APR 16 2015

J. Michael Nicholas, Ph.D.
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Teva Pharmaceuticals
11100 Nall Ave.
Overland Park, KS 66211

Re: Docket No. FDA-2015-P-1050

Dear Dr. Nicholas:

This letter responds to your citizen petition received on April 1, 2015 (Eighth Petition), in which you request that the Food and Drug Administration (FDA or Agency) not approve any abbreviated new drug application (ANDA) that references Copaxone (glatiramer acetate injection) unless and until the conditions specified in the Petition are satisfied. In the Eighth Petition, you request that:

1. FDA review and consider the new scientific data and information contained in the Eighth Petition prior to approving any ANDA that relies upon Copaxone as the reference listed drug (RLD).

2. FDA refrain from approving any ANDA that references Copaxone unless and until the ANDA contains:

   a. Information demonstrating that the proposed generic product contains the identical active ingredient as Copaxone, not merely an active ingredient that is similar (or even highly similar) to Copaxone's, including data from high-resolution physicochemical, biological, and genome-wide expression methods;

   b. Results of non-clinical and clinical investigations, including in-depth analyses of comparative gene expression profiles in several relevant preclinical systems, demonstrating that the immunogenicity risks associated with the proposed generic product are no greater than the risks associated with Copaxone, including a demonstration that the risks of alternating or switching between use of the proposed product and Copaxone are not greater than the risks of using Copaxone without such
alternation or switching; and

c. Results of comparative clinical investigations in relapsing-remitting multiple sclerosis (RRMS) patients using relevant safety and effectiveness endpoints demonstrating that the proposed generic drug is bioequivalent to Copaxone.

We have carefully considered your Eighth Petition. For the reasons stated below, it is denied.

We note that the Eighth Petition purports to incorporate by reference a series of citizen petitions that Teva previously submitted to FDA relating to Copaxone. FDA responded to each of your seven prior citizen petitions, except for one petition that you withdrew. As FDA explained in each response to those petitions, section 505(q)(1)(F) of the of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)(1)(F)) required the Agency to take final action on each petition within 150 (or, for certain petitions, 180) days of submission. However, at the time FDA issued each response, FDA had made no final determination about whether, or on what basis, to approve or not approve any ANDA for glatiramer acetate injection. FDA therefore denied the specific requests in each petition regarding the approvability of an ANDA referencing Copaxone because it would have been premature and inappropriate to opine on such outstanding matters at that time. FDA explained that providing such an opinion at that time could, in effect, render a decision on a specific aspect of an ANDA before the Agency had had an opportunity either to fully consider specific data and information in such an application or to provide the procedural rights that accompany FDA actions on applications. FDA stated that it intended to consider the issues that you had raised if and when FDA approved a generic version of Copaxone.

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1 See Eighth Petition at 3. You submitted the following seven citizen petitions, one of which you subsequently withdrew: Docket No. FDA-2008-P-0529, received on September 26, 2008, and responded to on March 25, 2009 (First Petition); Docket No. FDA-2009-P-0555, received on November 13, 2009, and responded to on May 11, 2010 (including Teva’s comment thereto submitted on May 10, 2010) (Second Petition); Docket No. FDA-2010-P-0642, received on December 10, 2010, and responded to on June 8, 2011 (including the supplement thereto submitted on February 22, 2011) (Third Petition); Docket No. FDA-2012-P-0555, received on June 4, 2012, and responded to on November 30, 2012 (Fourth Petition); Docket No. FDA-2013-P-1128, received on September 12, 2013, and withdrawn by Teva on January 6, 2014 (Fifth Petition); Docket No. FDA-2013-P-1641, received on December 5, 2013, and responded to on May 2, 2014 (including the supplements thereto submitted on January 27, 2014, March 10, 2014, and May 2, 2014) (Sixth Petition); and Docket No. FDA-2014-P-0933, received on July 3, 2014, and responded to on November 26, 2014 (including the supplements thereto submitted on July 17, 2014, August 12, 2014, and November 13, 2014) (Seventh Petition).

2 You withdrew the Fifth Petition before FDA issued a response.

3 See, e.g., Response to Seventh Petition at 7.

4 Id.

5 Id.

6 Id.

7 Id.
In prior court litigation regarding Copaxone, FDA represented that, as a courtesy, it intended to provide a substantive explanation to Teva regarding the issues raised in its citizen petitions if and when FDA approved any ANDA referencing Copaxone. Today, FDA is approving an ANDA for glatiramer acetate injection that references Copaxone. Accordingly, consistent with the Agency’s previous representations to the Court, this response includes a substantive explanation regarding the issues raised in the Eighth Petition and your related prior citizen petitions.

I. OVERVIEW

To obtain ANDA approval, an applicant must submit sufficient information to show that its generic drug product is bioequivalent to and has the same active ingredient(s), route of administration, dosage form, strength, previously approved conditions of use, and (with certain exceptions) labeling as the reference listed drug (RLD). The underlying premise of the ANDA approval requirements is that the generic drug product and the RLD can be substituted for each other with the full expectation that they will have the same clinical effect and safety profile.

Your petitions raise three principal issues relating to whether an ANDA referencing Copaxone may be approved and, more specifically, to the requirements needed to support such an approval. First, you claim that Copaxone’s structural complexity and other unique characteristics render it impossible at this time for an ANDA applicant to demonstrate that its proposed generic product has the same active ingredient as Copaxone, which is required for ANDA approval. Second, you claim that any ANDA referencing Copaxone should be required to demonstrate bioequivalence through in vivo studies—specifically, a comparative clinical investigation in RRMS patients using relevant safety and effectiveness endpoints. You contend that such a proposed generic product would be ineligible for a waiver of in vivo bioequivalence testing because Copaxone is a colloidal solution and because the structural and compositional differences in any ANDA product’s active ingredient could affect bioequivalence. Finally, you assert that a proposed generic product could have significant and unpredictable differences from Copaxone in its immunological mechanisms, and you claim that FDA therefore should require ANDA applicants to conduct additional non-clinical and clinical immunogenicity studies.

We do not find it necessary for an ANDA applicant seeking approval of generic glatiramer acetate injection to submit the information you describe. Nonetheless, we recognize that approval of ANDAs for glatiramer acetate injection raises complicated scientific and regulatory issues, which we have carefully considered.

8 Fed. Defendants’ Mem. in Supp. of Mot. to Dismiss and in Opp. to Pl’s Mot. for Preliminary Injunction, Teva Pharm. Indus. Ltd. v. Sebelius, No. 14-CV-786, at 31 n.27 (D.D.C. May 12, 2014). Because the dockets for the citizen petitions have closed, this explanation is necessarily separate from those dockets.

9 Certain non-public information of applicants is relevant to this response but cannot be disclosed publicly under applicable law. Such information is contained within underlying review memoranda and other records.

10 Although the dockets corresponding to the previous petitions remain closed, this response refers to those petitions for ease of reference. FDA declines to address the propriety of Teva’s effort to incorporate its prior citizen petitions by reference into the Eighth Petition.

11 See section II.A below.
With respect to active ingredient sameness, we recognize and have carefully considered the complexity of Copaxone. This complexity alone does not preclude a finding of active ingredient sameness between a generic glatiramer acetate injection and Copaxone. Based on our evaluation of all of the relevant data and other current relevant scientific information, our experience and expertise, Agency precedent, and applicable law, we find that glatiramer acetate has been adequately characterized for the purposes of approving a generic product; and we conclude that an ANDA applicant for glatiramer acetate injection can demonstrate active ingredient sameness by showing equivalence between the ANDA product and the RLD as to the following four criteria:

1. Fundamental reaction scheme;
2. Physicochemical properties including composition;
3. Structural signatures for polymerization and depolymerization; and
4. Results in a biological assay.

As described in further detail below, the first three criteria provide successively refined evidence of active ingredient sameness, while the fourth criterion provides confirmation of active ingredient sameness established by the initial three criteria. As with all complex scientific issues, though, it is possible that with an improved understanding of the biological and clinical properties of glatiramer acetate and/or advances in the analytical technologies that might be used to characterize glatiramer acetate, other approaches might emerge to establish the active ingredient sameness of glatiramer acetate.

With respect to the demonstration of bioequivalence, the bioequivalence of a generic glatiramer acetate injection that meets the criteria set forth in our regulation (21 CFR 320.22(b)(1)) is self-evident based upon other ANDA data, so there is no need for the in vivo bioequivalence studies that you claim are necessary. That regulation applies, in relevant part, if the generic product is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as Copaxone. We find that Copaxone is a solution, and we conclude that the bioequivalence of any proposed ANDA product referencing Copaxone is self-evident if the ANDA product: (1) also is a solution and (2) contains the same active ingredient (as shown by demonstrating equivalence of the four criteria identified in this response) and inactive ingredients in the same concentrations as Copaxone.

With respect to immunogenicity, we agree that a generic glatiramer acetate injection must not elicit a different immune response from that elicited by Copaxone. To ensure that impurities do not affect the immunogenicity of a generic glatiramer acetate injection, impurities including aggregates, leachates and process-related impurities will be evaluated and their levels will be rigorously controlled. We conclude that the criteria set forth in this response for active ingredient sameness will ensure that a generic glatiramer acetate injection has the same molecular diversity, and thus the same active ingredient, as Copaxone. We further conclude that once requirements relating to active ingredient sameness and impurities and other ANDA
approval requirements are met, a generic glatiramer acetate injection will be expected to have the same clinical effect and safety profile as Copaxone when administered to patients under the conditions specified in its labeling.

The issues set forth in this response have been considered extensively by various components of the Agency’s Center for Drug Evaluation and Research (CDER), including the Office of Generic Drugs, the Office of Pharmaceutical Quality (including Immediate Office, the Office of Lifecycle Drug Products, the Office of Process and Facilities, the Office of Biotechnology Products, and the Office of Testing and Research), and the Office of Translational Sciences (including the Division of Applied Regulatory Science).\(^\text{12}\) We made the decisions set forth in this response after carefully considering your petitions (including their supplements and comments), other correspondence, relevant scientific publications, and other relevant information.

This response contains six sections. Section II describes the statutory and regulatory framework for ANDA approval. Section III provides background information on glatiramer acetate, including its composition and synthesis. Section IV discusses the four criteria that provide sufficient information to enable us to find active ingredient sameness for glatiramer acetate. Section V addresses specific arguments raised in your petitions and explains why those arguments do not preclude a finding of active ingredient sameness for glatiramer acetate. Finally, section VI summarizes our conclusion.

II. APPLICABLE STATUTORY AND REGULATORY FRAMEWORK

A. ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the drug product. Instead, an ANDA applicant relies on the Agency’s previous finding that the RLD is safe and effective. To rely on FDA’s previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).\(^\text{13}\) In addition, an ANDA must contain sufficient information to show that the generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD

\(^{12}\) Some of these CDER components were reorganized and, in some cases, renamed in recent reorganizations. For example, the Office of Pharmaceutical Quality includes offices that previously were within the Office of Pharmaceutical Science. In addition, the Office of Generic Drugs previously was within the Office of Pharmaceutical Science.

\(^{13}\) Under the FD&C Act, “[a] drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.” See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.
(sections 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

The premise underlying the Hatch-Waxman Amendments is that drug products that are (1) approved as safe and effective, (2) pharmaceutically equivalent, (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations, are therapeutically equivalent and can be substituted for each other with the “full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed [RLD] product.”

B. Active Ingredient Sameness

Section 505(j)(2)(A)(ii)(I) of the FD&C Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient of the generic drug product is the “same” as that of the listed drug. Under section 505(j)(4)(C)(i) of the FD&C Act, we must approve an ANDA referencing a listed drug that has only one active ingredient unless the ANDA contains insufficient information to show that the active ingredient is the same as that of the listed drug.

These statutory provisions do not describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredient in the generic drug product is the same as the active ingredient in the RLD, nor do these provisions describe the type or amount of information on which we may rely in determining whether the ANDA applicant has provided

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14 See 21 CFR 320.1(c) (pharmaceutical equivalents means, in part, drug products in identical dosage forms that contain identical amounts of the identical active ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency).

15 Orange Book, 35th Ed., at viii. FDA classifies as therapeutically equivalent, and thus substitutable, those products that are (1) approved as safe and effective, (2) pharmaceutically equivalent (which means, in part, drug products in identical dosage forms that contain identical amounts of the identical active ingredient; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency (21 CFR 320.1(c)), (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations. See id., at vii.

16 FDA regulations (at 21 CFR 210.3(b)(7)) provide that “active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.” FDA regulations (at 21 CFR 314.3(b)) also provide that “drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient.” See also Proposed Rule: Abbreviated New Drug Applications and 505(b)(2) Applications, 80 FR 6802 at 6811 (Feb. 6, 2015) (proposing to add the definition of “active ingredient” currently in 21 CFR 210.3(b)(7) to 21 CFR 314.3(b))
sufficient information to show that the active ingredient is the same. Accordingly, Congress recognized that we must have broad discretion with respect to the information we may consider in making a finding on the “sameness” of an active ingredient.17

FDA regulations at 21 CFR 314.94(a)(5)(i) and 314.127(a)(3) parallel the statutory provisions of sections 505(j)(2)(A)(ii) and (j)(4)(C)). Specifically, these regulations provide that an ANDA is suitable for consideration and approval if the generic drug product is the same as the RLD (21 CFR 314.92(a)(1)). For instance, § 314.92(a)(1) states that the term “same as” means, among other things, “identical in active ingredient(s).” In the preamble to the final rule implementing Title I of the Hatch-Waxman Amendments, we specifically rejected the suggestion that we adopt requirements that active ingredients “exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process, and that the stereochemical characteristics and solid state forms of the drug have not been altered.”18 Instead, we adopted a more flexible approach, stating that we would “consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity.”19

As FDA’s regulations and preamble reflect, we have broad discretion in determining whether an ANDA applicant has submitted sufficient information upon which we can reasonably conclude that the generic drug product’s active ingredient is the “same” as that of the RLD.

C. Bioequivalence

An ANDA must contain information to show that the proposed generic drug product is bioequivalent to the RLD it references.20 The FD&C Act, regulations, and case law give FDA considerable flexibility in determining how this requirement is met. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .

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18 See 57 FR 17950 at 17958-59 (April 28, 1992).
19 Id. at 17959. FDA explained that “[i]n most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that are material to the ingredient’s sameness.” Id. In this instance, there is no USP monograph for glatiramer acetate, and the Agency has described the appropriate standards for identity (or criteria for active ingredient sameness) in this response.
20 Section 505(j)(2)(A)(iv) and (4)(F) of the FD&C Act; 21 CFR 314.94(a)(7) and 320.21(b).
FDA has broad discretion to determine the appropriate approach to demonstrate bioequivalence for a given drug product.\textsuperscript{21} Section 320.24(b) of FDA’s regulations describes preferred bioequivalence methods in what, for systemically absorbed products, is the descending order of accuracy, sensitivity, and reproducibility. They include: (1) in vivo (human subject) pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) clinical endpoint studies, and (4) in vitro (laboratory) studies.\textsuperscript{22} In addition, § 320.24(b)(6) of the regulation states that FDA has the authority to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”

Section 320.22 of the regulations provides that the bioequivalence of a drug product may be considered self-evident based on other data in the ANDA and that FDA therefore “shall” waive any requirement of in vivo (i.e., clinical) bioequivalence studies if specified conditions are met. These conditions include a proposed generic product that is a parenteral solution intended solely for administration by injection and that contains the same active and inactive ingredients in the same concentrations as the RLD.\textsuperscript{23} FDA’s regulations further provide that the Agency, for good cause, may require in vivo bioequivalence data if it determines that any differences between the drug product and the RLD may affect the bioequivalence of the drug product.\textsuperscript{24}

III. OVERVIEW OF GLATIRAMER ACETATE

A. Multiple Sclerosis

Multiple sclerosis is a chronic inflammatory disease affecting the central nervous system (CNS) and causing lasting neurological impairment. It is a heterogeneous autoimmune disease characterized by myelin degradation and concomitant axonal loss in the brain and spinal cord, but details of its pathogenesis are not well understood.\textsuperscript{25}

Although the exact cause of multiple sclerosis is not known, multiple sclerosis is known to involve degradation of the myelin protein sheath (essentially an insulating layer) that surrounds and protects neurons.\textsuperscript{26} Through an unknown mechanism, myelin specific autoreactive T cells in the peripheral nervous system are able to cross the blood-brain barrier into the central nervous system. Upon entering the central nervous system, the autoreactive T cells interact with myelin degradation products such as myelin basic protein (MBP), myelin associated glycoprotein

\textsuperscript{21} See, e.g., \textit{Schering Corp. v. FDA}, 51 F.3d 390, 398 (3d Cir. 1995) (recognizing FDA’s statutory “discretion to determine whether in vivo or in vitro bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process.”).

\textsuperscript{22} 21 CFR 320.24(b).

\textsuperscript{23} 21 CFR 320.22(b)(1).

\textsuperscript{24} 21 CFR 320.22(f).


(MAG), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). Such interactions stimulate inflammatory processes that activate B cells and autoaggressive T cells. Activated B cells release anti-myelin antibodies and stimulate the degradation of myelin peptides. Autoaggressive T cells release proinflammatory cytokines including TNF-α and IFN-γ which, in turn, activate macrophages. Activated macrophages can strip the myelin sheath and secrete molecules toxic to myelin, such as matrix metalloproteinases, nitric oxide, and free radicals. Together, these inflammatory processes cause disease progression that characterizes multiple sclerosis.

**B. Discovery of Glatiramer Acetate and Approval of Copaxone**

In 1971, a laboratory at the Weizmann Institute of Science initiated a study of amino acid copolymers designed to mimic MBP, one of the antigens postulated to cause multiple sclerosis and described above. The researchers expected to use their myelin mimics to initiate an immune response in animals and cause multiple sclerosis-like symptoms. Instead, they found that one of their copolymers inhibited the development of neurological symptoms in the animals under investigation. The study reported that a mixture of alanine, glutamic acid, tyrosine, and lysine formed a copolymer that inhibited experimental allergic encephalomyelitis (EAE), the primary animal model for multiple sclerosis. The EAE inhibitor was dubbed “copolymer 1” and was subsequently developed into the drug Copaxone. Glatiramer acetate is the active ingredient in Copaxone. In 1996, the FDA approved a New Drug Application submitted by Teva for Copaxone as a daily subcutaneous injection for the treatment of multiple sclerosis (NDA 20-622).

**C. Mechanism of Action**

Due to the heterogeneous nature of multiple sclerosis and the diverse population being treated, it has been postulated that an effective multiple sclerosis drug needs to invoke diverse immune system effects. Glatiramer acetate meets this need by providing a wide array of peptide

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32 In the literature, glatiramer acetate is also referred to as Copaxone (Teva Neuroscience), Copolymer 1, Cop 1, COP, GA, Poly (Ala, Glu, Tyr, Lys), GLAT, and YEAK. In the last few years, multiple sclerosis researchers have standardized their nomenclature and now consistently use “glatiramer acetate” or “GA” to refer to the drug.
copolymers that can activate the immune systems of many different individuals.\textsuperscript{33} However, the mechanism of action of Copaxone remains, at least to some degree, unknown and incompletely characterized, despite several theories of mechanisms of action under investigation.

\textbf{D. Composition and Synthesis}

\textbf{1. Peptide Copolymers}

Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-glutamic acid (Glu, E), L-lysine (Lys, K), L-alanine (Ala, A), and L-tyrosine (Tyr, Y) (see Figure 1), with an average molar fraction of 0.141, 0.338, 0.427, and 0.095, respectively.\textsuperscript{34} Glatiramer acetate has an average molecular weight of 5-9 kilodalton (kDa).\textsuperscript{35} The peptide copolymers in glatiramer acetate are synthesized via amino acid polymerization (followed by a subsequent cleavage or partial depolymerization step, each described further below). The resulting amino acid polymer chains vary in length and molecular weight.\textsuperscript{36}

![Figure 1. The four amino acids that make up glatiramer acetate.](image)

\textbf{a. Conserved Characteristics}

The sequences of these four amino acids in each chain of the copolymer are neither entirely conserved (i.e., replicated) from batch to batch (as described further below) nor completely


\textsuperscript{34} Current product labeling for NDA 020622 approved on January 28, 2014.

\textsuperscript{35} Id.

random. Rather, the sequences depend upon the physicochemical properties of the starting materials and upon the fundamental reaction chemistry used to manufacture glatiramer acetate, as well as upon the controls placed on various aspects of polymerization and depolymerization. The resultant drug product is, therefore, a mixture of peptide copolymers having an overall composition and physicochemical properties and, to the extent described below, amino acid sequences that are conserved, as described below, from batch to batch during its synthesis. The structural formula for glatiramer acetate is listed in the Copaxone labeling as:

\[(\text{Glu, Ala, Lys, Tyr}) \cdot x \text{CH} \cdot \text{COOH (C}^5 \text{H}_9 \text{NO}_4 \cdot \text{C}^3 \text{H}_7 \text{NO}_2 \cdot \text{C}^6 \text{H}_14 \text{N}_2 \cdot \text{O}_2 \cdot \text{C}^9 \text{H}_11 \text{NO}_3 \cdot \text{C}^2 \text{H}_4 \cdot \text{O}_2).\]

b. Batch-to-Batch Variability

The chemical synthesis of Copaxone results in certain of its characteristics being conserved (e.g., its overall composition and physicochemical characteristics). The nature of Copaxone’s synthesis process, however, also results in a product with inherent variability, even when it is tightly controlled; there is a negligible likelihood that the specific amino acid sequences along the entire copolymer chain will be conserved from batch to batch. Rather, Copaxone exhibits batch-to-batch amino acid sequence variations across the copolymer, coupled with conservation of shorter “local” sequences within the copolymer.

Therefore, both the conservation of certain characteristics from batch to batch of Copaxone (including Copaxone’s local sequences, overall composition, and other physicochemical properties that are described in greater detail below), as well as the variations of other characteristics (including such longer amino acid sequences) between batches of Copaxone are fundamental properties of Copaxone. These conservation and variations characteristics have been considered in establishing active ingredient sameness criteria for a generic glatiramer acetate.

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37 Copaxone has been described by Teva as having “a huge, perhaps incalculable number of active amino acid sequences” (First Petition at 6-7). We note, and have considered, the foregoing and other assertions made by Teva in its Citizen Petitions relating to the complexity of Copaxone and the large number of distinct amino acid chains comprising Copaxone (e.g., First Petition at 6-7, Second Petition at 2-3; 10; 21; Third Petition at 2, 14, 16; Fourth Petition at 10; Sixth Petition at 7 and the Jan. 27, 2014 Supplement to the Sixth Petition at 4). However, as described here and elsewhere in this response, this complexity does not preclude a finding of active ingredient sameness and ANDA approval.

38 We have observed this degree of batch-to-batch variability based on analyses of multiple batches of Copaxone conducted and submitted in connection with ANDAs as well as from FDA’s own internal laboratory analyses of samples of Copaxone. We note that even for characteristics that are described in this response as “conserved” from batch to batch, we have observed some degree of batch-to-batch variability in Copaxone in terms of their levels and the use of the term “conserved” in this response in connection with such sequences intended to include this degree of variability. As described in this response, both these variations and conserved aspects have been considered in establishing active ingredient sameness criteria for a generic glatiramer acetate, including through the use of equivalence ranges based on RLD variability.
c. Copolymer, Rather Than a Protein

Glatiramer acetate is a copolymer composed of amino acids joined by peptide bonds. Although proteins are also composed of amino acids joined by peptide bonds, glatiramer acetate is distinguishable from proteins because (unlike a protein) it does not, as described above, have a defined and specific amino acid sequence. Rather, as noted above in section III.D.1.b, in the glatiramer acetate mixture, there is a negligible likelihood of having identical amino acid sequences along entire copolymer chains from batch to batch. Conserved sequences in glatiramer acetate are instead limited to short amino acid sequences within the copolymer chain. Although these preserved local sequences may be reflected in analyses used to establish active ingredient sameness, there is also broader sequence variability inherent to Copaxone. As such, glatiramer acetate is best described not as a protein, but rather as a heterogeneous mixture of copolymers.

2. Synthesis

A fundamental reaction scheme for the manufacture of glatiramer acetate has been published. Additionally, patents describing the glatiramer acetate active ingredient (including its synthesis) have been published and, in some cases, listed in FDA’s Approved Drug Products With

39 Several of Teva’s assertions in its Citizen Petitions relate to Copaxone having a complex and “protein-like” structure, which (as asserted by Teva) would preclude an active ingredient sameness determination of a generic glatiramer acetate (e.g., Second Petition at 2-3, 10, 13, 19; Third Petition at 3, 7-8; Fourth Petition at 1; Sixth Petition at 1-2, 3, 40 and Jan. 27, 2014 Supplement to the Sixth Petition at 3-4, 5). However, as noted in this section and throughout this response, we disagree with this characterization.

40 We also note that several of Teva’s assertions in its Citizen Petitions seem to indicate that although regulated as a drug product, Copaxone is in many ways more like, or shares characteristics with, a biological product (e.g., Fourth Petition, 33, 34; Sixth Petition at 36, 37, 40-41). Copaxone is a listed drug approved under section 505(c) of the FD&C Act, and, thus, the ANDA approval pathway is available for generic glatiramer acetate injection.

41 Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 22, available at:


43 Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide. European Journal of Immunology, 1971 (1) 242-248 describes the synthesis of glatiramer acetate as follows:

“Cop 1 (glatiramer acetate) was prepared from N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate, and ε-N-trifluoroacetyllysine. The polymerization reaction was carried out at room temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl groups of the glutamic acid was carried out with hydrogen bromide in glacial acetic acid and was followed by the removal of trifluoroacetyl groups from the lysine residues by 1M piperidine.”
Therapeutic Equivalence Evaluations (the Orange Book). These patents describe a fundamental reaction scheme that yields the glatiramer acetate active ingredient.

The fundamental reaction scheme for the synthesis of glatiramer acetate that is described in published literature can be subdivided into two critical steps:

1. Polymerization (including initiation and propagation of polymerization) of the activated amino acids (NCA-amino acids) alanine, tyrosine, glutamic acid, and lysine, which yields a copolymer comprised of alanine, tyrosine, glutamic acid, and lysine (and which is referenced throughout this response as the intermediate copolymer); and

44 The Orange Book is available on the Internet at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. US Patent 7,199,098, previously listed in the Orange Book by Teva, describes the synthesis of copolymer-1 (glatiramer acetate) as follows:

“Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 [grams (g)], alanine (50 g), τ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000 ± 2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28 °C a test reaction is performed on every batch at different time periods for example, from 10 -50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular-weight 7,000 ± 2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26 °C the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10 - 20 °C against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.”

See also US Patent 6,048,898.

45 Generally speaking, amino acids do not spontaneously polymerize. Activated or NCA-amino acids (e.g. N-carboxyanhydride amino acids) are chemically modified so that they can spontaneously polymerize into a polymer or copolymer following the addition of an initiator. The polymerization of NCA-amino acids to yield copolymers has been well studied and described in the literature (KatchalskiE and Sela M. Advances in Protein Chemistry 1958; 13:243). Based upon these studies, the polymerization of the NCA-amino acids alanine, tyrosine, glutamic acid, and lysine used in first step of the synthesis of glatiramer acetate involve two fundamental steps: (a) initiation of polymerization; and (b) propagation of polymerization.

46 These amino acids, particularly glutamic acid and lysine, may have attached protected side chains (e.g. the γ–O-benzyl ester for glutamic acid and ε-trifluoroacetic acid amide for lysine), which are removed during a deprotection step. As indicated by the Teitelbaum article and U.S. Patent 7,199,098, previously listed in the Orange Book, two of the amino acids used in the preparation of glatiramer acetate have protected side chains (γ–O-benzyl ester for glutamic acid and ε-trifluoroacetic acid amide for lysine) in order to avoid side reactions during polymerization. Therefore, following the polymerization and depolymerization reactions used to manufacture glatiramer acetate, a deprotection step may be needed to remove protecting groups on the lysine amino acid residues (e.g. the HBr
2. Partial depolymerization of the intermediate copolymer to yield glatiramer acetate.

Although the patents and the published literature describe other steps (e.g., deprotection, filtration, and lyophilization) involved in the manufacturing process of glatiramer acetate, FDA determined from its analysis of publicly available synthesis-related information\(^\text{47}\) that the conserved local amino acid sequences are primarily determined by the two critical steps of polymerization and partial depolymerization listed above and further described below. Therefore, the details of these two critical steps, together with their characteristic properties and with the additional properties of glatiramer acetate injection (e.g., physicochemical properties) that are affected by all manufacturing steps, are also discussed in connection with the sameness criteria below.

\[\text{a. Initiation of Polymerization}\]

The first step of glatiramer acetate synthesis involves initiating the polymerization of NCA-amino acids. In a method described in the literature and in the patents\(^\text{48}\), the polymerization of the NCA-amino acids begins following addition of an initiator. The initiator reacts with an NCA-amino acid (tyrosine, glutamic acid, alanine, or lysine) to generate an initiator adduct (i.e., an amino acid bound to the initiator) (see Figure 2).\(^\text{49}\) The initiation step forms the C-terminus\(^\text{50}\) of what will become a growing copolymer chain. Because of the intrinsic properties of the NCA-amino acids (e.g., relative bulkiness), the relative reactivity of each activated amino acid with initiator is anticipated to differ from the others. Most notably, the distribution of the four different initiator adducts at the C-terminus of the intermediate copolymer arises primarily because of the initiation kinetics and is a reflection of the reaction rate\(^\text{51}\) of each of the NCA-amino acids and the initiator.

The amount of initiator used relative to the NCA-amino acids impacts the number of chains polymerized in a given polymerization reaction, which in turn impacts several characteristics of glatiramer acetate described below, including the length of the intermediate copolymer chains (which has a subsequent impact on local sequences in the chains) and the number of cleavages.

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\(^{47}\) See note 44.

\(^{48}\) See notes 43 and 44.

\(^{49}\) The initiation reaction described in this response is based upon the data evaluated by the Agency.

\(^{50}\) The C-terminus is the end of the copolymer chain in which the carboxylate group (or derivative thereof) is not linked to another amino acid. The N-terminus is the end of the copolymer chain in which the amine group is not linked to another amino acid.

\(^{51}\) We note that the overall reaction rate is influenced both by each individual NCA-amino acid’s intrinsic reactivity with the initiator, as well as (as described in greater detail below) the concentrations of the NCA-amino acids and initiator.
needed in the partial depolymerization. Each of these characteristics is incorporated into the active ingredient sameness criteria described below.

![Diagram of polymerization process](image)

**Figure 2.** Polymerization of NCA-amino acids (abbreviated AA) begins with the addition of an initiator (abbreviated I).

b. Propagation of Polymerization

Following the initiation of polymerization, the amino acid of the growing polymer chain reacts with another NCA-amino acid to generate a copolymer comprised of two amino acids. This copolymer, in turn, can react with another NCA-amino acid to generate a copolymer comprised of three amino acids. These copolymers will continue to react with remaining NCA-amino acids in a chain reaction and will yield a distribution of peptides composed of varying molecular weights and having varying sequences of alanine, tyrosine, glutamic acid, and lysine residues (see Figure 3). This sequential addition of amino acids that leads to a growing copolymer chain is termed *polymer chain propagation*. This process will continue until the NCA-amino acids in the reaction solution are consumed.

![Diagram of polymer chain propagation](image)

**Figure 3.** Depiction of the polymerization reaction used in the manufacture of glatiramer acetate to yield the intermediate copolymer. The addition of amino acids to the copolymer chain is known as *polymer chain propagation*. The abbreviations used are as follows: Y-tyrosine, E-glutamic acid, A-alanine, K-lysine.

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We note that as the copolymer chain grows, while the addition of NCA-amino acids to the copolymer chain is not determined by a pre-determined sequence, it is also not a purely random event. Rather, each addition depends, in part, on the specific reaction kinetics at a given instant in the reaction, including, for example, the intrinsic reactivity of the NCA-amino acid added to the growing chain relative to the others, which is influenced by the size and shape of each NCA-amino acid. For instance, NCA-alanine is the smallest, most compact amino acid present in glatiramer acetate (Figure 1), allowing it to react more quickly than larger or more bulky amino acids (such as NCA-tyrosine). Based solely upon the bulk of the amino acids, one would expect the relative intrinsic reactivities of amino acids to differ and this would impact their relative incorporation rate into the copolymer during chain propagation in the following order: NCA-alanine > NCA-lysine ~ NCA-glutamic acid > NCA-tyrosine.53

The reaction kinetics (and therefore the rates of addition of the four NCA-amino acids), however, are not only dictated by their relative intrinsic reactivities but also by the relative concentrations of the NCA-amino acids.54 This is notable because during polymerization, the relative concentration of each of the four NCA-amino acids changes during the course of chain propagation. As the relative concentrations of NCA-amino acids are depleted or enriched during propagation, their corresponding relative rates of incorporation into the copolymer chains will change, leading to the process phenomenon of propagational shift.55

c. Propagational Shift

The molar fraction of each of the four amino acids (i.e., tyrosine, glutamic acid, alanine, and lysine) in Copaxone is clearly defined.56 If the four NCA-amino acids used in the synthesis had the same intrinsic reactivity during the chain propagation, the rates of incorporation of the four amino acids into the copolymer chains would be proportional to their respective molar fraction at the start of the reaction, which means that the molar fraction of each of the four NCA-amino acids in the polymerization solution would remain constant throughout the polymerization reaction. However, the intrinsic reactivities of the four NCA-amino acids involved are different, as described above, meaning that their corresponding relative rates of incorporation into the copolymer chains are, at any given point during the polymerization reaction, different from one another; these differing rates of incorporation result in shifting (rather than constant) molar fractions of each NCA-amino acid in the reaction solution, which in turn causes relative rates of incorporation of each NCA-amino acid into the copolymer to change throughout the propagation.

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53 We note that, the intrinsic reactivities of polymerization reaction also depend on the specific amino acid residue including its derivatives (e.g. an amino acid residue with protecting group) in the copolymer, at which the propagation of a chain occurs. Nonetheless, the relative rank order of the four NCA-amino acids incorporated into the copolymer remains similar to the somewhat simplified discussion above and remains illustrative for purposes of the following discussion.

54 For example, the frequency with which an NCA-amino acid with a low intrinsic reactivity is added to a growing chain could be increased if its concentration relative to the other NCA-amino acids present in the polymerization reaction is also increased.


56 See Section III.D.1 above.
As a result, the molar fractions of each of the four NCA-amino acids in the intermediate copolymer chain vary across the synthesized chain\(^{57}\) (referred to throughout this response as propagational shift).

To further illustrate propagational shift, during the initial phases of chain propagation, NCA-alanine, which is the most reactive NCA-amino acid and present at the highest concentration in the initial reaction solution (with a relative molar fraction in glatiramer acetate of 0.427), will be incorporated into the growing copolymer chain at the fastest rate. At the other extreme, during this period, NCA-tyrosine, which is the least reactive NCA-amino acid and present at the lowest concentration in the initial reaction solution (with a relative molar fraction in glatiramer acetate of 0.095), will be incorporated into the growing copolymer chain most slowly. Therefore, during the initial phases of chain propagation, the initial portion of the growing copolymer chain will be composed of relatively high levels of alanine with correspondingly low levels of tyrosine.

However, during the course of polymerization, as NCA-alanine is being rapidly incorporated into the growing polymer chains, its concentration relative to the other NCA-amino acids in the reaction solution will be reduced. As a result, toward the latter end of the chain propagation, the concentration of NCA-alanine will be reduced and its relative rate of incorporation into the polymer (or reactivity) will decrease. Therefore, during the later phases of chain propagation, the corresponding portion of the copolymer chains will contain relatively fewer alanine amino acids, as compared to the initial portion of the copolymers. Conversely, as NCA-tyrosine is only slowly being incorporated into the copolymer, its relative concentration to other NCA-amino acids will be enriched over the course of the polymerization reaction and its relative rate of incorporation into the polymer will increase. Therefore, during the later phases of chain propagation, the corresponding portion of the copolymer chains will be enriched with tyrosine, as compared to the initial portion of the copolymers.\(^{58}\)

As described above, the propagational shift is a key characteristic of the polymerization step. The shifting of rates of incorporation into the copolymer chains as measured in this progression is governed by the reaction kinetics (i.e., the intrinsic reactivities and concentrations of the reactants) of the reaction solution and therefore is not a random event. Due to the non-random nature of the reaction, the chance of producing a conserved local amino acid sequence is increased, which is consistent with the conservation of local sequences between batches of Copaxone. There are many different factors that can affect the propagational shift (e.g., reaction scheme, reactant concentrations, and reaction conditions). To establish the active ingredient sameness and to ensure equivalence of conservation of local sequences, a proposed generic glatiramer acetate should not only have propagational shift in its synthesis of the copolymer chains, but also needs to have the same propagational shift as in Copaxone.\(^ {59}\)

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\(^{57}\) We have observed this conservation based upon analyses of Copaxone conducted by ANDA applicants and submitted in connection with ANDAs as well as from FDA’s own internal laboratory analyses of samples of Copaxone.

\(^{58}\) We note that a similar phenomenon and analysis applies to the amino acids of intermediate reactivities, lysine and glutamic acid, during both the initial and later phases of polymerization.

\(^{59}\) The batch-to-batch variability of Copaxone is considered when structural signatures of propagational shift (see Section IV.C) are measured and compared to proposed generic drug products.
d. Partial Depolymerization

As discussed above, glatiramer acetate polymerization creates amino acid sequences containing tyrosine, glutamic acid, alanine, and lysine in the intermediate copolymer chains that are not completely random, but rather are determined by the relative incorporation rates of the different NCA-amino acids. These copolymer chains, however, are not the final chains present in glatiramer acetate. The manufacturing process used to synthesize glatiramer acetate involves a second step, termed “partial depolymerization,” in which the intermediate copolymer chains are cleaved until the characteristic molecular weight distribution of glatiramer acetate is achieved.\(^{60}\) We note that this depolymerization is simply a cleavage step (i.e., breaking the intermediate copolymers into smaller fragments) that does not rearrange the amino acid sequences of the copolymers in any way.\(^{61}\)

![Figure 4](image.png)

**Figure 4.** Depiction of the partial depolymerization of the intermediate copolymer used in the manufacture of glatiramer acetate. After depolymerization, the C-termini will be composed of initiator adduct as well as free carboxyl (uncapped) termini, while the N-termini will be composed of Y-tyrosine, E-glutamic acid (or in some cases, a variant pyroglutamate), A-alanine and K-lysine.

\(^{60}\) See note 44.

\(^{61}\) We note that, although not a sequence modification, a pyroglutamate residue may be formed in the place of a glutamic acid residue during partial depolymerization, as a result of the chain carboxylate of a glutamate residue cyclizing with its amine group when the glutamate is located at a newly formed N-terminus resulting from a cleavage reaction during the partial depolymerization.
In addition to establishing the characteristic molecular weight distribution of Copaxone, there are two other noteworthy aspects of the partial depolymerization process. First, the depolymerization reaction introduces new C-termi at the end of glatiramer chains (see Figure 4), which, unlike the “capped” initiator C-termi generated during the initial polymerization step, have free carboxylate groups. Most notably, because each cleavage introduces a new “uncapped” (amino acid residue with free carboxylate) C-terminus to the copolymer mixture, the ratio of “uncapped” C-termi versus “capped” (amino acid residue with initiator) C-termi is a key characteristic of depolymerization related to the number of cleavage events that take place during this partial depolymerization step, which is incorporated into the active ingredient sameness criteria described below.

Second, the reaction mechanism of the depolymerization or cleavage step may be to some degree chemically selective, meaning that there may be some degree of preferential cleavage between specific pairs of certain amino acids. The degree and type of any selectivity of the cleavage determines the relative amino acid composition of resultant newly formed N and C termi. For example, in Figure 4, where cleavage occurs between lysine and alanine, the resultant newly formed alanine at the C-termi and lysine at the N-termi would be a direct reflection of any cleavage preference at the C and N terminal sides of an alanine-lysine peptide bond during partial depolymerization of the intermediate copolymer. The profile of amino acid residues at the newly formed N-termi and C-termi is another key characteristic of the partial depolymerization because it reflects the degree and type of any selectivity of cleavage present in a given depolymerization reaction. Specifically, the proportions of amino acids present at the N-termi of glatiramer acetate (position 1) reflect any biases to cleavage at the N terminal sides of peptide bonds during partial depolymerization. Likewise, the proportions of amino acids present in position 1 of uncapped C-termi of glatiramer reflect any biases to cleavage at the C terminal sides of peptide bonds during partial depolymerization.

Finally, as noted above, due to propagational shift, there will be different proportions of amino acids (and their local sequences) along the copolymer chains. Therefore, if, and to the extent, a selectivity of cleavage based upon amino acid N and C peptide terminal side preferences exists, differing regions of the intermediate copolymer chain may have differing propensities for cleavage based upon the varying composition of amino acids along the length of the copolymer. The interaction between these two unique process characteristics, propagational shift and any selective cleavage, ultimately determine the distribution of local sequences in the copolymer mixture of glatiramer acetate, creating unique structural characteristics of Copaxone, which are incorporated into the active ingredient sameness criteria described below.

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62 Chemical selectivity refers to, among other things, a bias for cleavage in the glatiramer acetate copolymer chains taking place at certain specific amino acid residues. Any chemical selectivity of the depolymerization step will influence the resultant sequences of the cleaved copolymer chains. To illustrate, a single glatiramer acetate copolymer chain with a sequence of KAYEAKAA may be depolymerized via a process having a chemical selectivity with a bias to cleave adjacent to the E (glutamic acid) residue, resulting in two fragments, KAY and EAKAA. Note that there is no rearrangement of the sequences during such a depolymerization reaction, but the extent of any chemical selectivity of depolymerization affects the final distribution of resultant copolymer chains. Note also that the foregoing holds whether or not the selectivity is simply a bias to cleavage (e.g., that the chain KAYEAKAA may also be cleaved in different ways, albeit with a lower probability, such as into fragments KA, YEAK, and AA), rather than cleaving in the same manner in every instance.
In conclusion, the amino acid chains formed through polymerization in the synthesis of glatiramer acetate are not completely random, but rather are a reflection of the physicochemical properties of starting materials and the fundamental chemistry used to manufacture glatiramer acetate, including polymerization of activated amino acids with an initiator to yield an intermediate copolymer, followed by partial depolymerization. The distribution of amino acid sequences is governed by these chemical reactions, including the relative rates of reaction between the amino acids during initiation and chain propagation during polymerization and cleavage during partial depolymerization. More specifically, the amino acid sequences present in glatiramer acetate are dictated by the interplay of polymerization initiation, propagational shift during polymerization and cleavage (including the number of cleavage events and any selectivity) during partial depolymerization. This fundamental chemistry used in the manufacturing process, the characteristics of which can be captured analytically, constitutes a key element in establishing active ingredient sameness between a generic glatiramer acetate injection and the RLD, as further described below.

IV. GENERIC GLATIRAMER ACETATE INJECTION CAN CONTAIN THE SAME ACTIVE INGREDIENT AS COPAXONE WITHIN THE MEANING OF THE FD&C ACT AND FDA REGULATIONS

Section 505(j)(2)(A)(ii)(I) of the FD&C Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient of the generic drug product is the “same” as that of the listed drug.

Thus, an ANDA applicant for a generic version of Copaxone must provide sufficient information to show that the proposed drug product contains the same active ingredient as Copaxone. Glatiramer acetate is an array of diverse peptide copolymers, and this presents a complexity in terms of demonstrating active ingredient sameness. Not only does this array of copolymers create a chemically complex product, but a determination of active ingredient sameness cannot focus on any one portion or fraction of glatiramer acetate, but must be applied to the array of copolymers as a whole. Thus, in order to demonstrate active ingredient “sameness,” we expect the diversity (including the conserved aspects) of a generic glatiramer acetate to be shown to be equivalent to that of the active ingredient in Copaxone.

Although currently there is no single physicochemical or biological characterization that can demonstrate active ingredient sameness between a generic glatiramer acetate injection and

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63 See note 15.
64 See section II.B.
65 Teva asserts that our sameness analysis cannot focus exclusively on any one quality of Copaxone (e.g., First Petition at 19-20, Second Petition at 3, 13-15, 16, 22-23; Third Petition at 3; Fourth Petition at 4, 5, 6; Sixth Petition at 8 and Jan. 27, 2014 Supplement to Sixth Petition at 6-8). We agree that active ingredient sameness must be considered holistically, but on different grounds than Teva, as explained in this response. Further, we note that these criteria are different in scope from, and serve a different function than, the manufacturing controls that Teva claims “provide information on Copaxone’s bulk properties and do not elucidate the specific sequences and structures that constitute the active ingredient.” (Sixth Petition at 32.) These criteria, when taken in concert and as further explained below, establish active ingredient sameness.
Copaxone, there is a battery of characterizations that, when combined, can be applied to comparatively characterize the glatiramer acetate and provide a collection of scientific evidence sufficient to establish active ingredient sameness.\(^6\) This collection of evidence is obtained from orthogonal measurements, which are complementary in nature. Therefore, when considered as a whole rather than piece-by-piece, generic glatiramer acetate can be shown to have the same composition and diversity of amino acid sequences and of peptide copolymers as the active ingredient in Copaxone. Based on our current understanding of the product, its indication and its mechanisms of action, this can be accomplished by showing equivalence between the ANDA product and RLD as to the following criteria:

1. Fundamental reaction scheme;
2. Physicochemical properties including composition;
3. Structural signatures for polymerization and depolymerization; and
4. Results in a biological assay.

These four criteria take into account the inherent molecular diversity associated with glatiramer acetate and, taken together, are designed to provide overlapping and confirmatory evidence of active ingredient sameness through which FDA can conclude that generic glatiramer acetate injection has the same active ingredient as Copaxone.\(^6\) As noted above, the first three criteria provide evidence to identify and increasingly refine the information supporting active ingredient sameness, while the fourth criterion serves as confirmation of the initial three criteria. Importantly, we note that we do not recommend that an ANDA applicant show that based on these four criteria, any given batch of the product described in its ANDA is identical to any single batch of the RLD. This is consistent with the nature of Copaxone, which has inherent batch-to-batch variability.\(^6\) Rather, we evaluate active ingredient sameness by considering the

\(^6\) We note that we disagree with Teva’s assertion that Copaxone is insufficiently characterized to make a determination of active ingredient sameness, as we describe throughout this response (Second Petition at 20 and Jan. 27, 2014, Supplement to Sixth Petition at 6-8).

\(^6\) Several assertions made by Teva in its Citizen Petitions relate to Teva’s position that the overlapping criteria for sameness established by the Agency in connection with enoxaparin should not be applicable to Copaxone (e.g., Third Petition at 5, 9, 10, 14, 15; Sixth Petition at 27-28, referencing Letter from Throckmorton, D., Docket No. FDA-2003-P-0273 (July 23, 2010) (“Enoxaparin Petition Response”)). We note, however, that while overlapping criteria have been adopted, the specific overlapping criteria described herein are different than for enoxaparin, and have been uniquely designed for, Copaxone, to take into account the nature of the active ingredient glatiramer acetate. On a related note, several of Teva’s assertions relate to the inadequacy of certain of the foregoing criteria in isolation (e.g., First Petition at 22, 23; Third Petition at 12-13, 14, 16-17; Sixth Petition at 35 and Jan. 27, 2014 Supplement to Sixth Petition at 6-8); however, these assertions do not challenge the adequacy of all of these criteria when considered in concert.

\(^6\) The statutory requirement of sameness “must be read in the context of the kind of drug at issue,” and “does not unambiguously require . . . complete chemical identity.” Serono, 158 F.3d at 1319-20 (noting that batch-to-batch variability of a reference product “would make the target of the comparison . . . indeterminate” if “absolute chemical identity were required.”)
level of variability in the RLD compared to that of the proposed generic product. A sameness evaluation of these criteria will be based upon qualitative and/or quantitative comparisons of a generic glatiramer acetate injection to multiple batches of Copaxone, taking into consideration the batch-to-batch variability, sampling of Copaxone, and analytical test variability.

A. Equivalence of Fundamental Reaction Scheme

The first criterion of sameness is to ensure that the active ingredient of a generic glatiramer acetate injection is produced by an equivalent fundamental reaction scheme. As noted above, a fundamental reaction scheme for the manufacture of glatiramer acetate has been published and features the polymerization reaction involving the activated amino acids and initiator, followed by a partial depolymerization. As published, the first step of polymerization involves the polymerization of NCA-tyrosine, NCA-alanine, NCA-glutamate, and NCA-lysine with an initiator. In addition, the step of partial depolymerization is based upon acid catalyzed cleavage. An ANDA applicant may satisfy this first criterion of active ingredient sameness by using the same (or equivalent): (1) NCA-amino acids and polymerization initiator to yield the intermediate copolymer and (2) chemical reagent(s) for acid-catalyzed cleavage conditions.

As discussed above, the amino acid sequences present in glatiramer acetate are not entirely random but are dictated by the polymerization and partial depolymerization steps used in its manufacturing process. More specifically, the amino acid sequences present in glatiramer acetate are dictated by the interplay of polymerization initiation, propagational shift in chain

69 This is in contrast to certain assertions made by Teva in its Citizen Petitions that, in effect, a determination of sameness would require a finding that a generic glatiramer acetate injection and Copaxone are identical (e.g., Second Petition at 11; Third Petition at 4, 7; Fourth Petition at 6, 9, 10; Sixth Petition at 8, 25, 30, 32, 34). However, we note that given the batch-to-batch variation inherent to Copaxone, the RLD itself is not identical between batches. As such, active ingredient sameness criteria for a generic glatiramer acetate injection should incorporate this batch-to-batch variation.

70 The critical importance of the well-controlled synthesis process is also highlighted by certain of Teva’s assertions in its Citizen Petitions (e.g., First Petition at 12, 13; Fourth Petition at 5; Sixth Petition at 8 and Jan. 27, 2014 Supplement to the Sixth Petition at 4, 10-11). Teva’s manufacturing process for Copaxone is also emphasized in a citizen petition submitted by Peptimmune, Inc. (Docket No. FDA-2010-P-0531) (Peptimmune Citizen Petition), at 27.

71 Several of Teva’s assertions in its Citizen Petitions suggest that, given Copaxone’s complexity, its manufacturing process cannot be reverse-engineered (e.g., Fourth Petition at 5; Sixth Petition at 30 and Jan. 27, 2014 Supplement to the Sixth Petition at 3, 4, 9-10). As described above, we disagree. By using publicly available information regarding the synthesis process coupled with the sensitivity and diagnostic capabilities of the structural signatures, a synthesis process can be established that results in an active ingredient that is the same as the active ingredient of Copaxone, which then may be further confirmed as described below.

72 In this document, we use NCA-Glutamic Acid and NCA-Lysine to denote N-carboxyanhydrides of γ-benzyl glutamate, and ε, N-trifluoroacetyllysine respectively. The side chain protecting groups are implicitly included in the notation.

73 Id.

74 See note 44, for example.
propagation during polymerization, and the cleavage reactions in partial depolymerization. Therefore, if an ANDA applicant uses the same (or equivalent) NCA-amino acids and initiator to yield the intermediate copolymer, then the synthesis reactions (including the underlying chemical kinetics involved to initiate the polymerization and to propagate the copolymer chains) will be qualitatively equivalent to those used to synthesize the intermediate copolymer used to produce Copaxone. Moreover, if an ANDA applicant uses the same (or equivalent) chemical reagent(s) for acid-catalyzed cleavage conditions, the depolymerization reaction (including any cleavage selectivity) will be qualitatively equivalent to that used to produce Copaxone.

The elements of a fundamental reaction scheme to manufacture glatiramer acetate can be determined and confirmed using publicly available information on the synthesis process in conjunction with diagnostic analysis of the RLD by orthogonal analytical measurements, as described below in connection with the remaining active ingredient sameness criteria. Using the same (or equivalent) fundamental reaction scheme is essential to the sameness criteria because doing so can ensure the qualitative, although (if used in isolation) not the quantitative, equivalence of the chemical kinetics used in glatiramer acetate synthesis, which in turn dictates the key characteristics (i.e., propagational shift and cleavage pattern) in glatiramer acetate.

As noted above, we do not consider this criterion alone to be sufficient to establish active ingredient sameness because, for example, employing the same (or equivalent) reaction scheme can only ensure a qualitatively equivalent propagational shift exists between a generic glatiramer acetate and the glatiramer acetate in Copaxone. As we discussed previously in Section III.D.2, the precise characteristics of the propagational shift can be affected by reaction conditions and other manufacturing process parameters. Therefore, while we consider equivalence of fundamental reaction scheme to be one of four criteria used to determine active ingredient sameness for glatiramer acetate, based on our current understanding, used alone, this would be insufficient to ensure active ingredient sameness. The additional criteria are described as follows.

B. Equivalence of Physicochemical Properties, Including Composition

The second criterion for demonstrating active ingredient sameness of generic glatiramer acetate injection to Copaxone is equivalence of physicochemical properties, which include, but are not limited to, molecular weight distribution, amino acid composition, and spectroscopic fingerprints. Properties such as these provide broad, but critical, characterizations that are able to confirm (1) active ingredient sameness at a greater level of quantitative detail and (2) equivalence of underlying reaction processes to a greater degree than may be guaranteed by the first criterion alone. As noted above, it is the combination of these two equivalence criteria

75 As discussed below, qualitative equivalence of these reactions does not necessarily mean that they are quantitatively equivalent. Equivalence of the fundamental reaction scheme, in conjunction with equivalence as to the remaining active ingredient sameness criteria, establishes that the RLD and ANDA synthesis and depolymerization reactions are both qualitatively and quantitatively equivalent.

76 See notes 43 and 44, for example.

77 Several of Teva’s assertions made in its Citizen Petitions indicate that individual characteristics of a proposed generic glatiramer acetate (e.g., average molecular weight) would not, alone, be sufficient to support a determination
with the two remaining criteria discussed further below, which add complementary evidence of active ingredient sameness on both a detailed chemical level and a broader, system-wide level.

1. **Amino Acid Building Blocks**

Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate are L-glutamic acid, L-lysine, L-alanine, and L-tyrosine, with an average molar fraction of 0.141, 0.338, 0.427, and 0.095, respectively. The amino acid content of glatiramer acetate can be determined by complete hydrolysis of the mixture to its amino acid components and, for purposes of establishing active ingredient sameness, the content should be equivalent to that of the RLD. In addition, the optical purity (i.e., chirality) of the four amino acids, which may be affected by certain manufacturing process conditions, should be measured and compared to the values found in Copaxone.

2. **Molecular Weight Distribution**

Glatiramer acetate is a synthetic copolymer having an average molecular weight of between 5-9 kDa. For the purposes of demonstrating sameness, it is essential for generic glatiramer acetate to have an array of chain lengths equivalent to that of the RLD. Comparing molecular weight distributions, including the molar mass moments (Mn, Mw, Mz) and polydispersity (Ip) for the generic drug and the RLD can be accomplished by using a variety of techniques including size exclusion chromatography, mass spectroscopy, or other appropriate methods.

3. **Spectroscopic Fingerprints**

To demonstrate equivalence of physicochemical properties, it is important to obtain information relating to the overall properties of the drug, as measured by spectroscopy, which must be equivalent when generic glatiramer acetate injection is compared to Copaxone, the RLD. Such spectroscopic methods (e.g., nuclear magnetic resonance (NMR) spectra, Fourier transform infrared spectroscopy (FT-IR) or other similar methods) can provide “spectroscopic fingerprints” of molecules, which are measurements of the emission or absorption of light by certain functional groups (e.g., carbonyl and hydroxyl groups by FT-IR) or certain elements (e.g., $^1$H...
and $^{13}$C by NMR) in different functional groups contained within a drug.\textsuperscript{81} These measurements are sensitive to the chemical environments within and around such molecules (i.e., glatiramer acetate copolymers). Equivalence between a generic glatiramer acetate active ingredient and the active ingredient of the RLD using spectroscopic fingerprints can further ensure the identity and composition of the copolymers.

Furthermore, circular dichroism (CD)\textsuperscript{82} is a spectroscopic method commonly used to study secondary structures in polypeptides. Secondary structures and their thermal stability are primarily determined by the amino acid sequence and length of a given polypeptide.\textsuperscript{83} Given this, analysis of CD spectra can be used as a method to determine the distribution of secondary structure types (e.g., alpha helix and beta sheet) in a glatiramer acetate injection.\textsuperscript{84} Equivalence achieved in the CD study of a generic glatiramer acetate active ingredient and the active ingredient of the RLD demonstrates equivalence in secondary structures and the related amino acid sequence information.\textsuperscript{85}

Taken together, overall characterizations of physicochemical properties provide important supporting evidence of active ingredient sameness that is complementary to the other criteria when a generic product is compared to the RLD. Given this, this criterion is also a critical element of establishing active ingredient sameness.

C. Equivalence of Structural Signatures for Polymerization and Depolymerization

As discussed above, the composition and sequence diversity of peptide copolymers in Copaxone are governed by the polymerization and depolymerization reaction kinetics used in its synthesis. Although a fundamental reaction scheme for manufacturing glatiramer acetate is published in the literature,\textsuperscript{86} other relevant information (including specific process conditions) by which Teva manufactures glatiramer acetate are not publicly available.\textsuperscript{87} If the same fundamental reaction


\textsuperscript{82} In the far-ultraviolet (UV) region (195-245 nm), the CD spectra of polypeptides are sensitive to secondary structure. Variations in secondary structure perturb the CD signature of the amide bond in this region and models for the spectrum of each type of secondary structure have been established.

\textsuperscript{83} We note that, based on our current understanding, Copaxone exists in a thermodynamically stable, reversible equilibrium state, meaning that the criteria for determining active ingredient sameness described herein are sufficient without additional characterizations of any higher order structure of glatiramer acetate.

\textsuperscript{84} A CD spectrum is composed of a population-weighted, linear combination of the theoretical pure secondary structures. The interpretation of the secondary structure content can be achieved by deconvoluting a CD spectra into the sum of components from each of its secondary structure type components, namely random coil, alpha helix, and beta sheet structures.

\textsuperscript{85} CD spectra may also be able to show equivalence of thermal stability over a temperature range.

\textsuperscript{86} See notes 43 and 44.

\textsuperscript{87} For example, the polymerization initiation and propagational shift in the first polymerization step may be dependent on process conditions such as temperature, concentration of NCA amino acids and initiator. Likewise,
scheme is followed, but if certain other process conditions are not incorporated or considered, the produced glatiramer acetate active ingredient may achieve “qualitative” similarity with the characteristics of the polymerization and depolymerization reactions, but may not, however, be the same as the RLD.\textsuperscript{88} Using propagational shift as an example, as described above, a generic applicant need not only show that its product was synthesized with a process resulting in a propagational shift, but such an applicant also needs to demonstrate that the propagational shift resulting from its process is the same as the propagational shift present in the RLD, as measured by characterizations and comparisons between the proposed generic and the RLD products.

Within the reaction schemes described above, certain characteristics of the reaction leave what is referred to in this response as “structural signatures” in the active ingredient, including initiation chemistry of peptide chains, coupling between the various amino acid pairs during the chain propagation and any cleavage preference of depolymerization. Therefore, to ensure active ingredient sameness between a generic glatiramer acetate injection and the RLD, and specifically to ensure equivalent polymerization initiation, propagational shift and partial depolymerization of the glatiramer acetate, ANDA applicants would need to identify and analyze structural signatures that are chemical attributes of glatiramer acetate and correlate to both the polymerization step (including initiation kinetics and propagational shift) and the cleavage step of partial depolymerization.\textsuperscript{89} Measuring structural signatures of generic glatiramer acetate in comparison to the same structural signatures of the active ingredient in the RLD provides evidence of active ingredient sameness as well as detailed, quantitative equivalence of the underlying reaction chemistry and kinetics. Such equivalence of the underlying reaction chemistry and kinetics, in turn, provides further confirmation of active ingredient sameness between the generic product and the RLD. Thus, in combination with the other sameness criteria described in this document, equivalence of these structural signatures ensures that the resultant molecular identity and diversity of amino acid sequences in generic glatiramer acetate’s copolymer chains will be equivalent to those of the active ingredient in Copaxone.

To demonstrate active ingredient sameness, structural signatures should cover the critical process steps of (1) polymerization initiation, (2) propagational shift during polymerization and (3) cleavage during partial depolymerization. We anticipate that each ANDA applicant will develop its own set of structural signatures for its generic product and will compare these signatures to the cleavage reactions during the partial depolymerization may be dependent on process conditions such as temperature, time, concentrations of hydrogen bromide, acetic acid, and water.

\textsuperscript{88} We note that the approach taken here is not inconsistent with, and addresses, arguments made by Teva in its citizen petitions regarding the impact of variations in the process parameters used in the manufacture of glatiramer acetate, as further explained here and elsewhere. (See, e.g., Jan. 27, 2014, Supplement to the Sixth Petition at 4.)

\textsuperscript{89} We note that an analogous concept was used in connection with establishing active ingredient sameness criteria for enoxaparin; however, as described in this response, the signatures to be used in connection with glatiramer acetate are unique to glatiramer acetate and are more extensive than those used in connection with enoxaparin. For example, we note that the sameness criteria in the case of enoxaparin focused on one primary step of its synthesis (i.e., cleavage), whereas in this instance, the sameness criteria focus on multiple aspects of the synthesis of glatiramer acetate, including initiation, polymerization and partial depolymerization. See, e.g., Lee S, Raw A, Yu L, Lionberger R, Ya N, Vertehelyi D, Rosenberg A, Kozlowski S, Webber K, Woodcock J. Scientific considerations in the review and approval of generic enoxaparin in the United States. Nature Biotechnology 2013; 31: 220-226. See also Enoxaparin Petition Response.
the RLD.\textsuperscript{90} Each applicant will also provide information to support the validity of its proposed structural signatures and the corresponding methods, which can be supported, for example, by (a) a mechanistic understanding of the synthetic process, (b) published literature, (c) pharmaceutical development studies that link changes in the ANDA manufacturing process to the corresponding structural signature, (d) negative control studies that introduce variations in the process and corresponding variations to the resulting product and structural signatures, and (e) the proposed equivalence range/acceptance criteria\textsuperscript{91} should be based on the batch-to-batch variations of the RLD product. Examples of structural signatures for polymerization initiation, propagational shift, and the cleavage reactions of partial depolymerization are discussed in greater detail below.

1. **Structural Signatures for Polymerization Initiation**

As discussed in Section III.D.2, the use of a polymerization initiator in the first step of glatiramer acetate synthesis is described in the method documented in Teva’s patents and the published literature. There are two characteristics of polymerization initiation, which should be captured as structural signatures:

a) the distribution (i.e., relative amounts) of the four amino acid-initiator adducts; and

b) the initiator content in copolymer.

The first property reflects the bias of amino acid incorporation upon initiation based on the initiation kinetics, including the intrinsic reactivity of each NCA-amino acid with the initiator and the concentration contributions of the four NCA-amino acids during the initiation stage. The second property, correlated with the relative number of copolymer chains initiated in the reaction, can also be correlated to the average chain length of the intermediate copolymer. Both properties have significant impacts on the propagation of polymerization and partial depolymerization.

2. **Structural Signatures for Propagational Shift During Polymerization**

As discussed above, the amino acid composition (i.e., molar ratios of the four amino acids) will not be uniform across the intermediate copolymer chain, but instead will differ along its length due to the phenomenon of propagational shift (also described above), which arises primarily due to the differences in relative intrinsic reactivities and relative concentrations among the four NCA-amino acids. As noted above, a structural signature for propagational shift is particularly important, as it plays a critical role in determining the distribution of local sequences in the glatiramer acetate copolymers and impacts the locations of potential cleavage sites for the

\textsuperscript{90} We note that Sandoz developed such structural signatures and established equivalence of such signatures between its glatiramer acetate injection and the RLD in connection with the ANDA that we are approving today.

\textsuperscript{91} Teva seems to assert in its Third Petition that a sameness determination for Copaxone would require a finding that specific sequences found in a generic glatiramer acetate injection and the RLD are identical (at 17-18). (See also Jan. 27, 2014, Supplement to the Sixth Petition at 6-8.) As described above, our approach instead is to ensure equivalence of diversity and distribution of sequences. This equivalence, when taken in concert with the other criteria described in this response, is sufficient to ensure active ingredient sameness.
subsequent depolymerization step to the extent of any cleavage preference. A generic sponsor should identify relevant amino acid sequence properties and corresponding analytical procedures, which can quantitatively measure the propagational shift in Copaxone.

3. Structural Signatures for Cleavage Reactions in Partial Depolymerization

As described above, in partial depolymerization of glatiramer acetate, the copolymers are cleaved until the characteristic length or molecular weight distribution of the chains is achieved. In each cleavage reaction, new N- and C-termini are formed. This process allows the development of structural signatures for the cleavage reactions of the depolymerization step. These structural signatures are intended to characterize any preference at the site of cleavage and the average number of cleavages for an intermediate copolymer chain. Details of examples of such structural signatures include:

- First, because the amino acids at position 1 of the N-termini result from a cleavage reaction, the relative proportion of amino acids present at position 1 of the N-termini of glatiramer acetate reflects potential cleavage biases at peptide bonds with such amino acids present at the N-terminal side during partial depolymerization;

- Similarly, because at least a portion of the amino acids at position 1 of the “uncapped” C-termini result from a cleavage reaction, the relative proportion of amino acids present at position 1 of the “uncapped” C-termini of glatiramer acetate reflects potential relative cleavage biases at peptide bonds with such amino acids present at the C-terminal side during partial depolymerization; and

- Finally, because each cleavage reaction introduces a new “uncapped” C-terminus, the ratio of “uncapped” versus “capped” C-termini correlates with, and serves as a structural signature of, the number of cleavage events that take place during partial depolymerization.

In summary, the structural signature examples discussed above in subsections 1, 2 and 3 capture key characteristics of polymerization (including initiation and propagation) and the partial depolymerization reaction. Specifically, these structural signatures provide quantitative measurements correlated with the amino acid preference of initiation, the average size of intermediate copolymer chains, the propagational shift, any cleavage site preference during partial depolymerization and the average number of cleavages applied to an intermediate chain. Using these structural signatures and the associated acceptance criteria, together with the first two sameness criteria (equivalent fundamental reaction scheme and equivalent physicochemical properties), the active ingredient sameness of glatiramer acetate can be established in terms of both its overall chemistry and in terms of conservation of its sequence diversity.

D. Equivalence of Biological Assay

As described above, the first three criteria for active ingredient sameness ensure that the molecular diversity of copolymers associated with an ANDA product’s active ingredient (glatiramer acetate) are the same as Copaxone’s glatiramer acetate. The fourth criterion serves as a confirmatory test of equivalence and provides complementary confirmation of sameness. As
noted above, the activity of glatiramer acetate was originally predicted based upon the effect of glatiramer acetate when tested against experimental autoimmune/allergic encephalomyelitis (EAE). This test has become the primary animal model for multiple sclerosis. In the EAE assay, mice, rats, or guinea pigs treated with a myelin-related, EAE-promoting agent, invariably develop EAE, which is manifested by hind limb paralysis. Glatiramer acetate attenuates the severity of the disease in test animals elicited by the EAE-promoting agent. Given that it is an established animal model, in addition to the broad array of potential mechanisms of action of glatiramer acetate, the EAE assay provides a system-wide confirmatory assay for sameness. equivalence in this assay provides important confirmatory evidence of active ingredient sameness between generic glatiramer acetate injection and the RLD.

There are a number of biochemical assays (e.g., T-cell activation, antigen presenting cell activation, anti-glatiramer acetate antibody) that measure certain biomarkers through in vitro or in vivo tests to assess the effects of glatiramer acetate. Due to the variability in these tests, and the narrow focus of a particular test compared to the broad potential mechanisms of action of glatiramer acetate, the results of any one such biochemical assay provide less information with respect to active ingredient sameness than the EAE assay. Therefore, while analysis of data arising out of such biochemical assays may be helpful in assessing an ANDA for a generic glatiramer acetate injection with respect to active ingredient sameness, based on our current understanding of the science, we currently consider the EAE assay to be the most useful biological assay for confirmation of active ingredient sameness.

**E. FDA Analytical Testing as Confirmation of Sameness Criteria**

In addition to the characterizations and assays performed by generic sponsors, FDA’s internal laboratory developed and performed its own testing of multiple batches of Copaxone, the proposed generic glatiramer acetate injection, glatiramer acetate-like products marketed outside

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93 Teva indicates that it employs an EAE blocking test to assess the consistency of its own batch-to-batch consistency of Copaxone (First Petition at 24).


95 Teva asserts that certain of these assays should be considered in a sameness determination (e.g., First Petition at 22-23), but, as described above, we have determined sameness can be established using other criteria.

96 This is consistent with several assertions made by Teva in its Citizen Petitions (e.g., Third Petition at 18, 19; Sixth Petition at 36).

97 We note that FDA has conducted similar testing of other complex drug products (e.g., cyclosporine), in part, to enhance its understanding of these products. See, e.g., Rahman Z, Xu X, Katragadda U, Kirshnaiah Y, Yu L, Khan M. Quality by Design Approach for Understanding the Critical Quality Attributes of Cyclosporine Ophthalmic Emulsion. Mol. Pharmaceutics 2014; 11:787-799.
of the United States, and negative controls, in each case using high-resolution analytical techniques. As further described below, these tests validate the findings of, and confirm the robustness of, the sameness criteria described above. The samples were first digested with lysyl endopeptidase, and then the digestion products were analyzed using a liquid chromatography-mass spectrometry (LC-MS) system, allowing for their use as a marker of conserved local sequence information. At the FDA laboratory, a method was developed to analyze the digestion products, where a variant of normal phase liquid chromatography (i.e., hydrophilic interaction liquid chromatography, HILIC) was applied with mass spectroscopy. Using this approach, over 1000 data points were collected for each sample. Furthermore, a quantitative data analysis method was developed and applied to the data sets collected. This method is sufficiently sensitive such that the batch-to-batch variations of Copaxone can be detected. Based on appropriate statistical analysis of the results, the glatiramer acetate-like products marketed outside of the United States and negative controls can be clearly distinguished from Copaxone batches. However, when applying the same testing, no significant differences were observed between the proposed generic glatiramer acetate injection under consideration by FDA and Copaxone. In other words, the quantitative characterization of the proposed generic samples is consistent with the same characterization of Copaxone, taking into account its batch-to-batch variability. Because these tests clearly distinguish products that meet active ingredient sameness criteria described above from those that would not meet these sameness criteria, these tests, while not currently considered by FDA to be necessary to establish active ingredient sameness, confirm and validate the robustness of criteria described above to assess the sameness of glatiramer acetate.

F. Conclusion

Copaxone (glatiramer acetate) is one of the few treatments for multiple sclerosis. Glatiramer acetate is comprised of an array of peptide copolymers, and this presents a unique challenge in terms of demonstrating active ingredient sameness between a generic glatiramer acetate injection and Copaxone. However, an ANDA applicant can demonstrate active ingredient sameness to the RLD by using the same (or equivalent) fundamental reaction scheme (developed through public sources and analysis of the RLD), exhibiting equivalence in key physicochemical properties (including composition), identifying and showing equivalence with respect to key structural signatures for polymerization and depolymerization chemistry, and finally demonstrating equivalence in a biological assay. A demonstration that these criteria are satisfied provides compelling evidence that the molecular identity and diversity of glatiramer acetate is equivalent to that of the active ingredient in Copaxone and establishes active ingredient sameness between a generic glatiramer acetate injection and Copaxone.

98 Specifically, these include samples of the Natco product marketed in India and Ukraine.

99 Other methods of analysis include Reversed Phase (RP) high-performance liquid chromatography (HPLC) with UV detection, which has more limited resolution and sensitivity of the RP-HPLC-UV and allows for qualitative, rather than quantitative, comparison of results.
V. RESPONSES TO CERTAIN ISSUES RAISED IN CITIZEN PETITIONS

This section addresses certain specific arguments raised by Teva in its citizen petitions.

A. Active Ingredient Sameness

1. Sameness Criteria in General

In its citizen petitions, Teva has asserted that FDA cannot approve any ANDA that references Copaxone as the RLD because current chemical analytical techniques are incapable of showing that the active polypeptide sequences in a proposed generic product are the same as those in Copaxone. For example, Teva asserts that it is not possible to demonstrate that generic versions of Copaxone have the same active moieties and are consistent on a batch-to-batch basis. As discussed above in Section IV, we disagree with this position. Glatiramer acetate is adequately characterized. Current analytical techniques are capable of supporting a demonstration of active ingredient sameness between the generic glatiramer acetate injection and its RLD.

2. Glatiramer-Like Products and Manufacturing Changes

Teva asserts that slight changes in the manufacturing process for glatiramer acetate can produce altered sequences of unknown safety and efficacy. Teva asserted that it demonstrated this outcome as it developed a glatiramer-like product known as TV-5010, which was synthesized by using the same four amino acids as are present in glatiramer acetate, but the manufacturing process was varied slightly to produce a higher molecular weight product. Teva reported that treatment with this higher molecular weight TV-5010 led to toxic side effects not seen with glatiramer acetate. These arguments do not undermine the determinations described in this response. We note that TV-5010 would have failed to satisfy the active ingredient sameness criteria described above. Most obviously, its described molecular weight would have failed to meet the sameness criteria of equivalence of physicochemical characteristics. Teva makes related assertions regarding several “glatiramer-like” products reviewed by regulatory bodies outside of the United States or otherwise not approved by the Agency. We note that these assertions have been considered by FDA in connection with the development and implementation of the sameness criteria described in this response and, regardless of the accuracy of these assertions, they do not alter our findings described in this response. We note that, as with any ANDA, the Agency would evaluate active ingredient sameness for glatiramer.

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100 For example, First Petition supra note 1 at 19, 25 – 25, 17; Second Petition at 20 – 24, 35; Third Petition 10 – 20 (comparing with Enoxaparin); Sixth Petition 24 – 29, 33 and Jan. 27, 2014 Supplement to the Sixth Petition at 3, among others referenced elsewhere in this response.

101 First Petition at 16; Second Petition at 15, 24, 26; Third Petition at 4, 25; Fourth Petition at 26; Sixth Petition at 19.

102 First Petition supra note 1 at 15, 33; Sixth Petition at 19.

103 See, e.g., Second Petition at 26, Fourth Petition at 31, 33; Sixth Petition at 31; Seventh Petition at 11-17; Nov. 13, 2014, Supplement to the Seventh Petition at 4, 12, Appendix 1.
acetate injection during the ordinary course of review and would only approve ANDAs that demonstrate active ingredient sameness and meet the other requirements for approval.

As early as 2009, several ANDA sponsors provided preliminary data for several “glatiramer-like” products that were synthesized under various process conditions and that were not under consideration as ANDA products, but rather were used as negative controls for products under review. These negative control products had the same overall physicochemical characteristics (e.g., molecular weight distribution and amino acid composition) as the RLD, but had different distributions of copolymer sequences, as assessed by ANDA applicants by using structural signatures of polymerization and depolymerization as described above and comparing these structural signatures to the RLD. For example, the differences in these sequences are reflected in the differences in the structural signatures for polymerization kinetics and are attributed to the varying kinetics used in the manufacture of each of these “glatiramer-like” products. Thus, our consideration of products that are “like” but not the same as glatiramer acetate injection has only confirmed that the sameness criteria are sufficient to establish active ingredient sameness because of their ability to detect slight differences in the active ingredient.

3. FDA’s Approach Is Consistent With Other Agency Decisions

As a general matter, the Agency makes active ingredient sameness determinations for each drug on a case-by-case basis and our finding of active ingredient sameness is based on relevant scientific information and is specific to each active ingredient. Nonetheless, Teva claims that the agency’s decisions as to active ingredient sameness for other complex drug products require “substantial certainty regarding the active ingredient’s composition . . . a clear understanding of the RLD’s mechanism of action and reliance on knowledge gained from past clinical experience to rule out the possibility that [any] differences are clinically relevant.” Although FDA does rely on knowledge gained from the Agency’s past practice in connection with its determinations, it does so when applicable and when such reliance is appropriate, given other relevant factors and considerations.

For example, Teva refers to FDA’s 1997 determination that a synthetically-derived generic conjugated estrogens product could not be approved as an ANDA using Premarin (a naturally-sourced conjugated estrogens product) as the RLD. In that decision, FDA determined that “because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be definitively identified.” FDA concluded that “[a]ny synthetic generic conjugated estrogens application based upon Premarin as the reference listed drug is not to be approved until the active ingredients of Premarin have been sufficiently

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104 Similar arguments are asserted by Teva (Sixth Petition at 21).
105 Second Petition at 7-8.
106 For example, First Petition at 20, Third Petition at 8-9; Sixth Petition at 28-29.
well defined to permit an ANDA applicant to establish that a synthetic generic form of Premarin has the same active ingredients as Premarin.\footnote{108}

Teva’s reliance on the Premarin example is misplaced. Unlike Copaxone, Premarin is naturally-sourced from the urine of pregnant mares and the Agency’s determination related to the ability of a synthetically-derived product to be approved as an ANDA when the RLD and all of its clinically meaningful components had not been adequately characterized.\footnote{109} In essence, in the case of Premarin, the Agency found that a synthetic manufacturing method could not be substituted for a naturally-derived source when there were not adequate assurances that all clinically meaningful components of the naturally-sourced materials would be reproduced in a synthetically-derived version. In this case, by contrast, Copaxone is synthetically derived, with an adequate control of the starting materials including NCA-amino acids and initiator, as described above. The sameness criteria described above would require that a generic glatiramer acetate be synthesized using the same (or equivalent) starting materials and initiator.\footnote{110} The Agency’s concerns regarding the characterization of Premarin do not, as asserted by Teva, apply to Copaxone. Furthermore, the Agency has determined that Copaxone’s glatiramer acetate has been adequately characterized for purposes of approving an ANDA for glatiramer acetate injection.

For similar reasons, Teva’s citation to an FDA determination relating to another naturally-derived RLD, Pergonal (menotropins), is misplaced. Pergonal is derived from the urine of postmenopausal women,\footnote{111} where synthesis occurs in vivo. In 1997, FDA found the “same active ingredient” for a proposed generic version of Pergonal, despite naturally occurring variations (microheterogeneity) in the products’ carbohydrate side chains.\footnote{112} Teva claims that two findings “were crucial to the Agency’s sameness determination”: (1) the ANDA applicant had established that the protein backbones and specific amino acid sequences in the RLD and proposed ANDA product were identical, that the two products were equally potent, and that the two products showed the same degree of batch-to-batch uniformity as measured by the same bioassays and specifications, and (2) FDA had long-term experience with another menotropins product (Humegon) that showed the same kinds of microheterogeneity as the proposed ANDA product, and clinical trials and published literature “demonstrated no differences in safety and

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108 Id.
109 Id.
110 Teva characterizes the source material of Copaxone not as its constituent NCA- amino acids, but rather as the polypeptide mixture resulting from the polymerization process (prior to deprotection/depolymerization) (e.g., Third Petition at 14; Sixth Petition at 33-34). We disagree with this characterization because, among other considerations, as described above, the initiation and polymerization steps in the synthesis process are distinctive and fundamental steps in the manufacture of Copaxone. Teva also asserts that it carefully controls the ratio and purity of the amino acid starting materials. (Sixth Petition at 33) As described further above, the sameness criteria described in this response require equivalence of fundamental reaction schemes, coupled with the remaining three criteria, which further confirm both sameness and equivalence of the underlying chemical synthesis, including the ratio and purity of the starting materials.
111 Serono, 158 F.3d at 1316.
112 Second Petition at 19 (citing Letter from Woodcock, J., Docket No. 92-0487, at 10-13 (June 17, 1997).
efficacy” between Pergonal and Humegon. The specific findings are not relevant here because Pergonal, a naturally-derived product, raised different considerations than Copaxone, a synthetically-derived product. For Copaxone, an ANDA would be expected to have equivalent batch-to-batch uniformity as the RLD; demonstrating that equivalence is part of the active ingredient sameness criteria that are unique to Copaxone, such as equivalent structural signatures for polymerization and depolymerization. Further, for Pergonal, FDA was aware that differences existed but concluded that they did not matter. For Copaxone, by contrast, a generic product meeting the four criteria will have all of the same components as Copaxone (within the context of its variability).

Nor are two additional FDA decisions involving naturally-derived products relevant here. Teva cites FDA’s determination that the complexity of certain naturally-derived pancreatic enzyme products (exocrine) renders currently available chemical and bioanalytical tools likely unable to demonstrate active ingredient sameness, and the Agency’s conclusion that the current lack of complete characterization makes it impossible to determine whether two hyaluronidase products are the same. Like the Pergonal example cited above, the specific findings regarding exocrine and hyalurodinase are inapplicable here because they were specific to those active ingredients and involved different considerations by the Agency; for example, the Agency’s reasoning relied upon the natural source of those drug products. As noted above, the Agency has determined that Copaxone’s glatiramer acetate has been adequately characterized for purposes of demonstrating active ingredient sameness for ANDA approval.

Teva does not and cannot identify similarities between glatiramer acetate injection and these other drug products (Pergonal, exocrine, and hyaluronidase) that would make FDA’s active ingredient sameness determinations as to those products relevant to glatiramer acetate injection in the way that Teva asserts. As explained above, this response sets forth an approach to determining active ingredient sameness that is based upon the unique chemical properties of glatiramer acetate injection and, therefore, is specific to this drug product.

4. **Copaxone’s Activity**

In addition, Teva asserts that Copaxone’s mechanism of action is akin to other product types and glatiramer acetate should be considered consistent with FDA’s scientific evaluations of those product types. For example, Teva asserts that Copaxone has therapeutic vaccine-like activity and impacts anti-glatiramer acetate-specific antibodies. Nonetheless, a complete

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113 Id.


115 See Hyaluronidase Petition Response, at 5 (“[T]he Agency cannot determine the specific enzyme or enzymes contained in any naturally sourced hyaluronidase product”); Exocrine Guidance, at 1 (noting that the relevant enzymes are contained in ingredients “which are of animal origin”).

116 For example, First Petition at 10, 11; Second Petition at 9, 16; Third Petition at 24, Fourth Petition at 4, 7, 26-28; Sixth Petition at 9, 38.
understanding of glatiramer acetate’s mechanism of action is not a necessary consideration in a
determination of active ingredient sameness. There are many approved drug products whose
mechanism of action is uncertain, but this has not precluded approval of ANDAs for those
products.118

B. Bioequivalence

1. Glatiramer Acetate Injection Is a Parenteral Solution

Glatiramer acetate injection is a parenteral solution. Therefore, if active ingredient sameness is
established based upon the above criteria by an ANDA applicant and the drug product is
qualitatively and quantitatively the same in terms of active and inactive ingredients, then
bioequivalence would be self-evident and any requirement to submit in vivo evidence of
bioequivalence may be waived under 21 CFR 320.22(b) (commonly referred to as a
“biowaiver”).119, 120

In its fourth and sixth citizen petitions, Teva asserted that an in vivo bioequivalence waiver is
inappropriate for glatiramer acetate injection because of colloidal characteristics of Copaxone.121

117 Demonstrating that a proposed drug product has the same mechanism of action is not a criterion for showing
active ingredient sameness, including as described in section 505(j)(2)(A) of the FD&C Act or 21 CFR 314.92(a)(1).
Several of Teva’s assertions in support of the company’s challenge to generic glatiramer acetate injection relate to
the limitations of understanding of Copaxone’s mechanism of action and several theoretical mechanisms of action
(e.g., First Petition at 7, 28, 29; Second Petition at 3-4, 13-15, 17, 22-23; Third Petition at 3-4; Fourth Petition at7, 8-
9, 30-31; Sixth Petition at 25, 31, 32-33, 47 and the Jan. 27, 2014 Supplement to the Sixth Petition at 10). Similar
assertions are made in the Peptimmune Citizen Petition, at 3, 6-7, 9. These limitations in understanding do not
preclude a finding of active ingredient sameness, as further described above.

118 For example, FDA has approved generic versions of valproic acid and propofol. We note that these ANDA
products have been approved despite poorly understood mechanisms of action.

119 We note that the proposed rule regarding biowaivers included the following explanation: “The agency does not
believe Congress intended that unnecessary human research be conducted in cases where an applicant could
demonstrate that a product is inherently bioequivalent to another product and therefore meets the statutory standard
of bioequivalence.” 54 FR 28872 at 28883 (July 10, 1989).

120 In its Fourth Petition (at 20-21), Teva asserts that comparative in vivo bioequivalence studies with clinical
endpoints should be required because, among other things, FDA refused to approve an sNDA for a modified
formulation of Copaxone that contained the same active ingredient in a higher concentration and lower volume. See
also Sixth Petition at 52-53. Teva contends that FDA explained that it could not approve the sNDA without clinical
efficacy studies because “[t]he uncertainty about the glatiramer acetate mechanism of action, and the fact that some
of the effect may be related to the activation of lymphocytes in the periphery, raise questions about a possible impact
of a higher concentration/lower volume formulation on the safety and efficacy of the product.” Teva contends that
“[i]f FDA cannot be sure that the absence of 0.5 mL of water will not affect safety or efficacy without requiring
clinical studies, it cannot possibly determine that a purported generic product with an active ingredient that
invariably will differ from the glatiramer acetate in Copaxone will have the same safety and efficacy profile without
requiring comparative in vivo studies with meaningful clinical endpoints.” Teva’s attempt to draw an analogy
between the approval of an ANDA for glatiramer acetate injection and FDA’s action on Teva’s sNDA is flawed
because – unlike a proposed generic product that satisfies the conditions for a biowaiver – the modified formulation
of Copaxone, which changed the strength of the product, was not qualitatively and quantitatively the same as the
original formulation.

121 For example, Fourth Petition supra note 1 at 4 – 9, 12; Sixth Petition at 42 – 53.
Teva cited FDA’s recommendation for in vivo bioequivalence studies for Ferrlecit (sodium ferric gluconate injection)\(^{122}\) and results of Dynamic Light Scattering (DLS) and Atomic Force Microscopy (AFM) evaluations of glatiramer acetate and a summary of results of ultracentrifugation/ reconstitution, cryogenic temperature transmission electron microscopy (Cryo-TEM), and zeta potential testing in support of these assertions.\(^{123}\)

2. **A Biowaiver Is Appropriate Because Glatiramer Acetate Injection Is a Solution**

As noted above, a biowaiver is appropriate for a glatiramer acetate injection that is a parenteral solution and qualitatively and quantitatively the same in terms of active and inactive ingredients as Copaxone because bioequivalence is considered self-evident under 21 CFR 320.22(b). The assertions made by Teva regarding Copaxone’s colloidal properties are not inconsistent with its characterization as a solution because solutions can have colloidal properties. For example, even if glatiramer acetate exists as nano-sized complexes of varying sizes in Copaxone (based on available dynamic light scattering (DLS), as asserted by Teva), this does not change the fundamental premise that glatiramer acetate is fully dissolved in aqueous solution and exists as a solution, like other typical parenteral solutions for which FDA has granted biowaivers.

Light scattering methods are typically used to characterize colloidal systems. The intensity of the scattered light \((I_s)\) increases exponentially to the sixth power with the size \((d_h)\) of the scattering center, regardless of whether the scattering centers are fully dissolved in true solutions or exist as phase disperse or undissolved species in colloidal dispersions. The scattering intensity of glatiramer acetate is consistent with a scattering center having a diameter on the order of 1 to 2 nm, however such scattering is simply a reflection of the size of the polymeric species (on the order of 5-9 KDa) that comprise glatiramer acetate, and does not separately suggest, as has been contended by Teva,\(^{124}\) dispersed or “undissolved” glatiramer acetate particles.

For example, oxytocin\(^{125}\) exhibits light scattering, and this property has been used to determine the particle size distribution, molecular weight and other physical characteristics. We note that oxytocin exhibits a scattering diameter > 1 nm, typical of a colloid.\(^{126}\) Similarly, hetastarch, a plasma volume expander, also scatters light and is considered a colloid.\(^{127, 128}\) Regardless of the

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\(^{122}\) Fourth Petition at 13.

\(^{123}\) Fourth Petition supra note 1 at 19 – 20; Sixth Petition at 45.

\(^{124}\) Sixth Petition at 8, 30-31.


\(^{126}\) Id.

There are several lines of evidence that demonstrate that, as long as glatiramer acetate injection is stored under Copaxone’s labeled storage conditions, glatiramer acetate is fully dissolved as in a true solution with no evidence of suspended glatiramer particles, such as would be contained in a colloidal dispersion.  

First, ultrafiltration studies reviewed by FDA in connection with review of the ANDA for glatiramer acetate injection that we are approving today show that glatiramer acetate has the same hydrodynamic diameter before and after ultrafiltration, which is consistent with the absence of undissolved glatiramer acetate particles.  This is in contrast to iron dextran, which contains suspended undissolved nanoparticulate iron particles and shows significant differences in hydrodynamic diameter following ultrafiltration due to the retention of the nanoparticulate iron dextran (which exists as a colloidal dispersion).  However, we note that, if glatiramer acetate injection is placed under stressed conditions outside approved Copaxone’s labeled storage conditions, it can form irreversible suspended high molecular weight particles that, like iron dextran, will be retained by ultrafiltration.  Conversely, evaluation of glatiramer acetate injection stored under Copaxone’s labeled storage conditions using multiple techniques to evaluate potential aggregates including analytical ultracentrifugation and asymmetric field flow fractionation do not show evidence of aggregates.  Therefore, provided glatiramer acetate injection is stored under Copaxone’s labeled storage conditions, it is fully dissolved as in a true solution.

Second, freezing point depression is a colligative property of solutions, where the freezing point depression is a function of the molar concentration of the solute.  By varying the concentration of glatiramer acetate between 0 milligrams (mg)/milliliter (mL) to 50 mg/mL, a linear relationship was observed between the glatiramer acetate concentration and freezing point depression.


129 Teva makes an analogous contention using zeta potential testing of Copaxone to demonstrate its colloidal properties.  (Sixth Petition at 45 (citing Bawa Declaration, Ex. 26)  Zeta potential testing is a measurement of electrokinetic potential over the surface of an object when exposed to a fluid and is often a key indicator of the stability of a colloidal system.  See, e.g., “IUPAC. Compendium of Chemical Terminology”, 2nd ed., compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997).  See also Derjaguin B; Landau L (1941) Theory of the stability of strongly charged lyophobic sols and of the adhesion of strongly charged particles in solutions of electrolytes, Acta Physico Chemica URSS 14, 633 and W. B. Russel, D. A. Saville, W. R. Schowalter (1989)  Colloidal Dispersions, Cambridge University Press, UK.  Teva’s assertions on this point do not impact FDA’s assessment of glatiramer acetate injection being a solution eligible for a biowaiver because, in a similar vein as described above with respect to the light scattering arguments, they are consistent with FDA’s determination.

130 Teva makes certain assertions that Copaxone would be more properly classified as a suspension rather than a solution.  (See, e.g., Sixth Petition at 45-46).  For the reasons described below, we disagree.

131 This observation was based on our review of information submitted in connection with the ANDA for glatiramer acetate injection that we are approving today.
indicating that across these concentrations (including the concentration of 20 mg/mL concentration of the proposed generic glatiramer acetate injection), glatiramer acetate is completely dissolved in solution. Conversely, a non-linear relationship would indicate incomplete solubilization.

Therefore, the above results demonstrate that, provided glatiramer acetate injection is stored under Copaxone’s labeled storage conditions, it is fully dissolved as in a true solution and does not show evidence of suspended or aggregated glatiramer acetate particles present as a colloid. As glatiramer acetate injection is a true solution, even if it has light scattering properties, like any other parenteral solution that is qualitatively and quantitatively the same in terms of active and inactive ingredients, it is eligible for a biowaiver, contrary to Teva’s assertions.132, 133

3. Ferrlecit (sodium ferric gluconate injection) Is Distinguishable From Glatiramer Acetate Injection

Ferrlecit is similar in many respects to iron dextran, as previously discussed, as it contains undissolved suspended nanoparticulate iron particles and, as such, exists as a colloidal dispersion and is not a true solution, unlike Copaxone. Therefore any parallels that Teva attempts to draw between Ferrlecit and glatiramer acetate injection are not applicable.

4. Pharmacokinetic, Pharmacodynamic, or Other Comparative Bioequivalence Studies Not Required

Among Teva’s assertions in its Citizen Petitions are arguments connected to Copaxone’s unknown mechanisms of action, suggesting potential local, injection site activity of the drug, and a lack of correlation between pharmacokinetics and drug efficacy.134 Teva also contends that pharmacodynamic parameters such as the development of anti-glatiramer acetate antibodies or

132 E.g., Fourth Petition at 12, Sixth Petition at 45-47. In Sixth Petition at 45, Teva claims “Copaxone constituents can be separated into layers by ultracentrifugation and then easily reconstituted, indicating that Copaxone is a lyophilic colloidal suspension . . . “ We disagree with this claim. Based upon our analysis of the data provided by Teva in the petition, we believe this change was induced by the strong centrifugal force and prolonged treatment time (530,000g over 24 hours), and the resulting association complexes in the segregated layer do not exist in the untreated sample. Therefore, Teva’s ultracentrifugation data do not support its claim that Copaxone is a lyophilic colloidal suspension. On the other hand, the fact that the reconstituted solution after ultracentrifugation resembles the physical characteristics of the solution before the treatment suggests that glatiramer acetate injection is thermodynamically stable as a true solution.

133 Teva contends that even if a glatiramer acetate injection is a solution eligible for a biowaiver, FDA should still require in vivo bioequivalence studies under 21 CFR 320.22(f). (See Fourth Petition at 13; Sixth Petition at 46-48.) Where a proposed generic glatiramer acetate injection is qualitatively and quantitatively the same in terms of active and inactive ingredients as Copaxone, we do not expect to find “good cause” to require evidence of in vivo bioequivalence, nor do we expect to find “any difference between the drug product and the listed drug [that] may affect the . . . bioequivalence of the drug product.” 21 CFR 320.22(f). As discussed above, the criteria set forth in this response for active ingredient sameness ensure that a proposed generic glatiramer acetate injection falls within the range of Copaxone’s batch-to-batch variability.

134 E.g., First Petition, at 7, 8, 25, 29-30; Third Petition at 5; Fourth Petition at 4, 9, 13-14, 15, 16-17; Sixth Petition at 49. Similar arguments are made in the Peptimmune Citizen Petition, at 3, 10, 27.
the stimulation of peripheral blood lymphocytes have not been validated to serve as markers of bioavailability and bioequivalence. Finally, Teva asserts that clinical endpoint studies would be required to establish bioequivalence. However, as noted above, glatiramer acetate injection is a parenteral solution and, if the criteria set forth in 21 CFR 320.22(b) are satisfied, a waiver of in vivo bioequivalence studies would be appropriate and would obviate the need for pharmacokinetic studies, pharmacodynamic studies, or other clinical endpoint studies because bioequivalence would be self-evident. If an ANDA meets the standards for a biowaiver, the Agency concludes that such a showing will be adequate to demonstrate bioequivalence between a generic glatiramer acetate injection and Copaxone.

C. Immunogenicity

In its citizen petitions, Teva asserts that FDA should require comparative clinical testing to show that the immunogenicity risks associated with any proposed generic product - including risks associated with switching from Copaxone to a generic product - are no greater than those associated with Copaxone. Teva has postulated a number of such risks, including immune-complex formation, hypersensitivity, additional autoimmune disorders, general immune suppression, immunotoxicity, and eosinophilia.

As discussed elsewhere in this response, Copaxone has an array of peptide copolymers that can activate the immune system and stimulate an immune response. We agree that a generic glatiramer acetate injection must not elicit a different immune response from Copaxone. Therefore, it is important that an ANDA applicant demonstrate that its generic glatiramer acetate product has the same active ingredient as Copaxone. The criteria listed previously – equivalence of fundamental reaction scheme, physicochemical properties, structural signatures for polymerization and depolymerization, and results in biological assay with respect to Copaxone –

135 E.g., First Petition at 8, 30-31 Second Petition at 17; Third Petition at 20, 21, 22; Fourth Petition at 10, 17-18; Sixth Petition at 50, 51, 52. Similar arguments are made in the Peptimmune Citizen Petition, at 28.

136 E.g., Fourth Petition at 19-23; Sixth Petition at 51, 52. Teva attempts to analogize glatiramer acetate injection to two drug products, sucralfate tablets and rifaximin tablets, for which FDA recommended clinical trials to demonstrate bioequivalence. See ANDA No. 70-848, Response to Consultation re: Biocraft Submission of April 27, 1988 (May 2, 1988) (Fourth Petition Ex. 19), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/070848.PDF, at 179-80. We note that these examples are inapplicable in this instance because, among other factors, these drugs products are oral tablets acting in the gut, rather than qualitatively and quantitatively equivalent parenteral solutions, like glatiramer acetate injection, for which in vivo bioequivalence may be considered self-evident if the drug product meets the criteria set forth in 21 CFR 320.22(b)(1).

137 Sixth Petition, supra note 1 at 23, 37 – 40; Third Petition at 23 – 25; Fourth Petition at 25 – 32.

138 Third Petition at 23; Sixth Petition, supra note 1 at 10, 24 – 25; 37, 38, 39-40.

139 Several of Teva’s assertions relate to minor variations of sequence between generic glatiramer acetate and the active ingredient in the RLD that could have immunogenic consequences (e.g., Third Petition at 23, 24, 25; Fourth Petition at 24-25, 26, 29). For example, Teva asserts that sameness criteria based on “bulk physicochemical characteristics” could present “different antigenic epitopes arising from small changes in the product’s primary structure.” (Third Petition at 23.) We note, however, that these assertions conflict with the batch-to-batch variability, or molecular diversity, inherent in Copaxone itself discussed above.
will ensure that a generic glatiramer acetate injection has the same molecular diversity (and active ingredient) as Copaxone.

In addition to active ingredient sameness, we have previously considered whether impurities may affect the immunogenicity of drug products, including in the case of enoxaparin. In the case of generic glatiramer acetate injection, impurities including aggregates, leachates and process related impurities will be evaluated and their levels will also be rigorously controlled. Aggregation is usually a result of non-specific interactions between molecules to form high molecular weight species. Based on information from the literature, the propensity for aggregation in glatiramer acetate is quite low. Nonetheless, the formation of irreversible aggregates in glatiramer acetate is possible under highly stressed conditions, outside Copaxone’s labeled storage conditions. Thus, aggregates of the glatiramer acetate copolymer are considered potential impurities and are critical to control because they may have a profound effect upon the immunogenicity of the drug product and may produce antigenic responses. The levels of peptide copolymer aggregates will be assessed by using size exclusion chromatography in conjunction with orthogonal techniques such as analytical ultracentrifugation and field flow fractionation. Because the aggregates of glatiramer acetates are undesirable in the drug product due to safety concerns, ANDA applicants need to ensure that the amount of aggregation in the generic product will be no more than in the RLD under stability testing conditions.

Provided that active ingredient sameness and the other ANDA approval requirements are met, the generic product will be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in its labeling and thus can be substituted for the RLD. As noted above, the underlying premise of the ANDA approval requirements is that a generic drug product that meets the approval requirements can be substituted for the RLD with the full expectation that it will have the same clinical effect and safety profile. Accordingly, we expect that any glatiramer acetate injection that meets the requirements for ANDA approval will not be associated with greater immunogenicity risks than Copaxone.


144 The ANDA approval standards for glatiramer acetate injection that are set forth in this response, including those relating to active ingredient sameness and impurities, reflect extensive and careful consideration by the Agency. FDA has concluded that the clinical trials that Teva suggests are not necessary to establish active ingredient sameness or for any other purpose because, among other reasons, they are less sensitive than the four criteria at detecting differences between products. Teva’s analysis of results from the GATE clinical trial comparing Copaxone to a Synthon product (GTR) and placebo does not affect our conclusions about active ingredient sameness because the appropriate methodology for any such clinical trial is not relevant. See Nov. 13, 2014 Supplement to the Sixth Petition, at 12-14 & Appendix 2; Eighth Petition at 2, 4

D. Gene Expression

In its Sixth, Seventh, and Eighth Petitions, Teva compared the effects of Copaxone to the effects of other glatiramer acetate (or glatiramer acetate-like) injection products (none approved by FDA) on gene expression in mouse splenocytes or human monocytes. The gene expression data were used in an effort to compare the pharmacological effects of generic drug products and Copaxone. In the Sixth Petition, Teva reported the results of (1) a study analyzing gene expression in mouse splenocytes activated with Copaxone, the unapproved product TV-5010 (produced by Teva for research and not approved in any jurisdiction), or the foreign product Glatimer (Natco Pharma, India), and (2) a study analyzing gene expression in mouse splenocytes activated with a foreign product or active pharmaceutical ingredient (including: Escadra (Argentina), Probioglat (Mexico), and Hangzhou (China)). In the Seventh Petition, Teva provided a more thorough discussion of its mouse splenocyte study, and also reported the results of experiments in the human monocyte (THP-1) line comparing Copaxone with other glatiramer acetate or glatiramer acetate-like products, including Probioglat. In a supplement to the Seventh Petition, Teva provided an initial report of preliminary findings from gene expression studies in the THP-1 cell line conducted on Polimunol (Synthon, Argentina). In the Eighth Petition, Teva reported new data including the results of gene expression studies in mouse splenocytes and the THP-1 cell line conducted to compare Polimunol with Copaxone. Teva claims that these studies identified differences between Copaxone and the comparators that “warrant further studies.”

After careful consideration of Teva’s data submitted in its Sixth Petition, the Agency determined that the basic experimental design was not appropriate for product comparisons, and that the results generated from the study would be problematic if used as a basis for considering the active ingredient sameness of a generic product versus a RLD. Specifically, we concluded that the mouse splenocyte studies were poorly designed, contained a high level of residual batch bias, and used non-standard statistical criteria for assessing the presence of differentially expressed genes. When FDA reanalyzed the microarray data from one Teva study using industry

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146 Sixth Petition at 10.
147 Sixth Petition at 18.
148 Seventh Petition at 19-46.
149 Nov. 13, 2014 Supplement to Seventh Petition at 31-38.
150 Eighth Petition at 41-43.
151 Seventh Petition at 4; Eighth Petition at 5.
152 We note that regarding the use of these kinds of studies generally in connection with a determination of active ingredient sameness, the Agency determined that, based on current scientific understanding, microarray-derived gene expression data alone will be inconclusive, but could be used as part of the total evidence presented in support of an assertion, not as standalone evidence; provided that certain key requirements for assessing product quality, data quality and biological relevance can be identified as critical to ensuring that microarray data are reliably collected, analyzed and interpreted. We also conclude that while gene expression data could be used as supportive evidence of an active ingredient sameness determination, it is not necessary in this instance because the active ingredient sameness criteria described above are sufficient in that the criteria are robust and provide overlapping and confirmatory evidence of active ingredient sameness.
standard practices and criteria, Copaxone and the comparator (Natco) product were found to have very similar effects on the efficacy-related pathways proposed for glatiramer acetate’s mechanism of action.

FDA identified similar methodological flaws in Teva’s gene expression data submitted in its Seventh Petition. Because that petition reported on the same mouse splenocyte studies that FDA had evaluated and found deficient in connection with the Sixth Petition, FDA concluded that any arguments concerning differences between Copaxone and comparator products based on the Teva’s analysis of the mouse splenocyte data could not be supported. With respect to Teva’s gene expression study in “human monocytes,” FDA found that it was not conducted with normal or patient human monocytes but rather with a transformed human cell line, THP-1. Although the THP-1 cell line is a widely used research model that retains a subset of characteristics of primary human monocytes, FDA concluded that Teva had not adequately justified how its gene expression studies alone in this cell line can be considered to adequately report on the complex therapeutic effect of glatiramer acetate in MS patients. In particular, Teva provided no evidence showing that the responses of THP-1 cells represented the response expected in normal human monocytes or that this experimental model reliably reproduced known therapeutic responses to glatiramer acetate. For example, the data in the Seventh Petition report that the maximal gene array response of THP-1 cells to glatiramer acetate was observed at 6 hours and was nearly absent at 24 hours. This contrasts significantly with the data from a published study with peripheral blood mononuclear cells (PBMC) from MS patients which showed the maximal response was not seen until 24 hours. FDA concluded that the Teva study designs and gene expression data were sufficiently flawed such that it is impossible to make any determinations about therapeutic mechanisms of action of glatiramer acetate in MS patients and their genetic components, and that Teva’s methods and data did not convincingly demonstrate any differences in gene expression among Copaxone and other glatiramer acetate or glatiramer acetate-like products.

The November 13, 2014 Supplement to the Seventh Petition also described a study described using the human acute monocytic leukemia cell line THP-1, which FDA had concluded was not a validated system and could not be interpreted as having any predictive value for human clinical responses. Moreover, in analyzing that study, Teva used non-standard statistical criteria for assessing the presence of differentially expressed genes. FDA concluded that the study design described in the Eighth Petition overstated treatment differences by artificially minimizing biological variability, and that Teva had reported the data in a way that maximized small effects between treatments that may not be clinically significant. FDA further determined that the THP-1 studies reported in the Eighth Petition suffer from the same fatal design flaws as the experiments reported in the Seventh Petition and the November 13, 2014 Supplement to the Seventh Petition.

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After reviewing all of the gene array experiments and resulting data submitted by Teva, FDA concluded that they did not provide useful information relevant to the issue of the approvability of an ANDA referencing Copaxone.

VI. CONCLUSION

For the reasons stated above, we conclude that a showing of equivalence between the ANDA product and the RLD as to the following criteria is sufficient to demonstrate sameness of the glatiramer acetate active ingredient:

1. Fundamental reaction scheme;
2. Physicochemical properties including composition;
3. Structural signatures for polymerization and depolymerization; and
4. Results in a biological assay.

A demonstration that these criteria are satisfied will ensure that the molecular identity and diversity of glatiramer acetate is equivalent to that of the active ingredient in Copaxone and will establish active ingredient sameness between a generic glatiramer acetate and Copaxone. For this reason, and for the reasons discussed above, we conclude that it is not necessary for an ANDA applicant seeking approval of a generic glatiramer acetate injection to submit the information that you request.

Sincerely,

[Signature]

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