Somatuline Depot is an *in situ* forming, slow releasing depot. As discussed above, Somatuline Depot is a structurally complex, semisolid substance in the dosage form, and undergoes a further transformation *in vivo* to present a solid phase to the surrounding tissue. 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. Without excising the depot from study subjects and subjecting the excised mass to further characterization, Ipsen has no clear evidence whether the solid substance is crystalline or amorphous. Nor does Ipsen have insight into the *in vitro* properties and attributes of the supramolecular structure that influence solid-state properties with consequence to *in vivo* bioavailability. The size, shape, and surface area of the resulting solid depot are also factors that influence the rate and extent of absorption from the depot.

Nonclinical findings and clinical pharmacokinetic data point to the shape of the depot and the surface area exposed to the local physiological environment as important factors implicating drug release. For example, the behavior of the formulation at the injection site was investigated in a dog model. Twenty-four hours after an IM administration of 60 mg, the formulation was recovered from the injection site by performing a tissue excision. [REDACTED]

⁵⁹ See, e.g., Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (Sept. 1997), available at <https://www.fda.gov/media/70939/download>; see also Kaur, P., et al., Applications of *in vitro-in vivo* correlations in generic drug development: case studies, AAPS J (July 2015) 17(4):1035-39 (Tab 10).

⁶⁰ NDA 22-074/S-001 (on file at FDA).

consistent with loss of structure in the liquid crystal and precipitation of lanreotide. It also had a distinctive [REDACTED].⁶¹

This phenomenon, and its potential role in the dynamics of depot formation and *in vivo* drug release, was further investigated through analysis of human pharmacokinetic data. [REDACTED]

Table 1: Ratio Comparisons of C_{min,ss} Values

C _{min,ss} Comparing Two Doses	Ratio	Acromegaly Study (E28.52030.717)	Pivotal Study (E28.52030.7091710)	Acromegaly Supportive Study (E28.52030.7091710)	Neuroendocrine Tumors Study (E47.52030.718)
90 mg/60 mg	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
120 mg/60 mg	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The experimental ratios obtained were therefore consistent with an [REDACTED] depot at the injection site, as observed from measurements taken on depots excised from dogs.⁶³

The data show that the shape of the depot is a factor governing the rate and extent of release. Based on Ipsen's experience, 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. The effects of these variables manifest

⁶¹ See Pre-NDA Meeting Briefing Book (Jun. 3, 2004) at 62-63 (on file at FDA); and NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review at 8 (noting that factors such as “surface area and density of the depot” are important).

⁶² See *id.*; NDA Module 3.2.P.2.2.3.2 (on file at FDA).

⁶³ *Id.*

themselves post-administration and support the need for *in vivo* bioequivalence studies. The product functions as a solid depot – one in which the solid state structure, shape and surface area are not evident until after the product is administered, at which point it cannot be subject to *in vitro* testing. Nor is there any access to or data on the *in situ* evolution and erosion of the depot. FDA's bioequivalence recommendations for implants and pellets all call for *in vivo* testing.⁶⁴ The need in this case for *in vivo* bioequivalence is greater because the solid state properties are not exhibited in the dosage form prior to administration.

B. Sponsors of Generic Versions of Somatuline Depot Must Conduct Comparative Impurity Analysis on the Finished Drug Product [REDACTED]

Degradation products in a drug product covered by an ANDA can require analytical comparison of the impurity profile of the generic drug product with that of the RLD “using the same validated, stability-indicating analytical procedure....”⁶⁵ This is critical for peptide based therapeutics, particularly those including peptides with disulfide linkages. For example, in approving a generic version of Miacalcin (salmon calcitonin), a 32 amino acid synthetic peptide hormone with a single disulfide bond, FDA required (among other things) a comprehensive analysis of comparable peptide-related impurities.⁶⁶

Somatuline Depot is a peptide-based product that is assembled into a complex supramolecular structure known to generate degradation products as an impurity.⁶⁷ The formation of dimers, trimers and oligomers of higher order is a degradation pathway well described in the literature for cyclic peptides and proteins containing one or more disulfide linkages attributed to the intermolecular exchange of the disulfide bridge. Based on its one disulfide bridge and the potential intermolecular linkages formed, different oligomers of lanreotide can be predicted. Five different [REDACTED] structures are possible, [REDACTED] of which can be detected in Somatuline Depot.⁶⁸ These structures pose potential aggregation and immunogenicity risk and therefore must be controlled and limited.

⁶⁴ See *supra* notes 28-29.

⁶⁵ See Guidance for Industry, ANDAs: Impurities in Drug Products (Nov. 2010), available at <https://www.fda.gov/media/71351/download>.

⁶⁶ FDA required comparability in product- and process-related factors, *i.e.*, comparable purity and quality, including evaluation of peptide-related impurities, aggregates, leachates from the container/closure system, and formulation factors. See Lee, S.L., *et al.*, Scientific Considerations for Generic Synthetic Salmon Calcitonin Nasal Spray Products. AAPS J (Mar. 2011) 13(1):14-19 (Tab 11); see also FDA Citizen Petition Response (Miacalcin), Docket No. FDA-2005-P-0367 (Nov. 17, 2008).

⁶⁷ See generally NDA 22-074, Amendment 0014, Ipsen Letter to Acting Division Director, Response to Chemistry Request for Information dated May 31, 2007 (Jun. 22, 2007) (on file at FDA).

⁶⁸ See *id.* at 14.

The impurity issue for Somatuline Depot is exacerbated by the [REDACTED] process. In developing an appropriate [REDACTED] process for Somatuline Depot, Ipsen investigated the effect of [REDACTED] on lanreotide purity and potency.⁶⁹ [REDACTED] was noted to induce [REDACTED] formation. In close consultation with FDA, Ipsen developed and validated analytics, and set specifications to tightly control and limit, for release and shelf-life, [REDACTED] impurities.⁷⁰

In addition, the [REDACTED]⁷¹ The application of [REDACTED]

[REDACTED]⁷² However, the [REDACTED]

[REDACTED]⁷³

There is no safety or efficacy concern for the RLD as both the toxicological and clinical batches of the drug product were [REDACTED]⁷⁴ However, the impact of [REDACTED]. Accordingly, to establish that the proposed generic exhibits the formulation properties of the RLD, and an impurity profile that is acceptable in terms of potentially immunogenic degradation products, comparative physicochemical analysis must be based on the finished dosage form [REDACTED]

C. ANDA Sponsors Must Conduct Comparative Performance Testing on the Delivery Device System to Ensure Device Sameness

Separate from, and in addition to, the need for an *in vivo* demonstration of bioequivalence, an ANDA referencing Somatuline Depot must include an assessment of the device constituent of the drug-device combination product to ensure equivalent performance and usability. While comparative usability may not typically be emphasized for generic versions of products administered by healthcare practitioners, in this case the performance and use of the device is critical given the extreme viscosity of the formulation and the difficulty of injecting the drug product.⁷⁵

⁶⁹ See generally *id.*

⁷⁰ See *id.* at 19.

⁷¹ See *id.* at 17.

⁷² *Id.* at 14.

⁷³ *Id.* at 17.

⁷⁴ *Id.*

⁷⁵ See *infra* Section II.B.

Under FDA standards, when a delivery device is approved under an NDA as a component of a combination product, any ANDA that references the RLD must also include a functionally equivalent device component. The proposed generic product's performance characteristics, operating principles, and critical design attributes must result in a product that will perform the same as the RLD under the conditions of use described in the labeling.⁷⁶ Specifically, FDA has determined that it will take into account differences in delivery devices, and will assign A-ratings only to products that can be expected to have the same clinical effect and safety profile as the RLD, when used under the conditions described in the labeling.⁷⁷ For purposes of generic drug-device combination products, the ANDA applicant must demonstrate that its proposed device components are functionally equivalent to the innovator's device in all relevant respects, including its design, performance, labeling, use and handling.⁷⁸ To that end, FDA may impose specific comparative performance criteria or requirements for human factor studies to confirm that any difference in device or labeling between the generic and RLD are acceptable for products expected to be substituted.⁷⁹

As FDA has recognized “[t]he prefilled syringe [for Somatuline Depot] has been designed to address known problems associated with . . . injecting viscous drug product . . .”⁸⁰ Given the viscosity of the product, among other factors, the delivery device is specifically designed to safely deliver the supersaturated solution of lanreotide acetate to the deep subcutaneous tissue in which the depot forms and resides. The container and container-closure ensure the integrity and stability of the drug substance inside the syringe and include [REDACTED].⁸¹ The choice of syringes and needles was based on the assessment of the key parameters that could affect the

⁷⁶ See, e.g., Citizen Petition Response to King Pharmaceuticals, Docket No. FDA-2007-P-0128-0006 (Jul. 29, 2009), available at <http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0128-0006> (*King Petition Response*); see also Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards (Dec. 2016) at 17, available at <https://www.fda.gov/media/86660/download> (*Refuse-to-Receive Guidance*).

⁷⁷ See *King Petition Response*; see also *Refuse-to-Receive Guidance* at 17 (“Any device used to deliver the drug should be similar enough to that used with/for the RLD so as to ensure, at a minimum, safe and proper administration of the product . . . to ensure that its performance characteristics, operating principles, and critical design attributes will result in a product that will perform the same as the RLD under the conditions of use described in the labeling. In addition, the patient instructions in the labeling, as it concerns use of the device, should meet the same labeling requirement for ANDAs.”).

⁷⁸ See *King Petition Response* at 6-7, 10-11.

⁷⁹ See Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (Jan. 2017) at 3-4, available at <https://www.fda.gov/media/102349/download> (*Comparative Analyses Guidance*).

⁸⁰ NDA 22-074/S-004, CDRH Human Factors Consult Review at 5, April 15, 2014, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022074Orig1s004.pdf.

⁸¹ See e.g., NDA 22-074 Modules 3.2.P.3.4 (Control of critical steps and intermediates); 3.2.P.7 (Container Closure System); 3.2.P.8.1 and 3.2.P.8.3 (Stability); 3.2.P.5.2 (Combination Product Specifications); and 3.2.P.8.2 (Post Approval Stability Protocol and Stability Commitment) (on file at FDA). See also NDA 22-074/S-004; NDA 22-074/S-021 (on file at FDA).

injectability of the product and its localization to the deep subcutaneous site.⁸² To assess the viscosity of the bulk supersaturated solution, [REDACTED]

[REDACTED]⁸⁵ A difference in the syringe design or performance introduced by a generic has a high likelihood of affecting the flow rate and syringe injection force calculations, directly impacting the usability and functionality of the product.

Ipsen has worked closely with FDA on all device modifications made to the delivery system to ensure that the critical design attributes of the device and essential performance characteristic were maintained. This includes [REDACTED]

[REDACTED]. Ipsen has also ensured that any design modifications to secondary or primary packaging did not introduce new error use patterns or affect the critical performance characteristics. For example, an improvement of the container closure system was approved by FDA in October 2014 as a prior approval supplement (PAS) to include an addition of a sharps protection system to the syringe to help preventing needle stick injury after use, and to harmonize the syringe dimensions for the three dosage strengths.⁸⁶ Ipsen performed numerous human factor studies and extensive performance testing to ensure the essential performance characteristics were maintained and that the updated delivery system could perform as expected.⁸⁷ In 2019, FDA approved a

⁸² NDA Module 3.2.P.2.4.4 (on file at FDA).

⁸³ *Id.* at 3.2.P.2.2.3.3. [REDACTED]

⁸⁴ *Id.* at 3.2.P.2.4.4.2.

⁸⁵ *Id.*

⁸⁶ See NDA 22-074/S-004 (on file at FDA). *See also* Module 2.3, Addendum to the Quality Overall Summary (Oct. 2011) at 43 (on file at FDA). In order to have the three dosage strengths packed with the same syringe and same needle rather than the original two syringe/needle types depending on the dose, Ipsen made two changes to the primary packaging components to harmonize the drug delivery system: (1) a change in the [REDACTED] and (2) a [REDACTED] which have been unchanged since approval and that showed greater patient acceptability. *Id.* The syringe [REDACTED]. Further, the performance of the modified container closure system was carefully assessed to ensure critical performance characteristics were maintained, such as [REDACTED]. Studies performed showed results comparable with data obtained with the original injection system. *See* NDA Module 3.2.P.2.7.3.2 (on file with FDA).

⁸⁷ See NDA 22-074/S-004 and *See* NDA Module 3.2.P.2.7.3.2 (on file with FDA). *See also* FDA Complete Response Letter (May 25, 2013), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022074Orig1s004.pdf (identifying verification of dose/expiration date, inserting at a 90 degree angle, and compressing the plunger to the button for the full dose

PAS for a more ergonomic and robust pre-filled syringe, requiring bridging analysis to ensure essential performance characteristics and human factor studies to confirm usability.⁸⁸ The essential design features were maintained in addition to essential performance criteria including [REDACTED],
[REDACTED]

Accordingly, at a minimum, FDA must require a comparative assessment of the critical design and performance attributes of a proposed generic to Somatuline Depot. Ipsen recognizes that a general description of the entire delivery device constituent part of the proposed generic product, including extractable/leachable studies, performance testing, and stability studies, will be included in the chemistry, manufacturing and controls (CMC) sections of the ANDA as specified by FDA's general guidance.⁸⁹ However, as FDA has recognized, there is also a need for comparative performance testing to support the delivery device of the proposed generic combination product.⁹⁰ To the extent any ANDA has a device feature that is different than the RLD or uses different labeling, it will be essential that adequate human factor studies are conducted.⁹¹ Ensuring the syringe design adequately matches the RLD is a minimum requirement, and FDA must refrain from approving any ANDA that does not include data, including human factors data, demonstrating that the proposed delivery device is equivalent to the RLD.

D. FDA Must Require an *In Vivo* Study with Partial AUC Analysis to Ensure That a Proposed Generic has the Same Rate and Extent of Release Over the Course of the 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 and beyond.

as critical error use patterns that should be re-addressed in additional human factor testing. FDA also noted that identifying the correct injection site is critical to control for because the "clinical impact of incorrectly injecting into the upper/middle buttock can be significant (i.e., paralysis).") (CRL).

⁸⁸ NDA 22-074/S-021 (on file at FDA). See also FDA Meeting Minutes (Apr. 18, 2018) at 5 (identifying essential performance characteristics) (on file at FDA).

⁸⁹ *Comparative Analyses Guidance* at 3.

⁹⁰ *Id.*

⁹¹ See, e.g., CRL (identifying verification of dose/expiration date, inserting at a 90 degree angle, and compressing the plunger to the button for the full dose as critical error use patterns that should be re-addressed in additional human factor testing. FDA also noted that identifying the correct injection site is critical to control for given the "clinical impact of incorrectly injecting into the upper/middle buttock can be significant (i.e., paralysis)."). See also *Comparative Analyses Guidance* at 4 n.12 (permitting comparative use human factors study "to account for how a particular proposed generic combination product might be used when substituted for the RLD.") FDA has also explained that, if clinical usability or human factor studies are required to demonstrate that the proposed generic product is safe and effective (i.e., because differences preclude simply extrapolating safety and effectiveness from the finding for the RLD), "such studies are beyond the scope of studies that can be reviewed and approved in an ANDA." *King Petition Response* at 10.

Although patients may be 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.

For other long-acting depot products, FDA has developed bioequivalence recommendations that require either a multiple-dose steady state study (where there is evidence of drug accumulation), or a single-dose study with analysis of additional partial AUC metrics.⁹² Multiple-dose studies in the depot space can require very long studies, often in patient populations. As a general proposition, FDA has recognized that single-dose PK studies are more sensitive than multiple-dose studies and thus are preferred where possible.⁹³ In the context of depots, FDA has recognized the need for additional analysis to ensure therapeutic equivalency in several cases. Specifically, partial AUC measurements based on a single dose *in vivo* PK study were recommended in order to help ensure bioequivalence across the length of the dosing interval.⁹⁴

The release of lanreotide from Somatuline Depot is both multiphasic and sustained. *In vivo* input profiles show that the release of lanreotide occurs over 112 days following administration of lanreotide acetate by deep subcutaneous injection at doses of 60, 90, and 120 mg in healthy subjects.⁹⁵ The release profile of the product is characterized by an initial controlled and limited “burst” release on the first day of administration that determines the C_{max} , followed by a sustained release to give a long terminal half-life of 23-30 days (the mean C_{max} after a single dose was 4.25, 8.39, and 6.79 ng/ml at each strength respectively, while the half-life was 23.3, 27.4, and 30.1 days).⁹⁶ The percentage for the ratio between

⁹² Most recent product-specific guidances for depot products recommend single-dose studies with partial AUC. See, e.g., Draft Guidance on Leuprolide Acetate / Norethindrone Acetate (Feb. 2018) (Lupaneta Pack), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Leuprolide_acetate_Norethindrone_acetate_NDA_203696_%20RC11-17.pdf; Draft Guidance on Triptorelin Pamoate (Trelstar) (Feb. 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Triptorelin%20pamoate_JMinj_20715_21288_22437_RV02-14.pdf; *Leuprolide Acetate - Lupron Depot Draft Guidance; Octreotide Acetate Draft Guidance; Draft Guidance on Naltrexone (Vivitrol)* (Sept. 2015), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Naltrexone_ER%20intramuscular%20inj.%20suspension_021897_RV09-15.pdf. There remain, however, several notable examples of steady-state recommendations. See, e.g., Draft Guidance on Aripiprazole (Dec. 2014) (Abilify Maintena), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Aripiprazole_ERinjechsusp_202971_RC12-14.pdf.

⁹³ See Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Dec. 2013) at 5, available at <https://www.fda.gov/media/87219/download>.

⁹⁴ See *supra* note 92.

⁹⁵ NDA 22-074 *Clinical Pharmacology and Biopharmaceutics Review* at 22-23.

⁹⁶ *Package Insert*, Section 12.3; *Clinical Pharmacology and Biopharmaceutics Review* at 5-6.

AUC₀₋₂ and AUC₀₋₂₈ was around 11% in a single dose study, confirming that dose dumping does not occur.⁹⁷

The apparent terminal half-life of the drug product is limited by release from the depot, not by disposition of the half-life of the lanreotide peptide (*i.e.*, the product exhibits characteristic “flip-flop” kinetics).⁹⁸ In other words, the release and absorption process is much slower than the elimination process and therefore the absorption process is the rate limiting step. The limited initial burst release immediately after administration results in a low peak-trough fluctuation index. Some accumulation of lanreotide in the body was observed at all dose levels, with a mean accumulation index of approximately 2.7. These accumulation results are not unexpected values, considering the long apparent half-life.

The limited initial burst release and controlled release over the entire 28-day period, after both single and multiple doses of Somatuline Depot at 60, 90 or 120 mg, demonstrates the robustness of the depot.⁹⁹ As discussed above, Somatuline Depot is thought to form a depot at the injection site due to interaction with physiological fluids.¹⁰⁰ While the ultimate mechanism of uptake is most likely passive diffusion of lanreotide from the solid surface of the depot into surrounding tissues, followed by the absorption into the blood stream,¹⁰¹ the rate of lanreotide absorption is likely dependent on factors governing the formation of the solid phase, surface area, solubility of the *de novo* solid phase *in vivo*, as well as macroscopic factors affecting the stability and decay of the *in situ* depot.¹⁰²

In PLGA formulations, an early phase of release is thought to be facilitated by swelling of the microsphere in response to hydration. The mechanism underlying the burst phase in Somatuline Depot is not known, but may be due to the initial solvency of the depot, prior to formation of a solid surface. The transient existence of a solution phase *in situ* causes rapid release with zero order kinetics. The transition to solid phase results in an extended release phase with first order kinetics. Accordingly, the product has multiple release phases and a relatively complex PK profile, providing extended release over the course of the dosing interval, and maintenance above the therapeutic minimum serum concentration of lanreotide.

Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL at 60 mg.¹⁰³ The primary pharmacodynamic effect of lanreotide is to suppress GH secretion by

⁹⁷ NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review at 24.

⁹⁸ *Id.* at 5.

⁹⁹ *Id.* at 24.

¹⁰⁰ See Package Insert, Section 12.3.

¹⁰¹ *Id.*; NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review at 8.

¹⁰² See *supra* Section II.A.4.

¹⁰³ Package Insert, Section 12.3.

normal pituitary somatotroph cells as well as adenomatous somatotroph cells. In the treatment of acromegaly, GH secretion is inhibited through lanreotide binding to human somatostatin receptor subtypes 2 and 5 present on the cell surface of the adenoma cells. Decreased GH secretion leads to decreased secretion of IGF-1, mostly by the liver, but also by other GH target tissues. Reduction of GH concentration to ≤ 2.5 ng/mL has been shown to improve the mortality rate of acromegalic patients. 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.¹⁰⁴

To correlate lanreotide levels with GH and IGF1 reductions in acromegalic patients, PK/PD modeling analyses (01/PKS/011 and 01/PKR/050) showed a direct relationship between lanreotide concentrations and the downstream decrease of GH and IGF1.¹⁰⁵ The GH lanreotide concentrations and the IGF-1 versus GH relationships were described using inhibitory E_{max} models.¹⁰⁶ This PK/PD model demonstrated a lanreotide concentration dependent decrease in GH within the range of serum levels achieved by the Somatuline Depot dose strengths. These analyses revealed that a concentration of about 1 ng/ml was associated with a clinically meaningful decrease of GH below 2.5 ng/ml among responders, indicating that the minimum concentration at day 28 (C_{min}) is a key parameter to ensure hormonal control of acromegaly (GH and IGF1).¹⁰⁷

These data establish that to reproduce the same effect as Somatuline Depot over the course of the dosing interval, a test product must maintain minimum concentration at Day 28 (C_{min}) to ensure hormonal control of GH and IGF1. The C_{min} parameter can be affected by a different terminal half-life of the generic product, which is limited by the release from the depot (“flip-flop” phenomenon). Thus, the rate of release from a generic product can be expected to have an impact on the minimum concentration at Day 28 and on hormonal control of GH and IGF1.

For long-acting injectable depot products, *in vivo* PK studies with partial AUC analysis are increasingly recognized as the most accurate, sensitive, and reproducible form of study, and are increasingly recommended by FDA for this class of products. In light of these recommendations, to demonstrate bioequivalence to the RLD in this case, FDA must require that ANDAs include a single-dose PK study and demonstrate bioequivalence based upon the geometric mean of the ratios of the test drug to the RLD for a partial AUC time point designed to ensure maintenance of release across the dosing interval, in addition to C_{max} , AUC_{0-4} , and $AUC_{0-\infty}$ (90% confidence interval within 80% to 125% for each measurement). Specifically, either, AUC_{0-2} (to characterize dose dumping, which is likely caused by the transition from semisolid to solid depot) and AUC_{0-28} (to characterize the controlled

¹⁰⁴ See NDA 22-074 Clinical Review at 42; NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review at 14-15.

¹⁰⁵ NDA 22-074 Clinical Pharmacology and Biopharmaceutics Review at 14-15.

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*

release phase) should be required.¹⁰⁸ Alternatively, due to the importance of the minimum concentration at Day 28 and the accumulation ratio of 2.7 between single and repeated dose, a repeated dose would be required to demonstrate bioequivalence at steady state.

III. CONCLUSION

For all of the reasons described above, Ipsen respectfully requests that FDA grant the actions requested in this citizen petition. Somatuline Depot is an *in situ* forming, slow releasing depot. The drug product in the finished dosage form is a semisolid liquid crystal formulation comprised of complex supramolecular and intramolecular arrays of lanreotide and does not itself have direct extended-release properties in this state. However, in forming the *in situ* depot, part or all of the supramolecular structure is thought to be lost through the precipitation process that occurs *in vivo*. 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 solid-state chemistry, shape, and surface area of the depot each may influence the rate and extent of bioavailability of lanreotide *in vivo*. In the more typical context of PLGA depot drugs, FDA has acknowledged the necessity to understand not just the complex chemistry of the PLGA excipient, but also the dimensions and properties of the microsphere, and the properties that affect development and aging of the depot. Without an understanding of what *in vitro* factors affect these outcomes, there is no well-founded basis for establishing bioequivalence based on *in vitro* studies alone.

¹⁰⁸ In a similar circumstance, for Sandostatin LAR (octreotide acetate) – a somatostatin analogue also approved to treat acromegaly – FDA has indicated that it will require that bioequivalence be established based on statistical analysis (90% confidence interval) of AUC_{0-28} and AUC_{28-56} , in addition to AUC_t , $AUC_{0-\infty}$, and C_{max} . See *Octreotide Acetate Draft Guidance*. Like Somatuline Depot, Sandostatin LAR has a 4 week dosing interval. Sandostatin LAR has a less pronounced initial transient phase in the first few days following administration, after which it ascends to a plateau phase that accounts for C_{max} . After 6 weeks, octreotide slowly descends and is detectable out to around Week 12-13. Sandostatin LAR Package Insert, Section 12.3, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021008s043lbl.pdf.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

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: July 23, 2014. 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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Enclosures