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THERA technologies

February 18, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rom 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: The "Deemed to be a License" provision of the BPCI Act: Questions and Answers; Request for Comments on Preliminary List of Affected Applications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

Dear Dockets Management Staff:

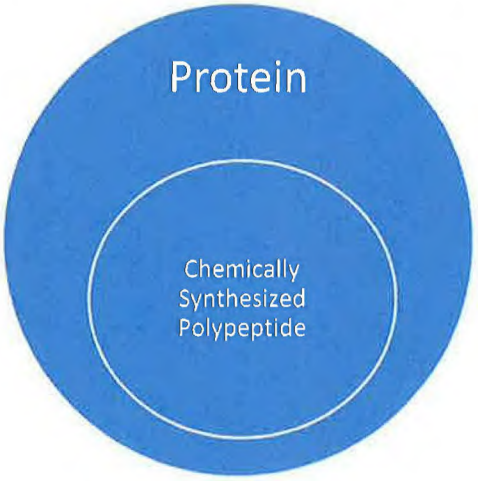
Theratechnologies Inc. (Theratechnologies) is writing in opposition to the Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (the "Preliminary List"), Docket No. FDA-2015-D-4750, regarding the anticipated reclassification of the approved NDA #022505 for EGRIFTA SV™ (tesamorelin acetate), herein referred as tesamorelin, to a Biologics License Application (BLA).

Theratechnologies is an innovative biopharmaceutical company with two products currently marketed in the United States. Our commercialized products and our research pipeline focus on specialized therapies addressing unmet medical needs in HIV and oncology. As we explain below, our product, tesamorelin, does not fall within the definition of a protein or biological product, and thus its New Drug Application (NDA) should not be deemed to be a BLA.

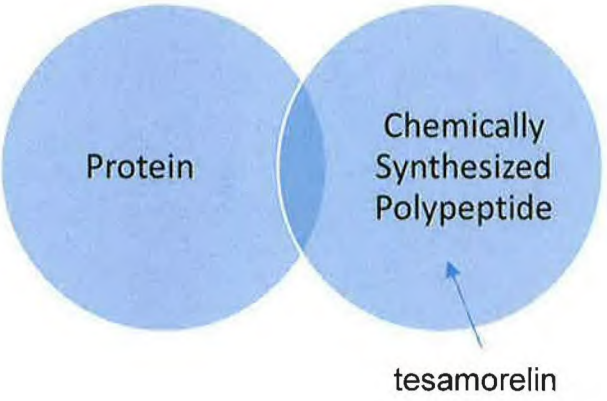
I. TESAMORELIN IS NOT A "PROTEIN" UNDER FDA'S DEFINITION

On December 20, 2019, when the Further Consolidated Appropriations Act, 2020 ("the Act") became law, it amended the definition of "biological product" by striking the language "(except any chemically synthesized polypeptide)," which had previously qualified the term "protein" in the Biologics Price Competition and Innovation Act (BPCIA) as originally passed. Yet, although the Preliminary List was adjusted to include all chemically synthesized

polypeptides above 40 amino acids as "proteins" (and thus biological products), this adjustment was overbroad. The striking of the language "(except any chemically synthesized polypeptide)" does not mean that *all* chemically synthesized polypeptides are proteins. Rather, it means that a protein cannot escape classification as a biological protein *only* by being chemically synthesized.[1] There is no indication that Congress intended to redefine the word "protein." If Congress had so intended, it could have included the term "chemically synthesized polypeptide" into the list of items that are "biological products."



FDA-Proposed Interpretation of BPCIA Amendment



Text- and Science-Based Interpretation of BPCIA Amendment[2]

II. Tesamorelin Is Not a "Protein" Because It Cannot Be Produced Biologically

The chemical structure of tesamorelin does not satisfy FDA's interpretation of the term "protein." First, FDA interprets the term "protein" to mean any "alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size."[3] Likewise, "chemically synthesized polypeptide" is interpreted to mean an "alpha amino acid polymer."[4] Although not

[1] For example, the large therapeutic *protein* erythropoietin has been prepared entirely by chemical synthesis. *See* Masumi Murakami et al., *Chemical Synthesis of Erythropoietin Glycoforms for Insights into the Relationship Between Glycosylation Pattern and Bioactivity*, 2 SCI. ADVANCES e1500678 (2016), https://advances.sciencemag.org/content/2/1/e1500678.

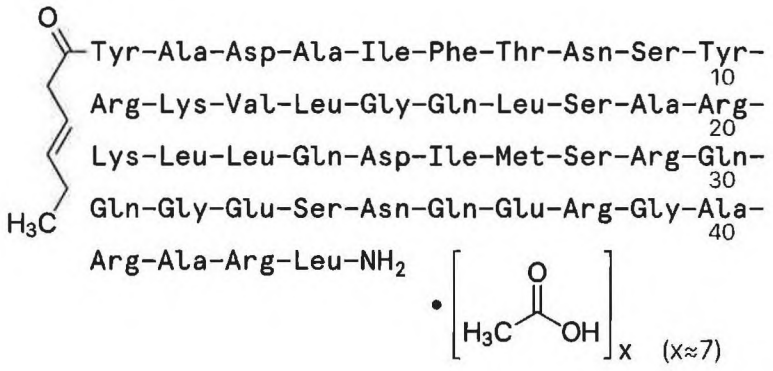
[2] Federal Register/Vol. 83, No. 238/Wednesday, December 12, 2018/Proposed Rules.

[3] U.S. FOOD & DRUG ADMIN., NEW AND REVISED DRAFT Q&AS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT (REVISION 2), at 12 (Dec. 2018), https://www.fda.gov/media/119278/download [hereinafter FDA BPCIA Q&A].

[4] FDA BPCIA Q&A, at 13.

all proteins consist *exclusively* of alpha amino acids, other structural features acknowledged in FDA's definition include only "post-translational modifications," a term which encompasses only natural variations such as glycosylation that occur during biosynthesis of proteins and peptides.[5] FDA's definition thus contemplates only either natural proteins or ones that completely structurally replicate a natural protein despite being produced chemically.

Tesamorelin is neither. Specifically, tesamorelin contains a non–naturally occurring chemical motif, *trans*-3-hexenoyl tyrosine, at one terminus, as shown below. The *trans*-3-hexenoyl moiety is not an "alpha amino acid" and thus the overall molecule is not an "alpha amino acid polymer." Nor is the *trans*-3-hexenoyl moeity a "post-translational modification," being entirely synthetic in origin. Accordingly, tesamorelin is not a "protein" under FDA's interpretation.



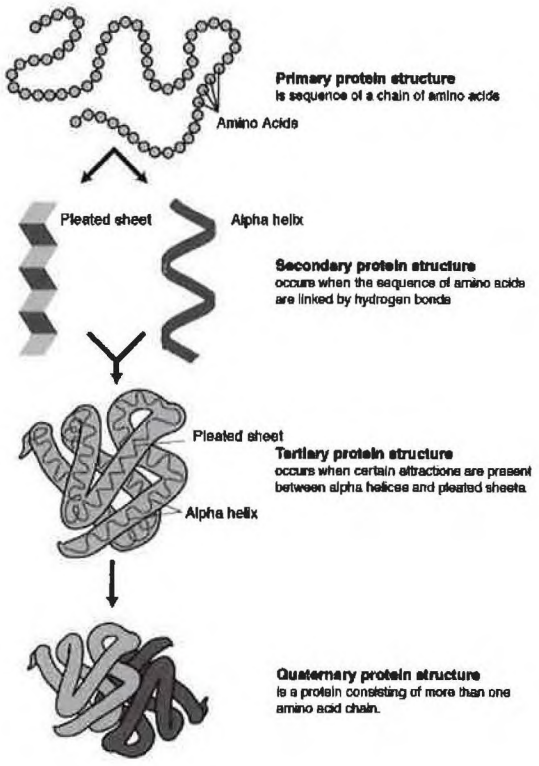
As discussed above, the amendment to the statutory definition of "biological product" had the effect of including within the definition proteins that are chemically synthesized. That revision did not change the underlying definitional principles concerning amino acid polymers.

III. TESAMORELIN IS NOT A "PROTEIN" UNDER THE SCIENTIFIC MEANING OF THE TERM

Beyond FDA's proposed definition of "protein," the scientific understanding of the term does not encompass tesamorelin, which largely lacks three-dimensional structure.

[5] FDA BPCIA Q&A, at 13.

A. The Functional Scientific Meaning of "Protein" Requires Secondary and Tertiary Structure



We appreciate that FDA seeks "consistency with the scientific literature" in classifying products as proteins or non-protein peptides.[6] Both peptides and proteins comprise chains of amino acids. But proteins are distinguished from mere peptides by their structural complexity, as proteins must possess a "stable multi-dimensional conformation."[7] Proteins possess secondary, tertiary, and often quaternary structure—that is, stable three-dimensional structure that distinguishes them from peptides and imbues them biological functions such as catalysis, signaling activity, receptor activity, and others.

Primary structure refers to the sequence of amino acids. Secondary structure refers to the presence of interactions between small groups of nearby amino acids that form α-helix, β-sheet (i.e., pleated sheet), and β-turn features. Tertiary structure refers to the overall stable three-dimensional shape of a protein and results from a process known as folding. Quaternary structure refers to the overall structure that results from the interaction of two or more distinct polypeptides.

In the absence of secondary structure, a peptide adopts a predominantly "random coil" structure. Secondary, tertiary, and quaternary structure is immensely important for protein function. A peptide without secondary structure thus lacks the characteristics that make proteins *proteins*. As FDA acknowledges, "a 'peptide' generally refers to polymers that are smaller, perform fewer functions, *contain less three-dimensional structure*, are less likely to be post-translationally modified, and thus are generally characterized more easily than proteins."[8]

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[6] FDA BPCIA Q&A, at 13.

[7] *See* Comment from PhRMA to FDA Regarding Docket No. FDA-2018-N-2732: Definition of the Term "Biological Product"; Proposed Rule, 83 Fed. Reg. 63817 (Dec. 12, 2018), filed Feb. 25, 2019.

[8] FDA BPCIA Q&A, at 13.

B. Tesamorelin, Unlike Proteins, Lacks Stable Three-Dimensional Structure

Experimental data confirm that tesamorelin lacks substantial secondary and tertiary structure that would be present in a protein. Rather, tesamorelin is essentially a linear, largely random-conformation chain without stable three-dimensional structure.[9]

First, analysis of tesamorelin using circular dichroism (CD) spectropolarimetry and nuclear magnetic resonance (NMR) has confirmed the absence of a stable secondary or tertiary structure. NMR is routinely used for precise characterization of secondary structure for molecules in solution.[10] Likewise, CD spectropolarimetry is a well-known technique for secondary structure characterization.[11] Results from this characterization indicate that both the drug substance and the active component of the drug product exist as a non-interacting chain characterized as partially α-helix (9.4%) and partially random-coil. The CD and NMR data do not support the presence of significant and stable β-structures, which would, if present, indicate tertiary structure. This structural characterization was consistent even with variation of conditions: varying pH between 4 and 7 had no influence on the structural properties observed. Aggregation, which would signal quaternary structure, has not been observed for either the drug substance or the drug product. And mannitol had no effect on the random structure of tesamorelin.

Second, analysis of tesamorelin using Fourier-transform infrared spectroscopy (FTIR) has confirmed the absence of a stable secondary structure. FTIR is a well-accepted method for characterizing secondary structure of proteins and peptides.[12] In the spectra of tesamorelin freeze-dried from aqueous solution, the band assigned to random coil/α-helix conformation (1650 cm^{-1}) preserves its position and relative intensity for up to 7 days of incubation. No band is detected at 1630 cm^{-1}; the presence of such a band would be indicative of an ordered intermolecular β-sheet structure. These findings provide further evidence that the random conformation of tesamorelin is stable in aqueous solution and that no aggregation-prone or stable β-sheet structure is formed. Aggregation or stable β-sheets would indicate quaternary and tertiary structure, respectively.

Thus, there is no secondary nor tertiary structure that would indicate that tesamorelin has a stable multi-dimensional conformation.

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[9] Data on file with FDA.

[10] *See, e.g.*, Andrea Cavalli et al., *Protein Structure Determination from NMR Chemical Shifts*, 104 PNAS 9615 (2007), https://www.pnas.org/content/104/23/9615.

[11] *See, e.g.*, Norma J. Greenfield, *Using Circular Dichroism Spectra to Estimate Protein Secondary Structure*, 1 NATURE PROTOCOLS 2876 (2006), https://www.nature.com/articles/nprot.2006.202

[12] *See, e.g.*, Huayan Yang et al., *Obtaining Information About Protein Secondary Structures in Aqueous Solution Using Fourier Transform IR Spectroscopy*, 10 NATURE PROTOCOLS 382 (2015), https://www.nature.com/articles/nprot.2015.024.

With the absence of a well-defined secondary and/or tertiary structure, the biological activity of tesamorelin is governed by the primary structure (sequence) of the peptide.

C. The Scientific Community Considers Tesamorelin to Be a Peptide, Not a Protein

Further, the scientific community at large does not regard tesamorelin to be a protein. Tesamorelin is a synthetic analogue of human growth hormone–releasing factor (hGRF). The scientific literature repeatedly characterizes tesamorelin and hGRF as a "hormone" or a "peptide."[13] For instance, THPdb, a peer-reviewed database of peptide and protein therapeutics, which distinguishes between the two, considers tesamorelin to be a "peptide."[14] We could not identify scientific literature referring to hGRF or tesamorelin as a "protein." To the extent that FDA seeks consistency with scientific understandings of peptides and proteins, it should take into account scientific consensus on tesamorelin.[15]

IV. TESAMORELIN IS MORE LIKE A SMALL MOLECULE THAN A BIOLOGIC

Congress passed the BPCIA in 2010 to create a biosimilar pathway modeled to some extent after the Hatch-Waxman Act's generic drug approval pathway. One of the reasons for this legislation was to create a legal pathway distinct for biosimilars and interchangeables for biological products, thereby acknowledging the differences between pharmaceutical drugs and biological products.

The NDA/ANDA pathway is well-suited to molecules that are structurally well-controlled and easily characterized, such as small-molecule drugs. This pathway is well-suited because, under current scientific standards, it is possible to determine whether two small-molecule drugs are analytically identical down to the atom, and thus whether two drug products containing them are "bioequivalent."[16]

In contrast, analytical technology for very large, complex biomolecules is still evolving and has not reached the same level of sophistication. Thus, the BLA/aBLA pathway works well

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[13] *E.g.*, Sohita Dhillon, *Tesamorelin: A Review of its Use in the Management of HIV-Associated Lipodystrophy*, 71 DRUGS 1071 (2011), https://link.springer.com/article/10.2165/11202240-000000000-00000.

[14] *See Tesamorelin,* THPdb, https://webs.iiitd.edu.in/raghava/thpdb/display_thppid_sub.php?details=Th1129 (database entry); Salman Sadullah Usmani, *THPdb: Database of FDA-Approved Peptide and Protein Therapeutics*, 12 PLOS ONE e0181748 (2017), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181748.

[15] *See supra* note 14.

[16] *See* 21 C.F.R. § 314.3 ("*Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.").

for complex molecules that require complicated characterization and analysis and whose manufacturing processes are not straightforward from their structures alone. This pathway, which asks not that a follow-on product be completely identical but merely "highly similar" in a way that results in no clinically meaningful differences between products,[17] is necessary because of limitations in analytical technology and the potential for the inherent variability of biological products.

Unlike small molecule drugs, complex biological products cannot be reverse engineered or fully characterized by analyzing the final product using currently known analytical techniques. Indeed, the manufacture of biologics is path-dependent:[18] The products can be so sensitive that any slight variation or change to the manufacturing process can impact the quality, safety, or efficacy of the final product in a way that might not be obvious from analyzing the end product.[19] The same path-dependent sensitivity to manufacturing processes, which is a characteristic of biological products, does not apply to chemically synthetized polypeptides without stable three-dimensional structure.

Like small molecules, chemically synthesized polypeptides like tesamorelin are smaller than proteins and can be completely structurally characterized, as well as synthetically reproduced from knowledge of their structure. They lack stable three-dimensional structure or complex post-translational modifications that make synthesis or characterization elusive. And similar to a small molecule drug, chemically synthesized polypeptides like tesamorelin can be synthetically reproduced with complete structural fidelity, and a follow-on company can confirm that its product is essentially identical to the innovator product—i.e., under a "bioequivalence" analysis of two products without needing, scientifically, to seek a more generous "biosimilarity" determination.

Therefore, in comparison to biologics, the relative simplicity of reverse engineering makes including small, well-characterized chemically synthesized polypeptides like tesamorelin within the biological products regime not scientifically sound: doing so would subvert Congress's intent in creating dual NDA and BLA pathways that reflect the underlying structural aspects of each class of products. Since tesamorelin is more similar to a small molecule than a complex protein, tesamorelin should not be classified as a biological product.

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[17] "A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." *Biosimilar & Interchangeable Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products (last updated Oct. 23, 2017).

[18] *See generally* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1032–37 (2016), https://ilr.law.uiowa.edu/print/volume-101-issue-3/manufacturing-barriers-to-biologics-competition-and-innovation/ (describing complexity of manufacturing and limits of analytical science).

[19] *See* Price & Rai, *supra*, at 1032–37.

V. THE FURTHER CONSOLIDATED APPROPRIATIONS ACT ALTERED THE FDA'S "BIOLOGICAL PRODUCT" DEFINITION ANALYSIS

In 2018, FDA proposed to amend its regulation that defines "biological product" to incorporate changes made by the BPCIA and to provide its interpretation of the statutory terms "protein" and "chemically synthesized polypeptide."[20] At the time of this proposed rule, "biological product" was statutorily defined to include "protein (except any chemically synthesized polypeptide)." Therefore, FDA's proposed rule would amend 21 C.F.R. § 600.3 to add definitions of "protein" and "chemically synthesized polypeptide."

FDA's main concern was administrative convenience and predictability. Although it acknowledged that there were *functional* differences, such as structural complexity, between proteins and mere peptides, FDA proposed a bright-line rule based on amino acid length. This made sense at the time, because that rule did tend to accurately sort proteins, which tend to be much longer, and peptides, which tend to be much shorter. This accuracy was only possible, though, because of the BPCIA's carve-out of "chemically synthesized polypeptides," which allowed FDA not to consider products such as tesamorelin that fell close to the dividing line; since these products would not be biologics regardless of the threshold.

In its proposal, FDA recommended that the term "protein" mean any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size and that "chemically synthesized polypeptide" mean any alpha amino acid polymer that is made entirely by chemical synthesis and is greater than 40 amino acids but less than 100 amino acids in size. The FDA stated that this rule was necessary to clarify statutory authority under which biological products are regulated and to prevent inconsistency in regulation.

The description of the proposed rule stated that "FDA reviewed the pertinent literature and concluded that a threshold of 40 amino acids is appropriate for defining the upper size boundary of a peptide" even though "there is support in the scientific literature for a threshold of 50 amino acids."[21] Additionally, within the Analysis of Regulatory Alternatives to the Proposed Rule, FDA considered a bright-line rule of 50 amino acids. In that analysis, FDA noted that the "same 89 existing approved NDAs for biological products would transition to [deemed] BLAs" if proteins were defined as greater than 50 amino acids.[22] Moreover, FDA explicitly identified that only one other NDA product, composed of 44 amino acids,[23] would not be affected if the threshold were 50 amino acids instead of 40 amino acids.[24] FDA did not factor that product into

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[20] Definition of the Term "Biological Product, 83 Fed. Reg. 63,817 (proposed Dec. 12, 2018) [hereinafter FDA Proposed Rule].

[21] FDA Proposed Rule.

[22] FDA Proposed Rule.

[23] Tesamorelin acetate has 44 amino acids.

[24] FDA Proposed Rule.

its analysis, however, because the NDA product was made *entirely by chemical synthesis*, which under the statutory definition of the time would not meet the definition of "biological product" regardless of the amino acid length threshold. Because the preliminary list of products that would transition under 40 amino acid regime or a 50 amino acid regime would be identical, FDA did not need, at the time, to consider in-depth the possibility of defining "protein" as greater than 50 amino acids in size.

Because the only NDA products that fell between 41 and 50 amino acids were chemically synthesized polypeptides, FDA did not truly consider NDA products between 41 and 50 amino acids in determining its definition. In light of the Act, the background considerations of FDA's analysis are no longer accurate, and **FDA should revise its definition.**

To the extent that size alone can differentiate peptides and proteins, there is scientific literature that suggests that 50 amino acids is an appropriate upper boundary of a non-protein peptide.[25] With the new change in the law[26], we argue that 40 amino acids is not an appropriate number to distinguish peptides from proteins. Therefore, we request FDA to reconsider its definition of peptide and protein under the new definition of biological product because chemically synthesized polypeptides are no longer per se excluded from "proteins." Indeed, FDA justified its "proposal to use a threshold of 40 amino acids for its 'bright-line' approach" because "amino acid polymers that are greater than 40 amino acids may often assume several of the structural and functional characteristics that are generally associated with proteins, lending a higher level of complexity to these products."[27] As described above, tesamorelin lacks these structural and functional characteristics.

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[25] *See, e.g.*, IUPAC, COMPENDIUM OF CHEMICAL TERMINOLOGY (THE "GOLD BOOK") (2d ed. 1997), https://doi.org/10.1351/goldbook.P04898 (last updated Feb. 24, 2014) ("Naturally occurring and synthetic polypeptides having molecular weights greater than about 10000 [Da] (the limit is not precise)."). The average molecular weight of individual amino acid residues in a peptide or protein is 110 Da, so a 10000 Da protein comprises around 90 amino acids. PROMEGA, TECHNICAL REFERENCE: AMINO ACIDS (2010), https://worldwide.promega.com/~/media/files/resources/technical%20references/amino%20acid%20abbreviations%20and%20molecular%20weights.pdf. *See also* Kara Rogers, *What Is the Difference Between a Peptide and a Protein?*, ENCYCLOPÆDIA BRITANNICA, https://www.britannica.com/story/what-is-the-difference-between-a-peptide-and-a-protein ("Traditionally, peptides are defined as molecules that consist of between 2 and 50 amino acids, whereas proteins are made up of 50 or more amino acids."); BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL (4th ed. 2002) ("Proteins come in a wide variety of shapes, and they are generally between 50 and 2000 amino acids long.").

Further, FDA has itself acknowledged that scientific literature supports a 50 amino acid cutoff. *See, e.g.*, U.S. FOOD & DRUG ADMIN., DEFINITION OF THE TERM "BIOLOGICAL PRODUCT": PRELIMINARY REGULATORY IMPACT ANALYSIS, at 12–13, https://www.fda.gov/media/122985/download; FDA Proposed Rule, at 63,820.

[26] Federal Register/Vol. 83, No. 238/Wednesday, December 12, 2018/Proposed Rules.

[27] FDA Proposed Rule.

VI. IMPACTS OF A THREE MONTH, RATHER THAN TEN YEAR, TRANSITION PERIOD

Nearly all companies affected by the BPCIA and its "Deemed to be a License" provision have had ten years to transition appropriately from the NDA framework to the BLA framework. These companies have been able to course-correct business plans, withdraw applications, discontinue label-expansion efforts, allow patents and market exclusivity to expire, and transition into the biologic framework.

In contrast, Theratechnologies saw its product suddenly ripped from the NDA regime and forced into the BLA framework without the notice afforded these other companies. Having had three months and not ten years, we have not had the opportunity to prepare for a biologics transition and were instead actively researching label-expansion initiatives for tesamorelin, which are no longer applicable under the BLA framework, as explained below.

For over a year, Theratechnologies has been conducting innovative research for a new indication for tesamorelin, seeking to expand knowledge of the efficacy of the drug. Tesamorelin, as part of an Investigator Initiated Trial, showed promising positive effect on normalizing liver fat and halting progression of nonalcoholic steatohepatitis (NASH) with liver fibrosis in HIV patients. In light of these findings, Theratechnologies has developed a clinical program to pursue a new indication for NASH patients. Under the NDA regime, tesamorelin would have been eligible for three-year marketing exclusivity for this new indication; the BLA framework expressly does not provide such exclusivity. Therefore, the transition of tesamorelin from an NDA to a BLA disincentivizes innovation and discourages further clinical development of this drug.

The transition also deprives Theratechnologies of the well-understood patent-based procedural protections of the Hatch-Waxman Act, which strikes a balance between the interests of innovator and generic firms. Under that framework, tesamorelin would benefit from a 30-month stay of regulatory approval following submission of an ANDA containing a so-called Paragraph IV patent certification. The corresponding process for biologics—the "patent dance"—is not well-settled and is the subject of frequent litigation.[28] As above, most firms have had ten years to develop a new patent strategy suited to the biologics patent dance. Theratechnologies will only have three months.

[28] *See, e.g.*, CONG. RESEARCH SERV., R44620, BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES, at 11–14 (June 6, 2019), https://crsreports.congress.gov/product/details?prodcode=R44620.

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VII. CONCLUSION

Proteins are distinguished from mere peptides by their structural complexity, as proteins must possess a "stable multi-dimensional conformation." There is no secondary nor tertiary structure that would indicate that tesamorelin has a stable multi-dimensional conformation. With the absence of a well-defined secondary and/or tertiary structure, the biological activity of tesamorelin is governed by the primary structure (sequence) of the peptide. For these and other reasons outlined herewith, Theratechnologies respectfully urges the FDA to reconsider categorizing EGRIFTA SV™ (tesamorelin acetate) as a deemed BLA under section 351 of the Public Health Service Act and to remove EGRIFTA SV™ from the Preliminary List.

Sincerely,

Christian Marsolais, PhD
Senior Vice-President and Chief Medical Officer
Theratechnologies Inc.

Cc: Maria Perrotta
Director, Regulatory Affairs, Quality and Compliance
Theratechnologies Inc.

Jocelyn Lafond
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