February 19, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2015-D-4750
The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers; Draft Guidance for Industry; Availability; Request for Comments on Preliminary List of Affected Applications

Dear Sir or Madam:

Ipsen Biopharmaceuticals, Inc. (Ipsen) submits these comments on the Food and Drug Administration's Preliminary List of Approved New Drug Applications for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (List of Transition Products). On December 20, 2019, Congress broadened the definition of "biological product" by removing the exclusion for "any chemically synthesized polypeptide." Ipsen believes that its synthetic polypeptide product, Somatuline Depot® (lanreotide acetate), is a biological product under the amended definition and should be included on the List of Transition Products. In response to FDA's request for comments on the List by February 19, 2020, Ipsen presents below the basis for concluding that Somatuline Depot (NDA 022074) is a biological product and respectfully requests the prompt addition of Somatuline Depot (lanreotide acetate) to the List of Transition Products.

I. Background

A. Somatuline Depot

Somatuline Depot is a viscous, gel-like injectable product that contains a supersaturated solution of lanreotide acetate and water in a semi-solid phase for subcutaneous injection. The active substance in Somatuline Depot is lanreotide acetate, an octapeptide analog of natural somatostatin that associates into large, complex, highly ordered supramolecular structures known as nanotubes, with a diameter of 244 Å and a length of 1-3 µm.[1] The structure and complexity of the nanotube is a result of

[1] *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):10258-10262 (Tab 1); Pouget, E., *et al.*, Hierarchical

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lanreotide's primary amino acid sequence, which drives intermolecular association of amino acid chains in the same manner as found in other biological protein assemblies, including insulin,[2] amyloid fibers,[3] and viral capsids.[4]

B. Definition of "Biological Product" and the "Deemed to be a License" provision

The term "biological product" is defined under the Public Health Service Act (PHS Act) based on the listing of specific categories of products and any product that may be considered "analogous" to one of the specifically listed products. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) added the term "protein (except any chemically synthesized polypeptide)" to the list of specific categories within the definition of "biological product." As with the other listed categories of biological products, the protein category also includes "analogous products."

The BPCI Act provided that, on March 23, 2020, an approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) shall be deemed to be a license under section 351 of the PHS Act.[5] To implement the BPCI Act, FDA recommended definitions of the terms "protein" and "chemically synthesized polypeptide" in a proposed rule and guidance documents. Generally, FDA defined "protein" to mean "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size."[6] Relying on this definition, FDA compiled a list of biological products that will transition to biologics license applications (BLAs) on March 23, 2020 (List of Transition Products). The agency has yet to address the scope of the statutory term "analogous product" when applied to the protein category.

Prior to the transition date, and before FDA finalized its proposed rule, Congress amended the definition of "biological product" under the PHS Act by broadening the scope of the term "protein." Specifically, the Further Consolidated Appropriations Act of 2020, enacted on December 20, 2019 (the Budget Act), removed the parenthetical limiting language "except any chemically synthesized polypeptide" that modified the term "protein."[7] As amended, the statutory definition of "biological product" is:

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architectures by synergy between dynamical template self-assembly and biomineralization. NATURE MATERIALS (Jun. 2007) 6:434-439 (Tab 2).

[2] *See* Mukherjee, S., *et al.*, What gives an insulin hexamer its unique shape and stability? Role of ten confined water molecules. J PHYS CHEM B (2018) 122:1631-1637 (Tab 3).

[3] *See* Lührs, T., *et al.*, 3D structure of Alzheimer's amyloid-β(1-42) fibrils. PROC NATL ACAD SCI USA (Nov. 2005) 102(48):17342-17347 (Tab 4).

[4] *See* Perlmutter, J.D., *et al.*, Mechanisms of virus assembly. ANNU REV PHYS CHEM (Apr. 2015) 66:217-239 (Tab 5).

[5] BPCI Act 7002(e)(4).

[6] 83 FR 63817, 63821 (Dec. 12, 2018); *Draft Guidance for Industry: New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (Dec. 2018) at 13.

[7] Pub. L. No: 116-94 (Dec. 20, 2019).

> The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, ***protein*** ~~(except any chemically synthesized polypeptide)~~, ***or analogous product***, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[8]

The apparent intent of the change is to place proteins manufactured through synthetic systems, and analogous products, on an even footing with proteins and analogous products manufactured through biological systems.

Somatuline Depot is comprised of alpha amino acid chains that associate with each other to form large amino acid polymers, which are structurally organized as nanotubes. FDA's proposed framework for proteins recognizes that the underlying amino acid polymer of a protein can be comprised of two or more amino acid chains associated with each other.[9] According to FDA, the association can be in a manner found in nature or in a manner that is not found in nature (*i.e.,* a novel manner that is not found in naturally occurring proteins). The different manners of association have different frameworks for determining whether the polymer is a protein. The lanreotide acetate polymer in Somatuline Depot meets the threshold for regulation as a protein under both frameworks.

To address the new definition of "biological product" under the Budget Act, FDA updated its List of Transition Products to include chemically synthesized products that FDA has identified as falling within the statutory definition of a "biological product." The List of Transition Products, which is current as of December 31, 2019, does not include Somatuline Depot (lanreotide acetate). As detailed in this comment, Ipsen believes the list should be updated prior to the March 23, 2020, final transition date to include Somatuline Depot (lanreotide acetate).

II. Lanreotide Acetate in Somatuline Depot is a Protein Under the Framework Described by FDA

Although FDA has not issued a final, binding rule to define the term "protein," the agency has stated its current thinking that a protein is "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size."[10] Based on the recent statutory amendment, a polymer falls within the scope of the statutory term "protein" irrespective of whether it originates from a biological or a synthetic system. Further, FDA has recognized that it will consider polymers that are composed of multiple chains of amino acids to be proteins where the chains collectively exceed 40 amino acids. This is particularly the case where the chains are associated "in a manner that occurs in nature."[11] As FDA explained:

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[8] 42 USC 262(i)(1), as amended by the Further Consolidated Appropriations Act of 2020 (emphasis added).

[9] 83 FR at 63821.

[10] *Id.* at 63824.

[11] *Id*.

> [W]hen two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer would be based on the total number of amino acids in those chains, and would not be limited to the number of amino acids in a contiguous sequence. In other words, the amino acids in each such amino acid chain would be added together to determine whether the product meets the numerical threshold in FDA's interpretation of the term "protein". . . . "[12]

We appreciate FDA's efforts to develop this regulatory definition, and the sophisticated scientific understanding that it embodies, particularly in recognizing the importance of multichain structures in the field of protein science and the variety of ways in which amino acid chains may be associated in the biological world. Addressing and including such structures is central to any reasonable interpretation of the term protein.

The frame of reference for analyzing the lanreotide acetate polymer in Somatuline Depot is the finished product. In the preamble to the 2018 proposed rule, FDA makes clear that the associated amino acid chains "would be added together to determine whether the *product* meets the numerical threshold."[13] A product for FDA regulatory purposes is based on the active substance as it exists in a finished dosage form in association with one or more other ingredients, *i.e.,* in formulation.[14] As the agency stated in its preamble discussion to the proposed rule, the focal point for the regulatory analysis is on "the product" and is "not limited to the number of amino acids in a contiguous sequence."[15] In the case of Somatuline Depot, the product consists of lanreotide acetate in a supersaturated aqueous formulation as an injectable dosage form contained within a prefilled syringe.[16] As discussed below, within the product and dosage form, lanreotide acetate exists in the form of highly complex, self-assembled structures composed of smaller subunits that associate naturally (based on the inherent properties of the lanreotide amino acid chain) and in a manner found in a variety of naturally occurring proteins. Therefore, according to the framework described by the FDA, Somatuline Depot meets the FDA's interpretation of the term "protein" as we explain below.

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[12] *Id*. at 63821.

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

[14] *See* 21 CFR 210.3(b)(4); 21 CFR 314.3(b).

[15] 83 FR at 63821.

[16] Lanreotide as a monomer in water does not exhibit extended release properties. Somatuline Depot is thought to form a solid depot *in situ* allowing for a 4-week long dosing interval for most uses and a 6- or 8-week interval at the highest strength in certain cases. Somatuline Depot Prescribing Information (rev. Apr. 2019) at Section 2.2; *see generally* 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):10258-10262 ("The exceptional self-assembling properties of Lanreotide acetate in water suggest a correlation between Lanreotide nanotube organization and the controlled release properties of [Lanreotide acetate hydrogel].") (Tab 1).

A. Is the lanreotide acetate polymer in Somatuline Depot an alpha amino acid polymer with a specific defined sequence?

Lanreotide in monomeric form is a peptide of eight amino acid residues, conformationally fixed into a hairpin structure by a disulfide bridge. The structure of lanreotide in Somatuline Depot is a polymeric macromolecular assembly of nanotubes composed of many thousands of lanreotide acetate monomers.[17] Each monomer is an alpha amino acid chain with the identical amino acid sequence, D-βNal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, and a disulfide bridge between the two cysteine (Cys) residues. This amino acid chain, or monomeric unit, forms a well-defined dimer that serves as the building block that further associates to form a polymeric nanotube. The overall structure has a defined sequence of repeating units of amino acid motifs in an antiparallel β-sheet protein array.

B. Does the amino acid polymer in Somatuline Depot exceed 40 amino acids?

To determine whether the defined sequence is more than 40 amino acids in size, FDA has indicated that, if (1) the amino acid polymer product contains two or more amino acid chains, (2) the chains in the product are associated in a manner that occurs in nature, and (3) the total number of amino acids in the associated chains is in excess of 40 amino acids, then the defined sequence would not be limited to the number of amino acids in a contiguous sequence. Rather, the amino acids in the associated chains would be added together to determine whether the product meets the size limit. In this case, the size of the self-assembled structures, based on the cumulative number of amino acid chains, far exceeds the numerical threshold that FDA has adopted.

1. Does the structure comprise two or more amino acid chains?

As described in Section II.A above, lanreotide as it exists in Somatuline Depot is a polymeric macromolecular assembly of nanotubes comprised of many thousands of lanreotide monomers, with each monomer constituting an amino acid chain.[18]

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[17] *See generally* 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):10258-10262 (Tab 1); 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):2484-2501 (Tab 6).

[18] 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):10258-10262 (Tab 1).

2. Are the amino acid chains associated with each other in a manner that occurs in nature?

i. Lanreotide acetate self-assembles in the same manner as found in naturally occurring proteins and other self-organizing biological systems

The lanreotide acetate in Somatuline Depot exhibits a high degree of structural organization, order and complexity, with precisely defined molecular and structural features. The interactions between amino acid chains in Somatuline Depot involve the same chemistry and thermodynamic ordering that drives protein self-assembly in all proteins, and such interactions are central to the assembly of large protein molecules and protein complexes.[19]

The key elements for assembly of natural protein structures are noncovalent interactions between the self-organizing molecules,[20] *i.e.*, hydrogen bonds, hydrophobic interactions, and electrostatic interactions (such as ionic interactions and van der Waals interactions). These interactions are determined by the amino acid sequence of the protein. Lanreotide exhibits the same relationship between sequence and structure;[21] its amino acid sequence provides for hydrogen bonding, hydrophobic interactions, and electrostatic interactions that drive self-association with a high degree of hierarchical ordering *via* the formation of β-sheet networks.

Specifically, the nanotubes are built up from helicoidal filaments, formed by peptide dimer building blocks self-assembled into antiparallel β-sheets through an alternating pattern of the aliphatic and aromatic amino-acid residues.[22] The higher order structure of lanreotide proceeds directly from the primary structure of the amino-acid sequence, which is a hallmark of protein chemistry. The intrinsic properties of the monomer to noncovalently polymerize cause the drug product to fold into nanotubes. The β-hairpin structure of the monomer stabilizes the 3D scaffold and facilitates the step-wise assembly to form β-sheet filaments and, ultimately, complex, stable nanotubes. This step-wise structural assembly, driven by a defined amino acid sequence, is fundamental to protein chemistry. The associations between amino acid chains in Somatuline Depot are not merely of a kind that occurs in nature – they are the driving forces in protein structure, including intermolecular association, *i.e.*,

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[19] *Id*.; *see also* McManus, J.J., *et al.*, The physics of protein self-assembly. CURRENT OPINION IN COLLOID & INTERFACE SCIENCE (2016) 22:73-79 (Tab 7).

[20] *See* Whitesides, G., *et al.*, Molecular self-assembly and nanochemistry – a chemical strategy for the synthesis of nanostructures. SCIENCE 254, 1312-1319 (1991) (Tab 8); McManus, J.J., *et al.*, The physics of protein self-assembly. CURRENT OPINION IN COLLOID & INTERFACE SCIENCE (2016) 22:73-79 (Tab 7).

[21] Mutations to the amino acid sequence of the monomer alter the nanotubes and sometimes suppress their formation entirely. *See* Valéry, C., *et al.*, Molecular origin of the self-assembly of lanreotide into nanotubes: A mutational approach. BIOPHYS J (2008) 94(5):1782-1795 (Tab 9).

[22] *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):10258-10262 (Tab 1); Pandit, A., *et al.*, Self-assembly of the octapeptide lanreotide and lanreotide-based derivatives: the role of the aromatic residues. J PEPT SCI (2008) 14:66-75 (Tab 10); 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):2484-2501 (Tab 6).

associations between two or more individual amino acid chains, that are critical to the role that proteins play in self-organizing biological systems.

ii. Protein assembly in Somatuline Depot

As further detailed in Figure 1 below, 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. These filaments gather together into bundles of 26 β-sheet fibers and begin to form long, flat ribbons. The ribbons curl into open helical structures that eventually close to form a hollow nanotube.[23] The nanotubes are then further bundled into hexagonal assemblies each composed of seven nanotubes and, particularly at the concentrations reached in Somatuline Depot, form a polydisperse array of embedded nanotubes in the final drug product.[24] The hexagonal organization of the nanotubes is lost, yet the embedded nanotubes exhibit "the same molecular and supramolecular organizations as the individual monodisperse nanotubes" and also demonstrate higher thermodynamic stability.[25]

A paper by Valéry et al. from 2003 was first to describe the structural assembly of lanreotide into nanotubes. The figure below from Valéry et al. 2003 depicts the structural assembly in schematic form up to formation of the hexagonal arrays.[26]

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[23] *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):2484-2501 (Tab 6).

[24] *Id.*

[25] *Id.*

[26] 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):10258-10262 (Tab 1). In a follow-up publication from 2004, Valéry elucidated the higher order structural organization that occurs when the lanreotide concentration is increased to the level used in Somatuline Depot. At that concentration, polydisperse embedded nanotubes are formed and the hexagonal lattice is lost. As noted in the text above, "the embedded nanotubes exhibit the same molecular and supramolecular organizations as the individual monodisperse nanotubes formed at lower peptide concentration." 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):2484-2501 (Tab 6).

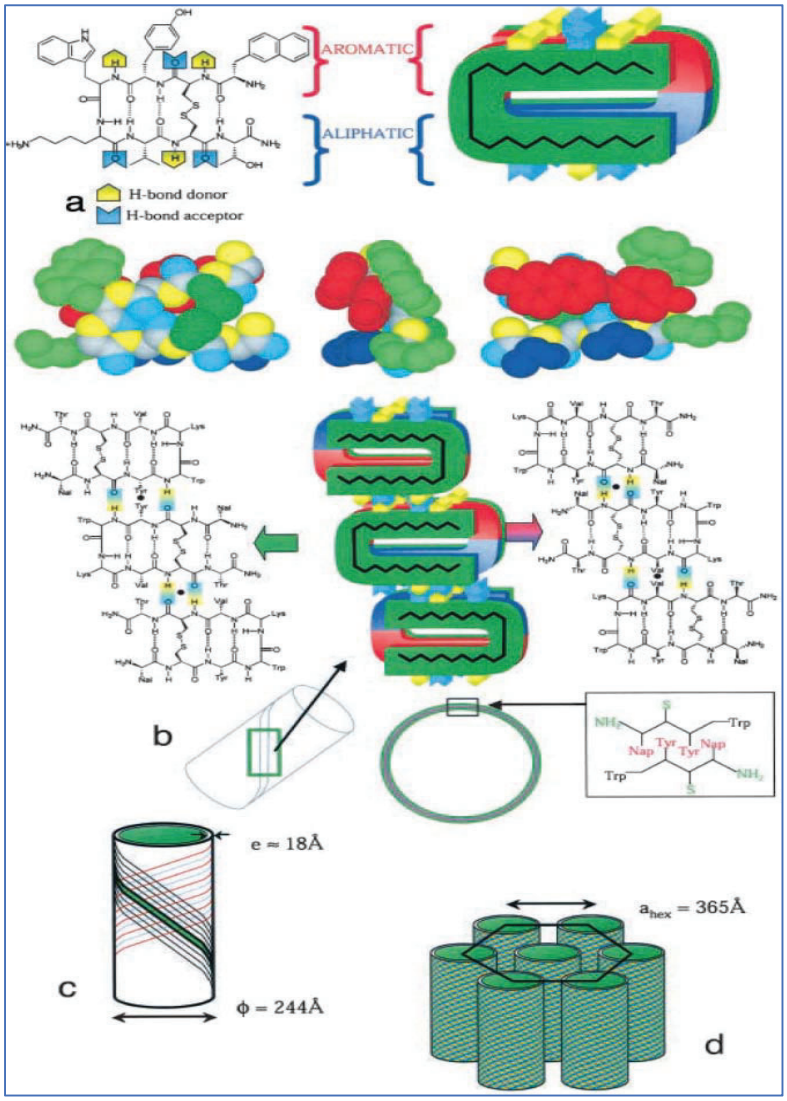

Fig. 1. Schematic view of the different hierarchical levels in the self-assembly of lanreotide-acetate nanotubes in water. (*a*) (*Left*) The Lanreotide molecule in the β-hairpin planar conformation, which is stabilized by the disulfide bridge, the turn, and intramolecular hydrogen bonds. (*Right*) Interaction between two Lanreotide molecules within the wall (bilayer) of the nanotubes. (*Bottom*) CPK models of a conformation in agreement with experimental data. The segregation of aromatic residues (red) from aliphatic residues (blue) and from hydrophilic region (green) is remarkable. (*b*) The structure of a filament with two different β-sheet fibers superimposed with their C_2 2-fold axes (black circles) meeting together. The segregation between aliphatic/aromatic residues is conserved within the filament organization. (*Inset*) Packing of the aromatic residues within the β-sheet fibers. (*c*) Self-assembly of 26 filaments to form a nanotube. (*d*) Liquid crystalline hexagonal columnar phase formed by the nanotubes.

iii. Comparison to other biological protein assemblies

The hierarchy, symmetries and interactions involved in the self-organization of lanreotide amino acid chains to form Somatuline Depot can be observed in a wide range of self-assembled proteins. This type of self-assembly plays a crucial biological role.[27] Cellular systems contain numerous functional nanostructures built from molecular self-assembly, such as membranes, actin filaments, tubules, chromosomes, flagella, and cytoskeleton. The key elements of molecular self-assembly are a complementary of shape and noncovalent interactions. For biological materials, these noncovalent interactions are typically hydrogen bonds (intra- and intermolecular and with water), hydrophobic effects, and electrostatic interactions such as ionic interactions and van der Waals interactions. Although many of these interactions are weak (1-5 kcal/mol), their large numbers make the final architectures highly stable.[28] Some of the most studied examples found in nature include, but are not limited to: insulin, amyloidal fibers, and viral capsids. A brief description of these protein structures follows:

- The natural polypeptide **Insulin** is composed of two peptide chains (21 and 30 amino acids), held together by three disulfide bonds, that form the insulin monomer.[29] Hydrophobic interactions and hydrogen bonding lead to the formation of insulin dimers.[30] In the presence of bivalent metal ions (in particular Zn^{2+}) the dimer self-assembles to hexamers.[31] Further self-assembly of the hexamers to a crystalline structure is also possible[32] as is the formation of β-sheets.[33] The lanreotide peptide self-assembles using the same mechanisms and stepwise process. Lanreotide association begins with a disulfide bridge that stabilizes the hairpin structure of the monomer during self-assembly and is stable throughout the self-organization process, which proceeds with the formation of dimers that in turn form antiparallel β-sheets and nanotube structures.

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[27] Ahnert, S.E., *et al.*, Principles of assembly reveal a periodic table of protein complexes. SCIENCE (2015) 350:62-66 (Tab 11).

[28] *See* Lodish, H., *et al.,* Molecular Cell Biology (4th Edition, 2000, W.H. Freeman) at pdf 1 (Tab 12).

[29] *See* Hua, Q., *et al.*, Mechanism of insulin chain combination: Asymmetric roles of A-Chain α-Helices in Disulfide Pairing. J BIOL CHEM (2002) 277(45):43443-43453 (Tab 13).

[30] *See* Mukherjee, S., *et al.*, What gives an insulin hexamer its unique shape and stability? Role of ten confined water molecules. J PHYS CHEM B (2018) 122:1631-1637 (Tab 3).

[31] *See* Dunn, M. F., Zinc−ligand interactions modulate assembly and stability of the insulin hexamer − a review. BIOMETALS (2005) 18 (4), 295−303 (Tab 14).

[32] *See* Rege, N.K., *et al.*, Structure-based stabilization of insulin as a therapeutic protein assembly via enhanced aromatic-aromatic interactions. J BIOL CHEM (2018) 293(28):10895-10910 (Tab 15).

[33] Jiménez, J.L., *et al.*, The protofilament structure of insulin amyloid fibrils. PROC NATL ACAD SCI USA (2002) 99:9196-9201 (Tab 16); Dische, F.E., *et al.*, Insulin as an amyloid-fibril protein at sites of repeated insulin injections in a diabetic patient. DIABETOLOGIA (1988) 31:158-161 (Tab 17).

- **Amyloidal** fibers formed by the peptide amyloid-β (1-42) are formed from the cleavage of the APP protein (amyloid precursor protein) by the enzyme, α-secretase, into small peptide molecules. These peptides self-assemble into parallel β-sheets where the proto-filaments are formed by intermolecular β-sheet association through hydrogen bonding, to create a network of filament structures. The β-sheets are formed by the peptide residues 18-26 and 31-42, and the inter-sheet contact/stabilization is further achieved by salt bridge interactions.[34] The mechanism of lanreotide self-assembly again proceeds through the same stepwise β-sheet formation and proto-filament formation, driven by the same forces. Similarly, lanreotide has two amine structures that provide an overall cationic charge of the peptide over a large pH range, which has been associated with further stabilization of the filament structure, mimicking the role of the salt bridge in amyloid fibers.

- The **Capsid** of the **TMV virus** self-assembles into a helical structure that is maintained by hydrophobic interactions and hydrogen bonding.[35] These non-covalent bonds provide a thermodynamically stable macromolecular structure composed of repeating units. The structure and stabilization closely resembles that seen in the self-assembly and molecular organization of the lanreotide peptide into largescale nanotube structures. Specifically, lanreotide self-assembles *via* an association of subunits that is driven by hydrophobic interactions and hydrogen bonding into a helical structure that then closes to form a nanotube.

The associations of amino acid chains observed in Somatuline Depot are directly aligned with those described here.[36] These types of interactions and self-assembly processes rely on the presence of an exact topography of hydrophobic to hydrophilic residues, and an amphiphilic-type amino-acid sequence, as seen in lanreotide. Self-assembly in these structures is characterized by specific association of molecules dictated by noncovalent interactions among the components.[37]

In sum, self-assembly, driven by the primary amino acid sequence, is a ubiquitous trait of proteins. Lanreotide in Somatuline Depot shares this trait: it self-assembles into nanotubes through the interaction of amino-acid chains that associate in a manner found in nature.

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[34] Vignaud, H., *et al.*, A structure-toxicity study of Aß$_{42}$ reveals a new anti-parallel aggregation pathway. PLOS ONE 8, e80262 (2013) (Tab 18); Lührs, T., *et al.*, 3D structure of Alzheimer's amyloid-β(1-42) fibrils. PROC NATL ACAD SCI USA (2005) 102:17342-17347 (Tab 4).

[35] *See* Perlmutter, J.D., *et al.*, Mechanisms of virus assembly. ANNU REV PHYS CHEM (Apr. 2015) 66:217-239 (Tab 5).

[36] *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):10258-10262 (Tab 1); Pandit, A., *et al.*, Self-assembly of the octapeptide lanreotide and lanreotide-based derivatives: The role of the aromatic residues. J PEPT SCI (2008) 14:66-75 (Tab 10); 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):2484-2501 (Tab 6).

[37] 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):2484-2501 (Tab 6).

3. When the associated amino acid chains in Somatuline Depot are added together, does the product meet the agency's numerical threshold for the term protein?

FDA has appropriately recognized that certain products contain multiple amino acid chains that associate with each other, and those associations must be considered when determining the length of the amino acid polymer. Lanreotide in Somatuline Depot is a polymeric macromolecular assembly of nanotubes. Each monomeric unit is an alpha amino acid chain. The overall structure has a defined sequence of repeating units of amino acid motifs in an antiparallel β-sheet protein array. The size of the self-assembled structures, based on the cumulative number of amino acid chains, far exceeds the numerical threshold that FDA has adopted to date. As shown above, the amino acid chains in Somatuline Depot associate in a manner that occurs in nature and is commonly found in protein chemistry and biological systems. Thus, the relevant size of the lanreotide acetate polymer in Somatuline Depot should be based on the total number of amino acids in the nanotube structures that make up the Somatuline Depot finished product. Accordingly, Somatuline Depot nanotubes should be added to the list of products approved under NDAs that will be deemed to be BLAs on March 23, 2020.

III. Lanreotide Acetate in Somatuline Depot is a Protein even if FDA Finds that the Amino Acid Chains Do Not Associate in a Manner Found in Nature

In the event FDA determines that the amino acid chains in Somatuline Depot do not associate in a manner that occurs in nature, FDA still must consider the structural and/or functional characteristics of Somatuline Depot nanotubes in determining whether the overall size of the amino acid polymer is greater than 40 amino acids. In this situation, FDA stated that it would conduct:

> a fact-specific, case-by-case analysis to determine whether the size of the amino acid polymer, for purposes of this definition, should be based on adding each of the amino acids in the amino acid chains together, or should be based on separate consideration of the amino acid chains (*e.g.*, the number of amino acids in the largest chain). In such cases, FDA would consider in its analysis, among other things, any structural or functional characteristics of the product."[38]

When applying the fact-specific framework to Somatuline Depot, the structural characteristics of Somatuline Depot (as detailed above) show that it has the characteristics of a protein product:

- The nanotubes exhibit a high degree of organization, order and complexity, with precisely defined molecular and structural features, with a diameter of 244 Å and maximal length of 3 μm.

- The interactions between amino acid chains in Somatuline Depot involve the same chemistry and thermodynamic ordering that drives protein self-assembly in all proteins, and such interactions are central to the assembly of large protein molecules and protein complexes.

[38] 83 FR at 63821.

- The nanotubes are built up from helicoidal filaments, formed by peptide dimer building blocks self-assembled into antiparallel β-sheets through an alternating pattern of the aliphatic and aromatic amino-acid residues. The higher order structure proceeds directly from the primary structure of the amino-acid sequence, which is a hallmark of protein chemistry.

- This type of self-assembly plays a crucial biological role, *e.g.*, cellular systems contain numerous functional nanostructures built from molecular self-assembly, such as membranes, actin filaments, tubules, chromosomes, flagella, and cytoskeleton.

Accordingly, the structural characteristics of the product, its self-assembling complexity, and the important functional role of the nanotubes to the safety, purity and potency of Somatuline Depot, indicate that the structure as a whole should be regarded as exceeding 40 amino acids in size and, therefore, that the Somatuline Depot NDA must be deemed to be a BLA.

IV. The Lanreotide Acetate Polymer Would be Considered a Protein under Commonly Recognized Scientific Principles

As described above, the lanreotide acetate polymer in Somatuline Depot is within the scope of the term protein under FDA's current framework. However, we recognize that FDA may need to re-open the public comment process and reevaluate its framework in light of the December 2019 statutory amendment. Even under another framework, based on prevailing scientific thought regarding common protein characteristics, the lanreotide acetate polymer would qualify as a protein.

Prevailing science identifies proteins based on inherent structural features and not only based on the length of the amino acid sequence.[39] For example, a 41 amino acid chain comprised only of lysine would qualify as a protein under FDA's bright-line rule, but probably would not be considered a protein by experts in the field because it would not have any of the typical sequence and structural complexity of a protein.[40] An approach based only on amino acid sequence length does not accurately reflect the complexity of proteins.[41]

A key structural feature of a protein is the capacity of an amino acid chain – of any length – to drive the formation of complex higher order three-dimensional structures.[42] This would exclude conventional peptides, but aptly captures the complexity and breadth of intra- and inter- molecular

[39] *See* Comment from The Biotechnology Industry Organization (BIO), Docket No. FDA-2010-N-0477 (Dec. 23, 2010) at E1-E2, *available at* https://www.regulations.gov/document?D=FDA-2010-N-0477-0035.

[40] Over a large range of conditions, polylysine adopts a random coil configuration. *See* Davidson B., *et al.*, The conformational transitions of uncharged Poly-L-lysine. α Helix Random-Coil-β Structure (1967) 6(6):1616-1629 (Tab 19).

[41] FDA's bright-line approach will undoubtedly misclassify certain products and treat similar products (*e.g.*, products with 40 and 41 amino acids) differently.

[42] *See* BIO Comment, Docket No. FDA-2010-N-0477, at E1.

protein structure regardless of size or mode of synthesis. Under such terms, lanreotide acetate in Somatuline Depot supersaturated solution is a protein. Specifically, it is an alpha amino acid polymer in which the primary structure drives self-assembly to form complex three-dimensional structures, a property that distinguishes it from a peptide under prevailing scientific thought. For a chemically synthesized product like lanreotide, this line of analysis is also consistent with FDA's current regulations, which identify "[t]herapeutic synthetic peptide products of 40 or fewer amino acids" as subject to biologics licensure.[43] Thus, the fact that the monomeric units of lanreotide have fewer than 40 amino acids would not be considered determinative in the field of protein science or even under FDA's own existing regulations governing biological products.

V. Somatuline Depot May Also Be Considered an "Analogous Product"

The amended statutory definition of "biological product" includes both chemically synthesized and naturally-derived proteins. It also includes related products that may not meet the standard to be classified as a protein but are nevertheless considered to be "analogous" to proteins.[44]

FDA has defined "analogous product" by regulation with respect to certain specific categories of biological products, as follows:

> A product is analogous: (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.
>
> (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.
>
> (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.[45]

Based on these definitions, which were last updated about 70 years ago, it is apparent that there is no uniform basis for assessing whether a product may be analogous to a specifically listed product. Analogous, for example, may be based on source material, structure, function or mode of action. This is consistent with the plain meaning of the term, in which "analogous" is defined as: "similar or comparable to something else either in general or in some specific detail."[46]

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[43] 21 CFR 601.2(a).

[44] 42 USC 262(i)(1) (the term "biological product" includes a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein, or an analogous product*" (emphasis added)).

[45] 21 CFR 600.3(h)(5).

[46] Merriam-Webster Dictionary, available at https://www.merriam-webster.com/dictionary/analogous.

As described above, the lanreotide acetate polymer in Somatuline Depot has significant structural similarities with other products classified as proteins by the agency. In the finished dosage form, lanreotide acetate is an alpha amino-acid polymer substance composed of associations between amino acid chains. The associated chains form an inherently complex structure similar to other proteins, and the structure and complexity of the nanotubes is comparable to biological tubular assemblies such as the capsid of the TMV virus, as discussed above. The lanreotide structures in Somatuline Depot have the key informational and structural qualities of a protein, including high-order structure driven by primary structure. Given the similarities between the lanreotide acetate polymer and other proteins, including the inherent tendency of lanreotide to self-assemble under the conditions described above, Somatuline Depot falls well within the plain meaning of the statutory term "analogous product."

VI. Conclusion

On March 23, 2020, all biological products approved under NDAs will be deemed to be licensed under BLAs. Recently, Congress broadened the definition of biological product to remove the exclusion for chemically synthesized polypeptides. Somatuline Depot is a synthetic polypeptide product that forms complex structures and should transition to a BLA. Whether analyzed under FDA's proposed framework that pre-dates the amended definition of biological product, under the prevailing scientific framework, or as a product "analogous" to a protein, Somatuline Depot should be classified as a biological product.

Respectfully submitted,

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