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January 27, 2014

VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-P-1641;
Supplemental Information in Support of Teva's December 5, 2013 Citizen Petition Requesting That FDA Refrain From Approving Any Abbreviated New Drug Application Referencing Copaxone® (glatiramer acetate injection) Until Certain Conditions Are Met

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva")[1] hereby submits supplemental information pursuant to 21 C.F.R. § 10.30(g) in support of its December 5, 2013 Citizen Petition requesting that the Food and Drug Administration ("FDA") refrain from approving any abbreviated new drug application ("ANDA") that references Copaxone® (glatiramer acetate injection) unless and until the conditions specified therein are satisfied to assure that follow-on products are safe and effective. In particular, Teva is submitting the Declaration of Jin Xu, Ph.D., Assistant Professor of Chemistry at the University of Massachusetts Lowell and Director of Protein and Analytical Sciences at UML's Massachusetts BioManufacturing Center. Dr. Xu's declaration supports Teva's arguments regarding active ingredient sameness, immunogenicity and bioequivalence requirements.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about January 21, 2014. If I received or

[1] Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary, and branded pharmaceuticals, and active pharmaceutical ingredients. Teva is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Neuroscience is the branded neurological products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration, and marketing of Teva's branded neurological products in North America, including Copaxone®.

Teva Pharmaceuticals
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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 organization: my employer, Teva. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Please do not hesitate to contact me if you have any questions or require additional information regarding this submission.

Respectfully submitted,

J. Michael Nicholas, Ph.D.,
Vice President, Global Specialty Medicines

cc: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

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Jin Xu, Ph.D.
Assistant Professor of Chemistry, Director of Protein Sciences

DECLARATION OF Jin Xu, Ph.D.

1. My name is Jin Xu, Ph.D. I am providing this declaration at the request of Teva Neuroscience, Inc. ("Teva"). I understand that the declaration will be used in support of a Citizen Petition that Teva filed with the United States Food and Drug Administration ("FDA" or "the Agency") regarding the approval requirements for Abbreviated New Drug Applications ("ANDA") for generic versions of Copaxone® (glatiramer acetate injection). I am being compensated at my standard hourly consulting rate as scientific advisor to Teva for the time spent preparing this declaration.

2. My background is summarized in the following paragraphs, and detailed in my attached *curriculum vitae.*

EDUCATIONAL BACKGROUND AND EXPERIENCE

3. I am an Assistant Professor of Chemistry at the University of Massachusetts Lowell ("UML") and Director of Protein and Analytical Sciences at UML's Massachusetts BioManufacturing Center ("MBMC"). I have extensive expertise in biochemistry, protein characterization, and pharmaceutical sciences. Trained as a biochemist, I have been an active researcher for more than a decade.

4. I have held the above faculty appointments at UML in Lowell, Massachusetts, since 2008. As an Assistant Professor, I have developed and taught graduate courses on *Functional Macromolecules* and *Advanced Protein Chemistry* as well as undergraduate courses in *Chemistry II* and *Biochemistry.* Prior to these faculty appointments, I served as a senior scientist and associate director in the biopharmaceutical industry at Wyeth Biopharma and Percivia for seven years and concomitantly served as an adjunct faculty member of the UML Chemistry and Chemical Engineering departments. I received my Ph.D in biochemistry from the University of North Texas ("UNT") in 2000 and subsequently did one year of postdoctoral research in Professor D. Root's Laboratory at UNT.

5. Since accepting faculty appointments at UML in 2008, I have established a state-of-the-art, nationally and internationally recognized protein chemistry research laboratory, with emphases on biopharmaceutical structural characterization and protein structure-function relationships. My research, which is funded by grants from both the National Institutes of Health ("NIH") and private biopharmaceutical companies, has focused on linking protein structural attributes to their pathophysiological and pharmaceutical functions. For example, my basic research has focused on protein aggregation mechanisms and their physiological and pathological significance in cardiovascular diseases and Alzheimer's disease. On the other hand, my collaborative research with biopharmaceutical companies has focused on protein analysis and characterization, including the relationships between protein folding and productivity, the

mechanism of action ("MOA") of protein therapeutics, the adverse effects associated with protein aggregation, and the role of posttranslational modifications in protein structure and function. My research has been used in support of several FDA filings for complex therapeutic protein products, including an Investigational New Drug application ("IND") and a Biologics License Application ("BLA").

6. I have authored sixteen articles in peer-reviewed scientific journals, including the *Journal of Biotechnology*, *Journal of Pharmaceutical Sciences*, and *Biotechnology & Bioengineering*, and more than fifty (50) technical reports based upon my industrial collaborative research, most of which will be converted into publications upon expiration of intellectual property restrictions. I am listed as the inventor or co-inventor on three patent applications filed in 2003, 2011 and 2012.

7. I have made numerous peer-reviewed presentations at local, regional, national and international scientific conferences and seminars and have presented my research at the Gordon Research Conferences on four occasions and have given a talk on "Disulfide Bond Shuffling in GPIb*a* Aggregation and its Potential Physiological Roles." I have served as advisor, consultant or expert to numerous biopharmaceutical companies. I have served as a grant reviewer for the American Alzheimer's Association as well as a peer reviewer for the scientific journals *Protein Sciences*, *Thombosis and Haemostasis* and *mAb*. I am a member of the American Biophysical Society, the American Chemical Society and the American Society of Biochemistry and Molecular Biology.

QUESTION ASKED AND INFORMATION RELIED UPON

8. I have been asked by Teva to provide my expert scientific opinion as to whether or not currently available physicochemical and biological analytical technologies are capable of adequately characterizing the glatiramer acetate in Copaxone® for purposes of demonstrating, from a scientific point of view, that a proposed generic product contains the same active ingredient. In other words, I have been asked to render an opinion as to whether or not glatiramer acetate could be "reverse engineered" based upon the scientific information gleaned from state-of-the-art analytical tools.

9. In order to render my opinion, I have reviewed the results of the scientific testing described in Teva's prior Citizen Petitions, including dynamic light scattering ("DLS"), atomic force microscopy ("AFM"), size exclusion chromatography, peptide mapping, Edman degradation, and gene expression studies, some of which included comparisons between the glatiramer acetate in Copaxone® and the active ingredient in purported generic versions marketed in foreign countries. I have also reviewed the Citizen Petition filed by Teva on December 5, 2013. Finally, I have conducted biochemical testing of samples of Copaxone® at my own protein chemistry research laboratory at UML, including various modes of high performance liquid chromatography (size exclusion, reversed phase, strong cation ion exchange, weak cation exchange) and gel electrophoresis (sodium dodecyl sulfate polyacrylamide gel electrophoresis). The similar methods have been performed at Teva and the results were included in FDA filing documents. By doing these experiments in my laboratory, I have obtained my hands-on experience on characterizing this product.

10. In rendering my opinion, I have also relied upon my general education, research experience and knowledge regarding biochemistry, protein characterization, and pharmaceutical sciences.

SUMMARY OF EXPERT OPINION

11. In my opinion, because of the complexity of glatiramer acetate (both structurally and compositionally) and the inherent limitations of current analytical technologies, it is not possible to adequately characterize glatiramer acetate to the extent necessary to make the scientific determination that a product created by a different manufacturing process is the same as the glatiramer acetate in Copaxone®. This is because current analytical technologies are capable only of providing information on glatiramer acetate's bulk characteristics and do not provide the level of resolution necessary to identify the primary structures of the vast number of individual polypeptides that comprise glatiramer acetate, much less the higher level structures of those polypeptides. Accordingly, two products may have significant differences in primary and higher order structures even if they appear to be the same based upon physicochemical and biological analytical testing.

12. In laymen's terms, this situation is akin to asking a person who is nearly blind to determine whether two people are identical twins using eyeglasses with the wrong prescription lenses. Although the deficient eyeglasses might be strong enough to permit the nearly blind person to identify the general contours and main features of the individuals in question (e.g., height, size), because of the inadequate clarity and resolution provided by the eyeglasses, the observer would not be able to discern more subtle features that directly bear on whether the individuals are, in fact, identical (e.g., facial features, eye color, sex). Accordingly, even if two individuals appeared to be identical to our hypothetical blind person, this would be based on no more than a blurry, poorly differentiated image and thus would provide no guarantee that the individuals were, in fact, identical (or even related).

13. In my opinion, because glatiramer acetate cannot be adequately characterized using current analytical technologies, and because its mechanisms of action are not fully understood, it is impossible for a different manufacturer to "reverse engineer" an identical copy of glatiramer acetate. The particular structural profile and batch-to-batch consistency of glatiramer acetate are achieved through the precise control of process parameters and raw materials. Any minor variation in key process parameters or raw materials could significantly change the product's structural profile, including primary and higher order structures, which in turn could alter product safety and effectiveness. Accordingly, the only way for another manufacturer to ensure that its active ingredient is identical to the glatiramer acetate in Copaxone® is to use the same manufacturing process as Teva.

THE COMPLEXITY OF GLATIRAMER ACETATE

14. Glatiramer acetate is an extremely complex drug product that is, in my opinion, inimitable. The complexity of glatiramer acetate is a function of two features. First, many of the polypeptides in glatiramer acetate are large molecules with some higher order structure, which

means that glatiramer acetate has a *structural* complexity akin to many proteins. Second, glatiramer acetate is composed of a huge number of distinct polypeptides, making it *compositionally* complex, as well. In my opinion, because it is a complex mixture of distinct macromolecules, glatiramer acetate is more difficult to characterize and copy than most proteins.

15. Glatiramer acetate is not composed of a single molecular entity with a well-defined structure (like acetaminophen) but rather is a complex mixture of synthetic polypeptides of varying sizes constructed from four amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine. It is my understanding that the glatiramer acetate in Copaxone® is prepared synthetically using a well-controlled, two-step manufacturing process. In the first step, extremely long chains of amino acids are synthesized from the four activated amino acids using a well-controlled polymerization process, thereby creating a "starting material" for the next manufacturing step. In the second step, these extremely large chains are subjected to a well-controlled, acidolytic cleavage reaction, which breaks them down into a mixture of smaller polypeptide chains. Although the polypeptide chains in the final product are smaller than those that comprise the "starting material," they are still quite large (as discussed further below) and would be considered macromolecules. The above-described process thus creates a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying sizes and amino acid sequences.

16. The amino acid sequences and polypeptide chain lengths are not entirely random, and it is my understanding that extensive quality testing by Teva demonstrates excellent batch-to-batch consistency. The particular structure and batch-to-batch consistency of the glatiramer acetate in Copaxone® are achieved through the precise control of the manufacturing process and raw materials.

17. For example, the primary structure of glatiramer acetate is established during the polymerization process. The term "primary structure" refers to the specific sequence of amino acid building blocks that comprise each polypeptide in glatiramer acetate. The factors that can affect the primary structure of these polypeptides include, among other things, the relative concentration of activated amino acids in the reaction mixture, the reactivity of the amino acids, the amount of the initiator, the specific reaction conditions (e.g., time, temperature, humidity), and the quality of the amino acids and solvent. Any minor variation in these process parameters could significantly change the primary structure of the resulting glatiramoid.

18. Likewise, the molecular weight distribution of glatiramer acetate is established during the acidolytic cleavage process. Generally speaking, the term "molecular weight distribution" refers to the distribution of polypeptides of varying chain lengths within the glatiramer acetate mixture. The factors that can affect the molecular weight distribution include, among other things, the sequence of the polymers (primary structure), the concentration and quality of the reagents, and reaction conditions (e.g., time, temperature).

19. The above-described manufacturing process creates a consistent mixture of polypeptides that is stunningly complex. First, many of the polypeptides that comprise glatiramer acetate are extremely large and complex, ranging from approximately 20 to 200

amino acids in length, with an average polypeptide length of about 60 amino acids.[1] Although there is no generally accepted scientific definition of "protein," the FDA has defined the term to mean "any alpha amino acid polymer with a specific defined sequence that is *greater than 40 amino acids in size*."[2] Accordingly, many of the polypeptides in glatiramer acetate are as large as or larger than molecules regarded as "proteins" by FDA. In addition, it is my understanding that, so far as their structure is known, many of the polypeptides in glatiramer acetate evidence some higher order structures like that typically observed in proteins. The higher order structures are determined by primary structure – amino acid sequence and the length of the peptide chain. In other words, each peptide in glatiramer acetate has its own upper level structures.

20. Second, because it is a mixture, the glatiramer acetate in Copaxone® is highly complex *compositionally*. The above-described manufacturing process creates a mixture of polypeptides with different primary structures, chain lengths and conformations. It has been estimated that this mixture likely contains more than 10^{12} different polypeptides and theoretically could contain more than 10^{29} possible primary polypeptide sequences.[3] Put another way, glatiramer acetate likely contains *more than a trillion* unique polypeptides and theoretically could contain more than a trillion times a trillion different polypeptides (i.e., 100,000,000,000,000,000,000,000,000,000 different polypeptides). This molecular diversity presents scientific barriers to the full characterization of glatiramer acetate that, as discussed further below, are currently insurmountable.

21. The distribution of molecular entities within the glatiramer acetate mixture is not completely random. It is my understanding that recent testing has revealed two distinct populations of stable, solvated glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase.[4] The first population is comprised of spherical nanoparticles with sizes of 4±2 nanometers ("nm"). The second population is comprised of string-like polypeptides with lengths of ~60 to 300 nm. The detection of two distinct populations of particles suggests that Copaxone® is more complex than a mere suspension of agglomerated particles and is actually comprised of a unique micro-structure of two, stable particulate populations.

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[1] Krull I, Cohen S. The complexity of glatiramer acetate and the limits of current multidimensional analytical methodologies in the attempt to characterize the product. Letter in reference to Citizen Petition FDA-2008-P-0529 to the Dockets Management Branch, Food and Drug Administration. January 16, 2009 (included as Exhibit 8 to Teva's December 5, 2013 Citizen Petition).

[2] *Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, p. 13 (Feb. 2012) (emphasis added).

[3] Krull I, Cohen S. The complexity of glatiramer acetate and the limits of current multidimensional analytical methodologies in the attempt to characterize the product. Letter in reference to Citizen Petition FDA-2008-P-0529 to the Dockets Management Branch, Food and Drug Administration. January 16, 2009 (included as Exhibit 8 to Teva's December 5, 2013 Citizen Petition).

[4] *See* Docket No. FDA-2013-P-1128 (Sept. 12, 2013).

CURRENT ANALYTICAL TECHNOLOGIES ARE NOT CAPABLE OF ADEQUATELY CHARACTERIZING GLATIRAMER ACETATE

22. Because of the complexity of glatiramer acetate (both structurally and compositionally) and the inherent limitations of current analytical technologies, it currently is not possible to fully characterize glatiramer acetate or to demonstrate that a "generic" version produced by a third party using a different manufacturing process is identical to the glatiramer acetate in Copaxone®. This is because current analytical technologies, including multi-dimensional analysis techniques, cannot provide enough resolution to characterize glatiramer acetate (or purported generic versions) with precision. The most that these techniques can do is demonstrate that two glatiramoids are *similar* in bulk characteristics (such as molecular weight distribution and amino acid ratio). Accordingly, even if two products appear to be the same based upon physicochemical and biological analytical testing, because of the inherent limitations of these technologies when applied to a complex mixture of macromolecules like glatiramer acetate, the products nevertheless may have significant differences in primary and higher order structures or in composition (e.g., concentrations of certain polypeptide species).

23. There are a number of reasons why the chemical composition of glatiramer acetate is so difficult to determine. The first challenge pertains to the size and structure of the individual polypeptides that comprise glatiramer acetate. As noted above, many of these polypeptides are as large and structurally complex as many proteins. Consequently, characterizing even a single, large polypeptide would present technological difficulties similar to characterizing a protein. From my own experience, it often is impossible to fully characterize a protein product that consists of a single molecular entity or to demonstrate that one protein product is identical to another protein product manufactured by a third-party. Because of the limitations of current analytical technologies, the most that can be shown is that one protein product is *similar* to another. Indeed, it is my understanding that FDA has expressed the same view, stating that because of the limitations of current analytical technology it usually will not be possible to demonstrate that one protein product is structurally identical to another, previously-approved protein product.

24. For peptide and protein products that consist of a single molecular entity, scientists use a standard "characterization package" to assess and characterize the structure of the molecule. This characterization package utilizes a number of state-of-the-art analytical techniques to assess, among other things, the molecule's size, charge, amino acid sequence (primary structure), higher level structure (e.g., protein folding and three-dimensional structure) and biological activity. In particular, a standard characterization package consists of the following scientific techniques: electrophoresis, various modes of high-performance liquid chromatography (HPLC), mass spectrometry, UV/fluorescence/circular dichroism spectroscopy, and other product-specific biochemical and biophysical methods.

25. While this testing package is very useful in characterizing peptide and protein products that consist of a single molecular entity, it cannot be used to adequately characterize a complex mixture like glatiramer acetate. First, such characterization testing could not be performed on individual polypeptides but rather would need to be performed on the mixture as a whole or on specific fractions of glatiramer acetate, each of which could contain thousands or

even millions of individual polypeptides. This is because, given the limitations of current analytical technologies, separating and isolating individual molecules from the vast number of polypeptides in glatiramer acetate is not possible. It is my understanding that many of the polypeptides in glatiramer acetate are similar in size, charge, and hydrophobicity and thus could not be separated and isolated from one another. On the contrary, even state-of-the-art separation methods, including multi-dimensional separation methods combined with mass spectrometry, do not have the ability to discriminate, separate, or quantitate each and every one of the peptide sequences in such a complex mixture.

26. The inability to separate and isolate individual polypeptides significantly decreases the characterization power of the analytical testing methodologies. The following examples illustrate this point. Reversed phase chromatography (RPC), a chromatographic technique separating molecules based on hydrophobicity, is commonly used to determine the purity and heterogeneity of a protein/peptide product. RPC separates proteins/peptides based upon hydrophobicity. Proteins/peptides that are less hydrophobic elute earlier whereas proteins/peptides that are more hydrophobic elute later. For a single-molecular entity product, the peaks resolved in RPC represent the main species and product-related isoforms (truncated species, aggregates, species with different chemical medications, etc.), each of which can be subsequently identified by mass spectrometry and other techniques. Glatiramer acetate, however, displays a broad "hump" on RPC without any resolved peak. This is due to the high complexity of glatiramer acetate, where the presence of thousands and even millions of peptides is far beyond the resolving capacity of RPC. In this case, the RPC analytical method would not provide meaningful structural information on glatiramer acetate.

27. Another analytical testing methodology that is commonly used to characterize peptides and proteins is size exclusion chromatography (SEC), which is a chromatographic method for separating molecules based on their size. Although SEC is a useful characterization tool, it cannot separate glatiramer acetate to individual polypeptides. Similarly to its behavior on RPC, glatiramer acetate does not show sharp peaks but rather a broad "hump" on SEC. Even though two mixtures show similar profiles on SEC, the mixtures nevertheless could contain very different individual polypeptides. Assuming that one could obtain a chromatogram with distinct peaks (this appears to be impossible for glatiramer acetate), because the following hypothetical polypeptides are the same size, they might appear the same under SEC even though they have different primary structures: A-B-C-D versus D-A-C-B.

28. Peptide mapping, another analytical testing method, suffers from the same resolution deficiencies when applied to a complex mixture like glatiramer acetate. Peptide mapping is a "finger-printing" method for single-molecular-entity protein products, where the protein is cleaved with a proteolytic enzyme and the digest is then resolved on reversed phase chromatography (RPC), giving a signature chromatographic profile specific for this protein. As described above, the complex peptide mixture in glatiramer acetate cannot be resolved on RPC (see paragraph 26). Upon protease digestion however, some peaks appeared in the RPC chromatogram. This is because the digestion simplifies the complexity of glatiramer acetate. For example, three peptides – ABC, ABCABC and ABCABCABC- will be digested into one peptide ABC if the protease cleave after residue C. Therefore, peptide mapping cannot serve as an analytical method for directly characterizing the peptide composition in Copaxone® or

primary structure of any single peptide. Moreover, due to the complexity of glatiramer acetate, each peak in the peptide map represents a multitude of different molecules with similar hydrophobicities rather than individual species. Accordingly, in my opinion, even if two glatiramoids show similar results with peptide mapping, it would not be scientifically justified to conclude that they contain the same amount or concentration of the same polypeptides.

29. Edman degradation is used to identify the sequence of amino acids in a peptide (i.e., its primary structure) by cleaving off one amino acid at a time (starting from the N terminus) and then identifying the cleaved residues. Because this technique only works for the first 13 to 15 amino acids, it can provide no information about the sequence of subsequent amino acids in longer polypeptides such as glatiramer acetate, which has an average polypeptide length of about 60 amino acids, with some reaching up to 200 amino acids in length. Moreover, for complex mixtures, Edman degradation shows only the ratio of amino acids at various positions in the mixture, not the actual primary structure of any particular polypeptide. It thus cannot indicate whether two complex mixtures are identical. For example, testing might indicate that for one hypothetical mixture the first amino acid is either A (40%), B (10%), C (20%) or D (30%), the second amino acid is either A (10%), B (20%), C (40%) or D (30%) and so forth. Even if the ratios for a second mixture were identical, the actual polypeptides in the mixtures nevertheless could be significantly different. Indeed, in the example below, Mixture 1 and Mixture 2 have identical ratios through the first five amino acids but are composed of entirely different peptides with markedly different primary structures.

Mixture 1	**Mixture 2**
A-C-D-A-B	B-D-A-A-A
A-B-A-B-B	C-B-A-B-B
C-C-C-C-A	D-C-C-B-D
B-C-A-D-D	A-A-A-C-A
D-B-A-C-A	C-D-C-A-D
A-D-A-C-B	A-C-C-C-B
A-D-C-B-D	A-C-B-C-C
D-D-C-D-C	D-C-A-D-A
C-C-B-C-B	D-D-A-C-B
D-A-A-A-A	A-B-D-D-B

Indeed, not a single peptide in Mixture 1 is the same as a peptide in Mixture 2 even though the ratios that would be obtained from Edman degradation are identical. I note that this problem would be much more pronounced for glatiramer acetate, which contains millions of distinct polypeptides (rather than the ten polypeptides in each mixture depicted in the above hypothetical) with polypeptide lengths up to 200 amino acids (rather than the five amino acids depicted above).

30. The large peptides in glatiramer acetate likely possess certain upper level structures. Even for a single molecular protein product, determining the upper level structures is the most challenging task. X-ray crystallography is the ultimate method to determine the three-dimensional structure of a protein. This method requires sample purity over 99% and it is hence

impossible to perform it on a peptide mixture like glatiramer acetate. Circular dichroism (CD) and fluorescence spectroscopy are practical methods for obtaining some superficial upper level structural information, largely for comparability studies of a single molecular entity product. The mixture nature of glatiramer acetate essentially abolishes the characterizing ability of these methodologies. I firmly believe that the current available biophysical techniques are incapable of providing meaningful data on determining higher level structures of peptides in glatiramer acetate. As the function of a protein is based on its structure, the biological activity of a biopharmaceutical product reflects its correct structure. *In vitro* activity assays (such as binding affinity and cell-based activity assay) are commonly performed to ensure the product has the expected structure. Since all these activity assays are designed based on the molecular mechanism of action of a specific product, and because the mechanism of action for glatiramer acetate is far from clear, there is no *in vitro* functional assay available. Clinical efficacy and safety appear to be the only functional evaluation of Copaxone®, and a comprehensive clinical trial is therefore indispensible for generic version development.

31. For the reasons discussed above, the current, state-of-the-art analytical technologies do not provide enough resolution to adequately characterize glatiramer acetate or to demonstrate that a version manufactured by a third party is identical to the glatiramer acetate in Copaxone®. Instead, such testing provides information only about glatiramer acetate's bulk properties, not the specific polypeptides that comprise glatiramer acetate. Consequently, even if two products appear to be identical based upon such testing, this does not mean that the products contain the same polypeptides or the same concentrations of such polypeptides. The currently available test methods simply are not capable of making that determination, either alone or in combination. On the contrary, they provide no more than a blurry, poorly differentiated image of glatiramer acetate and thus can provide no guarantee that two glatiramoids manufactured by different processes are, in fact, identical. The most that these techniques can do is to demonstrate that two glatiramoids are *similar* in certain bulk characteristics (such as molecular weight distribution and amino acid ratio).

GLATIRAMER ACETATE CANNOT BE "REVERSE ENGINEERED"

32. In my opinion, glatiramer acetate cannot be "reverse engineered" by a third-party manufacturer. First, as described in detail above, glatiramer acetate cannot be adequately characterized using current analytical technologies, making it virtually impossible to identify the structure and function of its individual polypeptides. Second, and of equal importance, the mechanism or mechanisms of action of glatiramer acetate are not fully understood, making it impossible to identify the specific epitopes responsible for its safety and effectiveness or to assess how slight changes in a proposed "generic" product might impact safety and effectiveness.

33. Reverse engineering generally involves thoroughly analyzing the components, structure, function, and operation of a product to gain an understanding of its technological principles in order to replicate it. As a general matter, reverse engineering is not possible if one (a) cannot characterize the structure or components of a product, or (b) does not understand how the product works.

34. In this case, as described in paragraphs 22 through 31 above, it is my opinion that current analytical technologies are not capable of adequately characterizing glatiramer acetate. On the contrary, such testing is capable of providing information only on glatiramer acetate's bulk characteristics and cannot provide the level of resolution necessary to identify the primary or higher-level structures of the numerous polypeptides that comprise glatiramer acetate. Without this more precise, granular information on the structure and function of individual polypeptides, it simply is not possible for a third-party to reverse engineer glatiramer acetate.

35. In addition, reverse engineering is not feasible because the mechanism or mechanisms of action of glatiramer acetate are not well understood. Although glatiramer acetate is known to be an immunomodulator, nobody knows precisely how it works or what species of polypeptides are responsible for its safety and effectiveness. As a result, a third-party manufacturer could not demonstrate that its product contains all therapeutically active epitopes (and in necessary concentrations) or provide assurance that any differences between its product and the glatiramer acetate in Copaxone® (which are an unavoidable consequence of the use of a different manufacturing process) will not have a negative effect upon safety or effectiveness. Accordingly, without a thorough understanding of how glatiramer acetate works and what species are responsible for its safety and effectiveness, it simply is not possible for a third-party to reverse engineer it.

36. Although slight product differences might be acceptable if they could be shown not to affect safety or effectiveness, they simply cannot be justified (without clinical testing) if there is not a thorough understanding of how the product works. For example, biosimilar versions of Herceptin® (trastuzumab) are found to have different levels of terminal amino acid truncation compared to the innovator version. Herceptin® is a recombinant antibody with two identical heavy chains (~500 amino acids each) and two identical light chains (~250 amino acids). The last amino acid of the heavy chain is supposed to be lysine. During the manufacturing process however, the terminal lysine is partially cleaved off by a protease. Some biosimilar versions are found to have more terminal lysine residues retained than the innovator version. This difference has been justified from a scientific and medical point of view only because scientific evidence has been developed to demonstrate that this lysine residue has no role in Herceptin®'s efficacy, safety or metabolism.

GLATIRAMER ACETATE IS DEFINED BY ITS MANUFACTURING PROCESS

37. Because of its extreme complexity and the limitations of current analytical technologies, glatiramer acetate is, in my opinion, defined primarily by its well-controlled manufacturing process.

38. The formation of links between the four amino acids that comprise glatiramer acetate is a random chemical reaction that is highly dependent on the manufacturing process and conditions. The particular structural profile and batch-to-batch consistency of glatiramer acetate thus are achieved by Teva through the precise control of process parameters and raw materials. Any minor variation in key process parameters or raw materials, such as the quality or purity of the amino acids, the amount of the initiator during the polymerization process, or the specific reaction conditions during the polymerization and cleavage processes, could significantly change

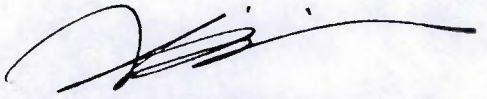
the product's structural profile, including primary and higher order structures. Because peptide function is determined by primary and higher order structure, these types of structural changes could, in turn, alter product safety and effectiveness.

39. This reliance upon the manufacturing process to define the structural profile of glatiramer acetate is similar to many biological products, which likewise are defined primarily by their well-controlled manufacturing processes. Moreover, it distinguishes glatiramer acetate from other non-biological complex drugs, such as sodium ferric gluconate complex in sucrose, which are relatively insensitive to manufacturing changes.[5]

40. Accordingly, in my opinion, the only way for a third-party manufacturer to ensure that its active ingredient is identical to the glatiramer acetate in Copaxone® is to use exactly the same manufacturing process as Teva. For the reasons discussed above, the failure to do so will result in unavoidable structural and compositional differences compared to the glatiramer acetate in Copaxone®. Because of the limitations of current analytical technology (as described in paragraphs 22 through 31 above), many of these structural and compositional differences may be impossible to detect. Moreover, because glatiramer acetate's mode of activity is not fully known, it will not be possible to determine whether such differences, even if detected, have a negative impact upon safety or effectiveness without clinical and/or non-clinical investigations.

I declare under penalty of perjury under the laws of the United States of America, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on January 17th, 2014.



Jin Xu, Ph.D.

[5] FDA Response to Ferrlecit Petition, at 9-10, FDA-2004-P-0494 (March 31, 2011) (FDA explained that the "fundamental chemistry will drive the manufacturing process").