TEVA CNS

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VIA HAND DELIVERY

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

Re: Citizen Petition Requesting That FDA Refrain From Approving Any Abbreviated New Drug Application Referencing Copaxone® (glatiramer acetate injection) Until Certain Conditions Are Met

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva") hereby submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 and sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 355(j) and 355(q).[1] For the reasons that follow, Teva respectfully requests that the Commissioner of Food and Drugs refrain from approving any abbreviated new drug application ("ANDA") that references Copaxone® (glatiramer acetate injection) unless and until the conditions specified in this Petition are satisfied.

I. Actions Requested

Teva manufactures and distributes Copaxone®, a treatment for the reduction of frequency of relapses in relapsing-remitting multiple sclerosis ("RRMS"). The unique characteristics of both RRMS and Copaxone® have been thoroughly discussed in Teva's prior Citizen Petitions[2]

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

[2] The four prior Citizen Petitions were submitted in 2008, 2009, 2010, and 2012, respectively, and are incorporated herein by reference. *See* FDA-2008-P-0529 (Sept. 26, 2008) (Exhibit 1); FDA-2009-P-0555 (Nov. 13, 2009) (Exhibit 2); FDA-2010-P-0642 (Dec. 10, 2010) (Exhibit 3); FDA-2012-P-0555 (June 4, 2012) (Exhibit 4). Teva also incorporates by reference any exhibits to those petitions although, for efficiency's sake, such exhibits are not being re-submitted because they are either FDA documents that are routinely available to the public (e.g., approved

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Teva Pharmaceuticals
901 E. 104th Street, Suite 900 | Kansas City, MO 64131 | Tel. 816.508.5000 | www.tevapharm-na.com

and will not be repeated here. Instead, the purpose of this Petition is to provide supplementary scientific information and data confirming Copaxone®'s colloidal nature and the complexity of the glatiramer acetate active ingredient to support the requests made by Teva in those prior Petitions regarding active ingredient sameness, bioequivalence standards and immunogenicity testing.[3]

In particular, Teva argued in those Petitions that because of Copaxone®'s complexity and the limitations of current analytical technologies, it is not possible to definitively characterize the composition or structure of each of the drug's protein-like polypeptides, or to identify the amino acid sequences associated with drug efficacy. Consequently, it currently is not possible for the sponsor of an ANDA to demonstrate that its proposed generic product has the "same active ingredient" as Copaxone®, as required by the FFDCA. Although the Food and Drug Administration ("FDA" or "the Agency") has allowed some ANDA applications for other complex drug products, such as oligosaccharides, to rely upon "overlapping" criteria of sameness to satisfy the statutory "same active ingredient" requirement. Teva explained in its third Petition that this approach cannot be applied to Copaxone®, which has a complexity equal to or greater than many proteins.

Teva also explained that even if FDA were to rely upon "overlapping" criteria to determine that a proposed generic product has the "same" active ingredient as Copaxone®, approval of an ANDA would be impermissible in the absence of data from *in vivo* studies demonstrating that the proposed generic product is bioequivalent to Copaxone®. Teva argued that a waiver of *in vivo* bioequivalence testing is not appropriate because (1) Copaxone® is a colloidal suspension, and (2) even if Copaxone® were a "true" solution, the inevitable structural and compositional differences in any generic product's active ingredient could affect the bioequivalence of the proposed generic product, thereby potentially resulting in decreased efficacy, increased toxicity, or both. 21 C.F.R. §§ 320.22(b)(1), (f). Because pharmacokinetic and pharmacodynamic testing methods are infeasible for glatiramer acetate, Teva asked FDA to require that bioequivalence be demonstrated via a well-controlled, comparative trial with clinical endpoints, which is the most sensitive, accurate, and reproducible method for determining bioequivalence under FDA's regulations. 21 C.F.R. § 320.24(b)(4).

Finally, Teva requested that FDA require ANDA applicants to conduct non-clinical and clinical immunogenicity studies demonstrating that the risk of an untoward immune response is not greater for a proposed generic product than for Copaxone®, including an assessment of immunologic safety when the products are switched. Teva pointed out that because Copaxone® is an immunomodulator, a purported generic product could have significant and unpredictable differences from Copaxone® in its immunological mechanisms, raising major safety and efficacy concerns.

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labeling, guidance documents and petition responses) or recognized medical or scientific textbooks or articles that are readily available to the agency. *See* 21 C.F.R. § 10.20(c)(1)(iii), (iv).

[3] Because this submission contains new scientific information, Teva is required to file it as a new Citizen Petition rather than as a Petition for Reconsideration. *See* 21 C.F.R. § 10.33(e).

In its responses to Teva's prior petitions, FDA has taken the position that it would be "premature and inappropriate" to provide a substantive decision on the approval requirements for ANDAs for glatiramer acetate while FDA is still reviewing pending ANDAs.[4] Nevertheless, in its most recent response issued on November 30, 2012, the Agency questioned whether the available scientific evidence, including data from dynamic light scattering ("DLS") and atomic force microscopic ("AFM") methods,[5] demonstrates that Copaxone® is a colloidal suspension.[6]

As part of its ongoing commitment to better characterize Copaxone®, Teva continues to evaluate the physiochemical and biological properties of Copaxone® using state-of-the-art technology. In order to address FDA's questions and substantiate that Copaxone® is, in fact, a colloidal suspension, Teva is submitting the results of additional, recent tests evaluating the physiochemical properties of Copaxone® using several sophisticated analytical techniques. These tests, which include traditional colloidal assessment experiments such as ultracentrifugation, particle size and zeta potential, not only shed further light on the extreme complexity of the glatiramer acetate active ingredient, but also conclusively demonstrate that Copaxone® is a lyophilic, stable colloidal suspension rather than a true solution.

Based upon this additional scientific information and data, as well as the information and arguments in its prior petitions (which are incorporated herein by reference), Teva respectfully requests that the Commissioner refrain from approving any ANDA that relies upon Copaxone® as the reference listed drug ("RLD") unless and until the ANDA contains:

1. Information demonstrating that the proposed generic product contains the "same" active ingredient as Copaxone® using one of the two standards identified in Teva's prior petitions;[7]

2. Results of comparative clinical investigations in RRMS patients using relevant safety and effectiveness endpoints demonstrating that the proposed generic drug is bioequivalent to Copaxone®; and

3. Results of non-clinical and clinical investigations 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

[4] *See, e.g.*, FDA's Response to First Copaxone Petition, FDA-2008-P-0529 (March 25, 2008); FDA's Response to Fourth Copaxone Petition, FDA-2012-P-0555 (Nov. 30, 2012) (Exhibit 5).

[5] Teva previously submitted the results of DLS and AFM testing of Copaxone® to FDA in a letter dated May 31, 2012.

[6] FDA's Response to Fourth Copaxone Petition, FDA-2012-P-0555, at 9 (Nov. 30, 2012) (Exhibit 5).

[7] The two proposed sameness standards are set forth in Teva's third petition (Docket No. FDA-2010-P-0642) as well as in section II.B herein.

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.

II. Statement of Grounds

A. The Results of Traditional Colloidal Assessment Experiments Demonstrate That Copaxone® Is a Stable, Lyophilic Colloidal Suspension

Copaxone® is a first-generation nanomedicine produced using well-established solution polymerization techniques.[8] The nanoscale size of glatiramer acetate molecules are an intrinsic process-related property associated with its chemical nature. The consistent manufacturing process employed by Teva creates a mixture of glatiramer acetate polypeptides with average molecular weights ("MW") ranging from 5000-9000 Daltons (the MW distribution of the glatiramer acetate components spans a range of 2,500 – 20,000 Daltons).[9] The polypeptides in glatiramer acetate appear to range from approximately 20 to 200 amino acids in length, with an average polypeptide length of about 60 amino acids.[10] If one assumes that an average molecule of 7000 Daltons contains 60 amino acids, the theoretical length of glatiramer acetate molecules ranges from 3 to 30 nanometers (nm). However, as described further below, the molecules and molecular associations in glatiramer acetate appear to range from 1.5 nm to 550 nm.

The FDA has defined the term "colloid" for regulatory purposes as "a chemical system composed of a continuous medium (continuous phase) throughout which are distributed small particles, 1 to 1000 nanometers in size (disperse phase), that do not settle out under the influence of gravity; the particles may be in emulsion or in suspension."[11] While this definition, which appears to be derived from *Dorland's Medical Dictionary for Health Care Consumers*,[12] is generally considered accurate, a more precise scientific definition is as follows:

> A colloid, or disperse phase, is a dispersion of small particles of one material in another. In this context, 'small' means something less than about 500 nm in diameter (about the wavelength of visible light). In general, colloidal particles are aggregates of

[8] Duncan R, Gaspar R. Nanomedicine(s) under the microscope. *Mol Pharm* 2011;8(6):2101-41 (Exhibit 6).

[9] Varkony et al, The glatiramoid class of immunomodulator drugs. Expert Opinion Pharmacother (2009); 10:657-68 (Exhibit 7).

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

[11] Letter to David Zuchero, M.S., J.D., *et al.*, FDA-2004-P-0494, p. 4, n. 13 (March 31, 2011) (Exhibit 9).

[12] The definition of "colloid" from the 2007 version of *Dorland's Medical Dictionary for Health Care Consumers* is available online from The Free Dictionary at http://medical-dictionary.thefreedictionary.com/colloid.

> numerous atoms or molecules, but are too small to be seen with an ordinary optical microscope. They pass through most filter papers, but can be detected by lightscattering and sedimentation.[13]

Moreover, in its response to Teva's most recent Petition, FDA stated that one of the defining characteristics of colloidal suspensions is "thermodynamic stability."[14] Although Teva agrees that colloidal suspensions must be stable in the sense that the particles in the disperse phase "do not settle out under the influence of gravity," *thermodynamic* stability is not required to achieve this physical state of equilibrium.[15] Many stable colloidal systems are *kinetically* stable, while not necessarily exhibiting a negative potential energy state that is indicative of thermodynamic stability. Indeed, when scientists describe a colloidal system as "stable," they generally are referring to kinetic stability, not thermodynamic stability. In other words, the term "stability" with respect to colloids generally describes the extent to which the colloidal particles remain uniformly distributed throughout the system without flocculating under normal gravitational forces. *See* Declaration of Raj Bawa, M.S., Ph.D. ¶ 15 ("Bawa Decl.") (Exhibit 12).

Regardless of the definition applied, Copaxone® unquestionably is a colloidal suspension. Bawa Decl. ¶¶ 13, 20, 21, 35 (Exhibit 12). Glatiramer acetate nanoparticles are within the typical colloidal size range of 1 to 1000 nanometers (1μm) (denoted as radius (r) in Stoke's law) and are uniformly suspended in a continuous medium (mannitol solution). The mannitol solution is a "true" solution, i.e, it is a homogenous solution in which the ratio of solute to solvent remains constant and in which all of the solute particles have diameters less than 10^{-7} centimeters (<10 nm), and the mannitol in solution cannot be centrifuged or filtered from the solution. As such, the aqueous mannitol solution constitutes a continuous medium. The glatiramer acetate nanoparticles dispersed in the mannitol solution do not precipitate under the influence of normal gravitational forces, even when stored at 2°-8°C for up to 2 years;[16] thus, Copaxone® is stable under these conditions.

The results of traditional colloidal assessments capable of distinguishing compositional features of Copaxone® at the molecular level further confirm the colloidal nature of

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[13] Peter Atkins and Julio de Paula. *Physical Chemistry, 8th Ed. W. H. Freeman and Company, New York, 682,* March 10, 2006 (Exhibit 10).

[14] FDA's Response to Fourth Copaxone Petition, FDA-2012-P-0555 (Nov. 30, 2012) (Exhibit 5).

[15] The premise that thermodynamic stability is a characteristic property of all colloidal suspensions appears to have arisen from a misinterpretation by the Agency of an article by Yang et al. (*J Pharm. Sci* 2010; 99(1):142-53) (Exhibit 11) which was cited by the Agency in its response to Teva's most recent petition. *See* FDA's Response to Fourth Copaxone Petition, FDA-2012-P-0555, at 10 (Nov. 30, 2012) (Exhibit 5). The authors of this paper were trying to provide evidence that colloidal sodium ferric gluconate exhibits properties of a colloid which are consistent with those of a thermodynamically stable colloid. The author's own conclusions support this assessment: "In conclusion, sodium ferric gluconate was found to be a lyophilic colloid that ***might*** be thermodynamically stable."[emphasis added] Nowhere in this article do the authors claim nor imply that thermodynamic stability is a characteristic of ***all*** colloidal suspensions.

[16] Data on file.

Copaxone®.[17] These experiments, which included ultracentrifugation, DLS, AFM, cryogenic temperature transmission electron microscopy, and zeta potential testing, demonstrate the following:

- Copaxone® is composed of two, distinct populations of polypeptides, both of which are within the size range for colloids (i.e., 1 to 1000 nanometers);
- The glatiramer acetate polypeptides are stable and distributed uniformly throughout the aqueous mannitol medium;
- Copaxone® constituents can be separated into layers by ultracentrifugation and then easily reconstituted, indicating that Copaxone® is a lyophilic colloidal suspension in which the dispersed particles are well-solvated and stabilized rather than a true solution in which the dispersed particles are dissolved; and
- Copaxone® has a high zeta potential, suggesting that it is highly stable and resists flocculation and settling under normal gravitational forces.

The results of this testing are discussed in more detail below.

1. Separation by Ultracentrifugation and Resuspension

Stable colloids do not "settle out under the influence of" normal gravitational forces. However, they will potentially exhibit separation of the disperse phase under increased gravitational forces, such as ultracentrifugation.[18] The stability of colloidal suspensions is characterized by, among other things, Stoke's law ($dx/dt = 2r^2(d_c - d_p)g / 9h$). By increasing gravity (g) through ultracentrifugation for suspensions where ($d_c - d_p$) is negative, dx/dt can be increased sufficiently to separate the suspended particles in the stable colloidal suspension.

To show that Copaxone® is not a "true" solution, a Copaxone® sample was ultracentrifuged for 24 hours at 4°C under 530,000g ("treated sample"). The sample was segregated into a concentrated layer of higher MW polypeptide moieties (a whitish, dispersed phase in the lower layer of the centrifuged sample) and a layer of lower MW polypeptide moieties (a more translucent upper layer). The upper and the lower layers of the treated sample were tested for glatiramer acetate concentrations, which were measured using size exclusion chromatography and compared with the untreated Copaxone® sample (**Figure 1**). The concentration of glatiramer acetate in the upper layer of the treated sample was about $1/10^{th}$ of the concentration in the lower layer.

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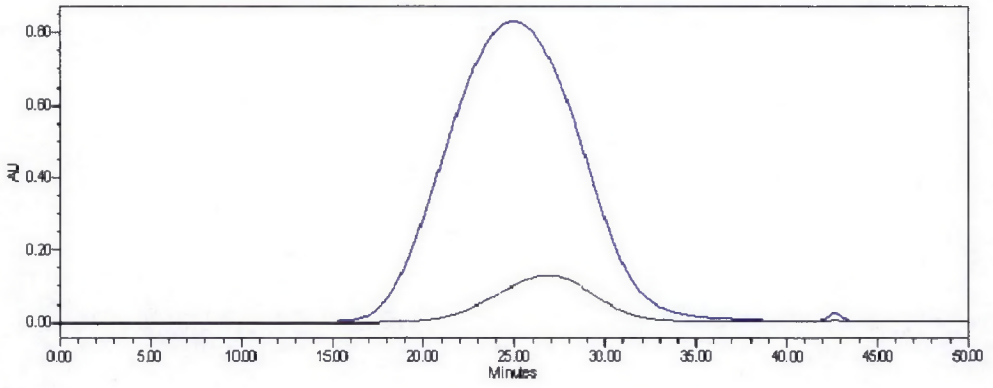
[17] Yang Y, Shah RB, Faustino PJ, Raw A, Yu LX, Khan MA.. Thermodynamic stability assessment of a colloidal iron drug product: sodium ferric gluconate. *J Pharm. Sci* 2010; 99(1):142-53 (Exhibit 11).

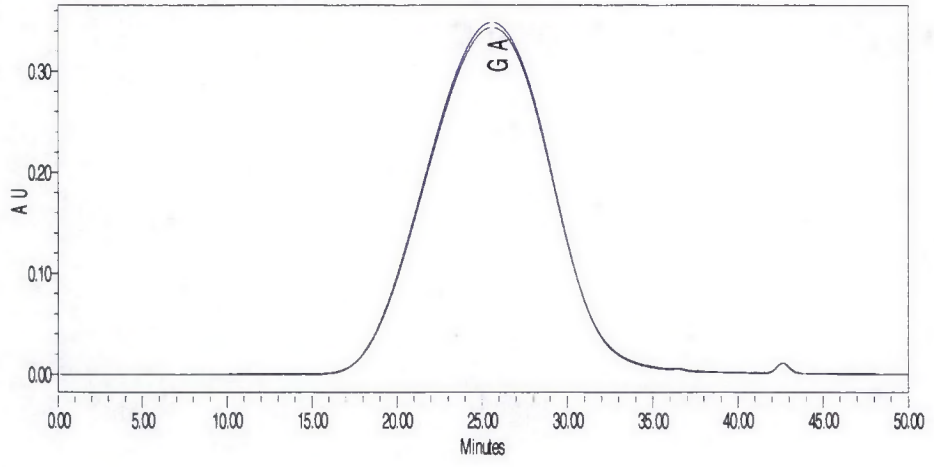
[18] Yang et al. (*J Pharm. Sci* 2010; 99(1):142-53) (Exhibit 11) demonstrated this very phenomenon in the case of Ferrlecit, where ultracentrifugation of sodium ferric gluconate samples for 18h at 385,000g under 4 °C resulted in the formation of "two clearly distinguishable layers, the top dispersion medium phase with a light color and the bottom dispersive phase with dark color."

Figure 1: Size Exclusion Chromatography – relative concentrations and molecular weight distribution profiles of the the upper (blue), and lower (black) layers of the Copaxone® sample after ultracentrifugation.



The treated sample layers were then re-mixed by vortexing, and the concentration of glatiramer acetate in the reconstituted suspension was measured again. The concentration of the reconstituted sample was 20.0 mg/mL, equivalent to that of the original untreated sample (**Figure 2**).

Figure 2: Size Exclusion Chomatography overlaid profiles of the untreated (black) and reconstituted (blue) Copaxone® samples



This testing demonstrates that Copaxone® constituents can be concentrated under strong centrifugal force, and the resulting concentrate can be easily reconstituted to its original composition. In other words, Copaxone® can be reversibly re-suspended, a property expected only for a colloidal suspension, not a true solution. Bawa Decl. ¶ 23 (Exhibit 12). Hence, this

experiment clearly shows that the suspended particles in Copaxone® are solvated and that, as in the case of Ferrlecit®, the "colloidal system might be thermodynamically stable and reversible."[19]

2. Dynamic Light Scattering (DLS)

DLS determines particle sizes in solution by measuring their diffusion rate (Brownian motion). Small molecules diffuse more quickly than large molecules. Molecules of different sizes scatter light at different intensities. DLS measures intensity as a function of particle sizes; however, it is important to note that DLS results are qualitative and not quantitative. The capacity of a large molecule to scatter light is significantly higher than that of a small molecule; therefore, a single large molecule can scatter light more intensely than a large population of small particles. Thus, the results of DLS should be evaluated accordingly: the area under the peak does not correlate with the number of particles (population size) represented by that peak.

Scientists at Teva developed and optimized operational DLS conditions for the glatiramoid class[20] of compounds. Measurements were sensitive to particle sizes in the nm range (1 – 1000 nm). Assay consistency was demonstrated by the reproducibility of results of multiple measurements on many different Copaxone® batches manufactured at varying time periods. DLS measurements were performed on Copaxone® diluted with a 20mM NaCl solution and filtered through a 1.2μm disc filter prior to analysis, and on samples obtained by ultracentrifugation at different G-forces (the upper layers and the constituents concentrated at the bottom).

DLS analysis shows that the untreated Copaxone® mixture consists of two main polypeptide populations. The first population is characterized by a distribution of particle sizes in the range of 1.5 to 15 nm, with the most abundant size of approximately 5.6 nm. The second population contains particles in the range of 20 to 550 nm, with the most abundant size of approximately 111 nm (**Figure 3**).[21] The first population likely represents "mono-particles," or separated molecules, which comprise the most abundant fraction; whereas the second population can be attributed to larger entities (e.g., labile intermolecular associates) that may be formed by interactions between amino acid sequences on the polypeptide chains.

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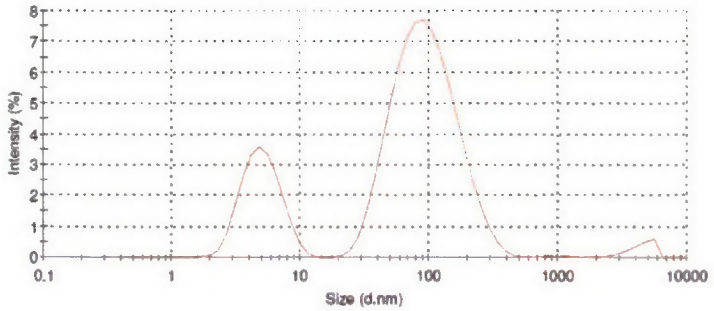
[19] Yang et al. (*J Pharm. Sci* 2010; 99(1):149) (Exhibit 11); *see also* G. S. Zografi, H. Swarbrick, Disperse Systems; In: Remington's Pharmaceutical Sciences. (18th Edition) Mack Publishing Co, Easton 1990 (Exhibit 13).

[20] Synthetic copolymer mixtures comprising the four amino acids, L-glutamic acid, L-alanine, L-lysine, and L-tyrosine, in a defined molar ratio.

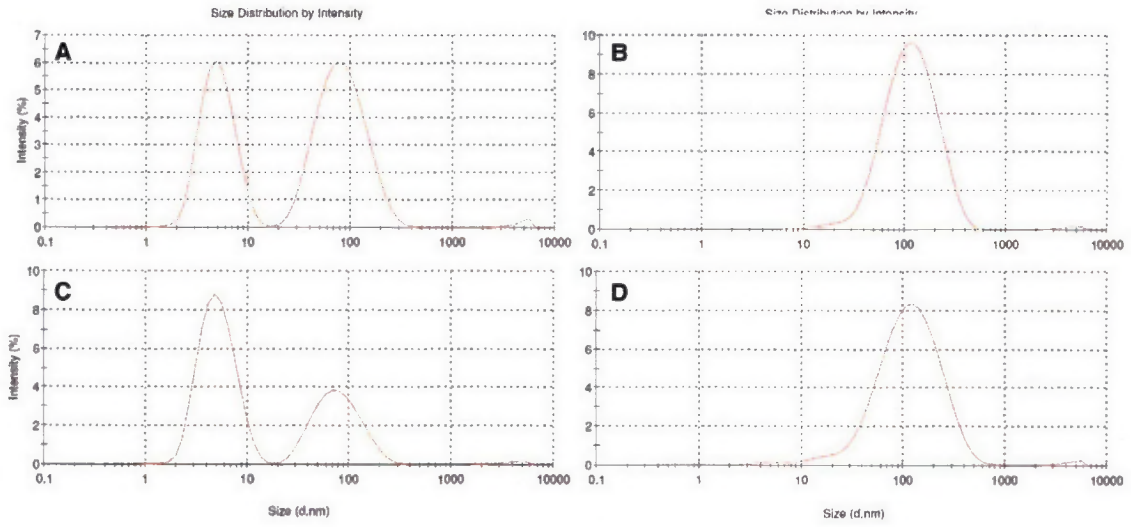
[21] Teva previously submitted the results of DLS testing of Copaxone® to FDA in a letter dated May 31, 2012.

Figure 3. A typical (untreated) Copaxone® DLS scan



The dispersed Copaxone® solution was exposed to ultracentrifugation at different G-forces. As mentioned above, ultracentrifugation resulted in a clear upper layer and a viscous whitish fraction. The upper layer and the material concentrated at the bottom were then tested by DLS (after reconstitution in water). At 290,000g, the upper layer still contained both "light" and "heavy" peaks (**Figure 4A**), whereas the lower fraction contained the "heavy" peak only (**Figure 4B**), Ultracentrifugation at higher G-force (650,000g) resulted in a more effective concentration of the heavy peak (**Figures 4C and 4D**).

Figure 4 – DLS results of the Copaxone® sample after ultracentrifugation at different G-forces. The Copaxone® sample was subjected to ultracentrifugation at the conditions described in panels A-D. **A)** Upper layer after 2-hour ultracentrifugation at 290,000g: two populations are observed; the relative amount of smaller particles is increased compared with non-treated Copaxone®. **B)** Bottom fraction after 2-hour ultracentrifugation at 290,000g re-suspended in water: only the larger size components are observed. **C)** Upper layer after 2-hour ultracentrifugation at 650,000g: the relative amount of larger particles is even more reduced due to further separation under higher G-force. **D)** Bottom fraction after 2-hour ultracentrifugation at 650,000g re-suspended in water: only the higher size constituents are observed.



Thus, after ultracentrifugation, there was a change in the profile of the suspended glatiramer acetate nanoparticles with regard to their size distribution, i.e., the larger molecularly associated nanoparticles were found at the bottom of the centrifuge tube, whereas the smaller nanoparticle associates remained in the upper layer. The extent of concentration of the larger associates at the bottom was proportional to the applied G-force value. This separation would not have been observed if Copaxone® was a true, homogenous solution. Bawa Decl. ¶ 26 (Exh. 12).

In summary, the Copaxone® suspension was successfully separated into several populations of constituents according to their sizes, as determined by analyzing the sedimented moieties and the supernatant solution by DLS.

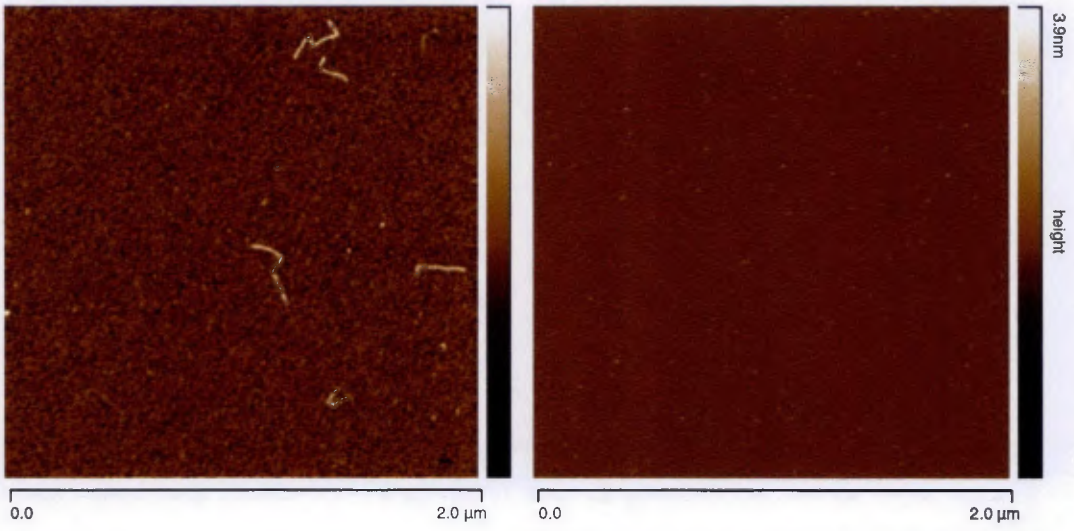
It is noteworthy that the re-suspension in water of the larger molecularly associated nanoparticles from the material obtained at the bottom of the tube resulted in the observation of only the larger particles in suspension. This indicates that the larger particles are labile intermolecular associates of several nano-sized "mono"-molecules arranged in a thermodynamically preferable disposition and thus are relatively stable. The observation of the two distinct populations of particles in the original analysis further supports this conclusion. If the suspension were merely a mix of agglomerates, one would have expected a continuum of particle size distribution over the range. The appearance of two distinct populations of particles shows that Copaxone® is a colloidal system that is more complex than a mere suspension of agglomerated particles and is actually comprised of a unique micro-structure of two particulate populations. In other words, this DLS testing demonstrates that Copaxone® is comprised of thermodynamically stable, nano-sized association complexes. Bawa Decl. ¶ 26 (Exhibit 12).

3. Atomic Force Microscopy (AFM)

AFM is a type of scanning tunneling microscopy. AFM produces images of the surface ultrastructure of a substance with molecular resolution under physiological conditions. The samples are dried with nitrogen prior to scanning. The resolution of this technique varies from about 0.1 nm to the sub-micron range. In an AFM experiment, the size (length, width, and height) of individual particles can be measured and the results can be visualized in three dimensions.

A typical topographic image of a Copaxone® dried sample is shown in **Figure 5**. A Copaxone® aliquot from a syringe and a placebo sample from an identical syringe were dried with nitrogen on a flat support, and then scanned to produce the surface ultrastructure with molecular resolution. AFM analysis of Copaxone® samples revealed dispersed "dot-like" and "string-like" components. In the placebo syringes, no such entities were apparent, indicating that the particles observed in the Copaxone® samples did not originate from mannitol or from any part of the syringes (i.e., they are characteristic of glatiramer acetate).

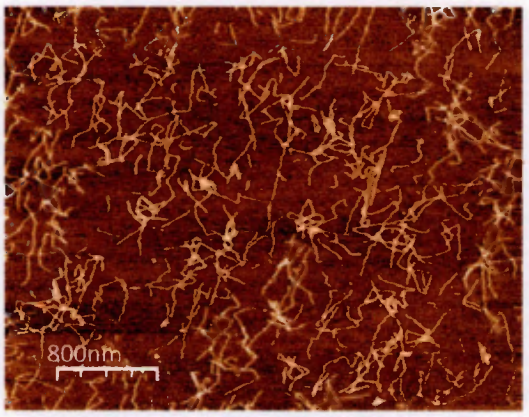
Figure 5. Typical topographic image of Copaxone® and placebo bulk solutions. AFM analysis of Copaxone® samples (left) from a bulk solution in a syringe revealed dispersed "dots" and "strings" particles. In the placebo syringes (right), no such entities were visible, indicating that the particles observed in the Copaxone® samples (left) did not originate from mannitol or from any part of the syringes (they are characteristic of glatiramer acetate).



The DLS study above indicated that the population of larger sized particles under the peak on the right (Figure 3) (about 110 nm average size distribution) can be concentrated at the bottom of a tube by ultracentrifugation. In order to characterize the strings detected by the AFM technique in the Copaxone® sample and to investigate correlations between the results of the DLS scans and the AFM images, samples of Copaxone® were ultracentrifuged under the same conditions described in the DLS study above and the bottom fractions were collected, diluted with water, dried with nitrogen and analyzed.

AFM results for those fractions from a Copaxone® batch are shown in **Figure 6**. The concentrated "heavy" material appeared to contain the same string-like entities seen in the un-centrifuged Copaxone® samples (**Figure 5,** left), although, as expected, at a higher concentration. No round shaped particles were detected in the lower layer. By contrast, analysis of the upper layer revealed none of the string-like particles present in the lower fraction, which correlates with the data obtained by DLS testing indicating two subpopulations of particles with different average sizes, and supports the assumption that the strings are the larger sized particles in the Copaxone® sample.

Figure 6. Topographic image for "heavy" fraction from Copaxone®, separated by ultracentrifugation. Results shown in this figure complement results of the DLS study, in that AFM established that the heavier population of Copaxone® polypeptides consists of string-like entities of variable sizes.



Together, DLS and AFM confirm the colloidal characteristics of Copaxone®, which maintains a homogenous appearance throughout its 2 year shelf life (i.e., contains polypeptide particles of different sizes that do not precipitate under gravity) but can be separated into subpopulations under ultracentrifugation. Both methods also demonstrate the presence of stable polypeptide particles within the colloidal size distribution range (1 – 1000 nm). Bawa Decl. ¶ 24 (Exhibit 12).

In its response to Teva's most recent, prior Citizen Petition, FDA asserted that these DLS and AFM data were not dispositive of Copaxone®'s status as a colloidal suspension, stating:

> [A]lthough nano-sized association complexes of varying sizes are known to exist in Copaxone®, there exists no evidence that such complexes result in insoluble, thermodynamically stable forms that are considered characteristic of colloidal suspensions. Moreover, it is unlikely that DLS and AFM methods can affirmatively show the existence of un-dissolved particles in the solution. DLS is not dispositive of the presence of undissolved particles in solution, as one of the inherent physical properties of amino acid polymers is that both dissolved molecules and aggregates in solution scatter light.[22]

As noted above, thermodynamic stability is not a requirement for colloidal suspensions although, as discussed above, Copaxone® nanoparticles appear to be thermodynamically stable. Moreover, while Teva agrees that DLS can detect higher order aggregates in a "true" (homogenous) solution by scattering light, the presence of colloidal nanoparticles in Copaxone® in a solvated state was clearly evident in both DLS and AFM experiments, in which large

[22] FDA's Response to Fourth Copaxone Petition, p. 9, FDA-2012-P-0555 (Nov. 30, 2012) (Exhibit 5).

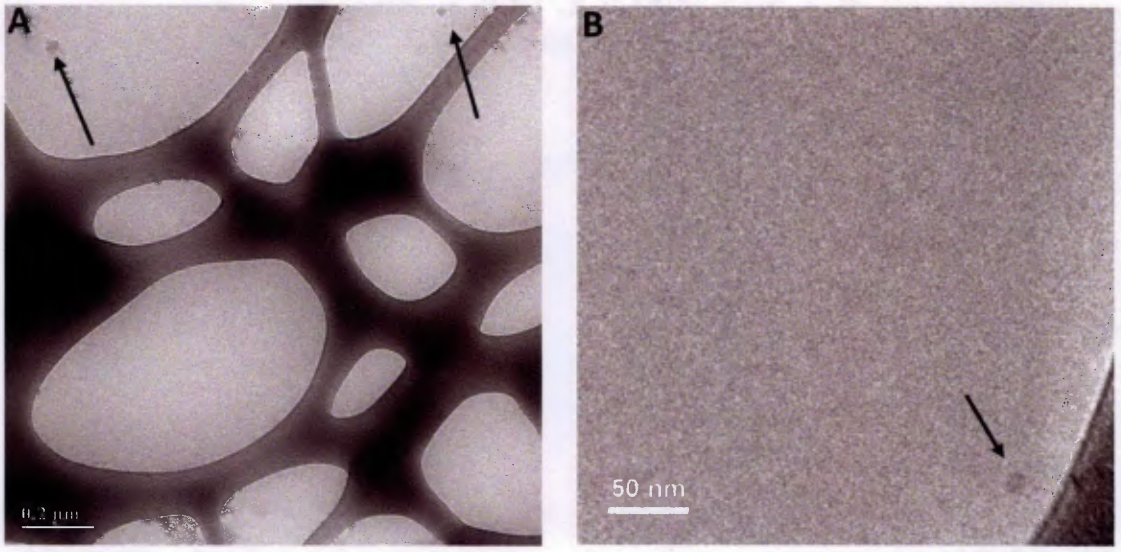
molecular associations, which appear to correspond with the larger sized moieties identified by the DLS technique, were detected in the dried, separated heavy fraction. Bawa Decl. ¶ 28 (Exhibit 12).

4. Cryogenic temperature transmission electron microscopy (Cryo-TEM)

Cryo-TEM is a method of obtaining high-resolution, direct images of molecules or molecular assemblies in their native environment. Thus, it can elucidate the nature of the basic building blocks that make up a sample, covering a wide range of length scales from a few nm to several microns. Rapid freezing of the sample under study prevents alterations to the sample and eliminates potential ultrastructural changes, redistribution of elements, and/or the washing away or evaporation of substances originally present in the sample.[23] This technique was used to confirm results of DLS and AFM testing, and to eliminate the impact (if any) of sample preparation on the size, shape, and type of Copaxone® molecular assemblies.

A drop of Copaxone® was placed onto a TEM copper grid to prevent the formation of ice crystals and analyzed at -170°C. The samples were analyzed in different locations on the grid, using variable magnification, in an attempt to detect the potential existence of both larger and smaller structures in the sample. A placebo (mannitol solution) was tested as a control (**Figure 7**).

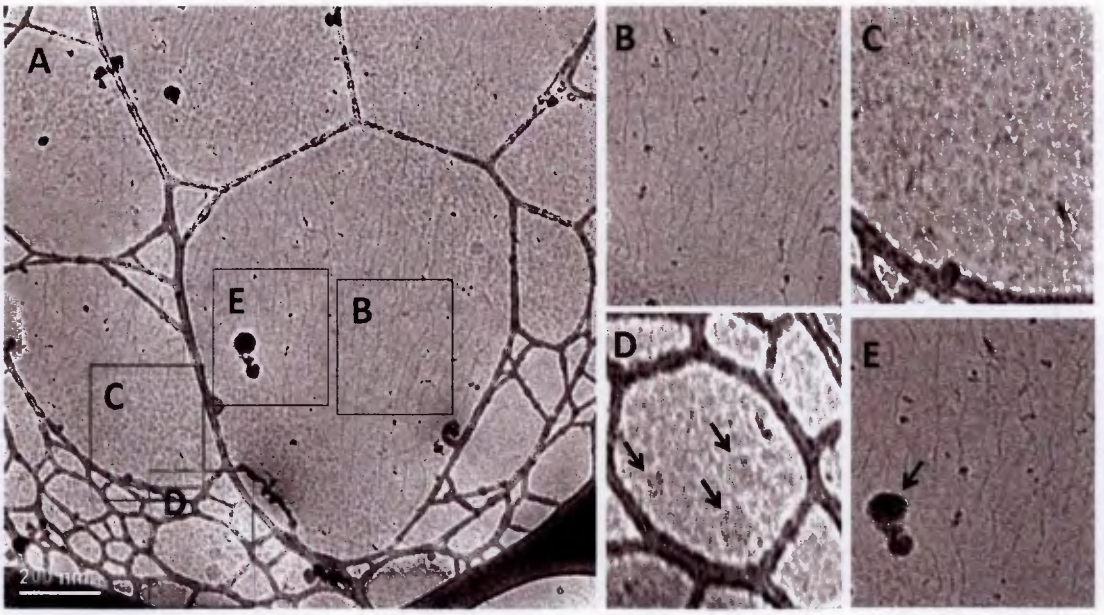
Figure 7 – Typical Cryo-TEM results for a placebo (mannitol solution) sample: (A) Moderate magnification, (B) High magnification. The sample contained globule particles, with varying sizes of 30±5nm, as indicated by the black arrows. These globules most likely originated from the silicon oil droplets present in the syringe.



[23] Danino D, Talmon Y. In: *Molecular Gels. Materials with Self-Assembled Fibrillar Networks*, R.G. Weiss and P. Terech (eds.). Springer. The Netherlands; 2005:pp:251-72 (Exhibit 14).

Copaxone® samples tested under the same conditions appear quite different (**Figure 8**). They largely contain three populations of particles dispersed in the continuous mannitol solution: fibers (or strings) of 60-300nm length, spherical particles of ~ 4nm, and globules of ~30nm; the latter are consistent with the globules in the placebo sample.

Figure 8: (A) Cryo-TEM image of typical structures present in Copaxone® samples. Images B through E are enlarged areas of image A. **(B) Fibers** of 60-300nm length and width of 6±1nm; **(C) Spherical particles** of ~ 4 nm in diameter; **(D) Globules** of ~30 nm in diameter (also detected in placebo samples, see **Figure 5**, above); **(E) Black frost particles** (not related to the sample).



Results of Cryo-TEM analysis support results of DLS and AFM testing. Examination of native structural features of the Copaxone® sample, as in the DLS and AFM experiments, revealed two populations of glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase:

- One population of Copaxone® nanoparticles were spherical with sizes of 4±2nm (Figure 8C), which correspond to the smaller polypeptide moieties shown on the DLS scans (Figure 3, peak on left), and with the "dot-like" structures on topographic AFM images (Figure 5, left).

- The second population of polypeptides appeared as "strings" with lengths of ~60 to 300nm (Figure 8B), which correspond with the DLS peak indicating larger moieties (Figure 3, peak on right) and the topographic images from the AFM analysis showing elongated fibers (Figures 5 [left] and 6).

The polypeptide's particle size distribution and their dispersion in the continuous mannitol aqueous phase shown in the Cryo-TEM study provide additional evidence of the colloidal nature of Copaxone®. Bawa Decl. ¶¶ 24, 29 (Exhibit 12).

5. Zeta Potential

The stability of colloidal suspensions "is determined by the balance of attractive and repulsive forces between individual particles. The repulsive force prevents two particles from approaching one another and adhering together."[24] If the repulsive force is sufficiently high, the colloidal suspension "will resist flocculation and the colloidal system will be stable."[25]

Zeta potential is a measure of the electrokinetic potential in colloidal systems. The magnitude of the zeta potential gives an indication of the stability of a colloidal system. If all the particles in suspension have a large negative or positive zeta potential then they will tend to repel each other and, as noted above, there is no tendency to flocculate. Bawa Decl. ¶ 31 (Exhibit 12). However, if the particles have low zeta potential values then there is no force to prevent the particles coming together and flocculating. The dividing line between stable and unstable suspensions is generally taken at either +30mV or -30mV. Particles with zeta potentials more positive than +30mV or more negative than -30mV are normally considered stable.[26]

Representative zeta potential results for three Copaxone® batches are shown in **Figure 9** and results are summarized in **Table 2**. Placebo (mannitol solution) exhibited a zeta potential that was close to zero.

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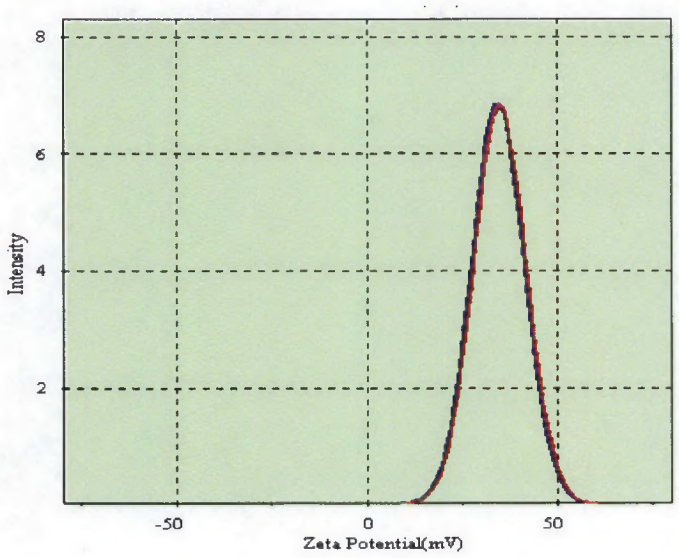
[24] Yang et al. (*J Pharm. Sci* 2010; 99(1):151) (Exhibit 11).

[25] Yang et al. (*J Pharm. Sci* 2010; 99(1):151) (Exhibit 11).

[26] M. S. Jayaraman, D. J. Bharali, T. Sudha, S. A. Mousa, *Molecular Vision* 2012;18:2300-8 (Exhibit 15).

Figure 9. Zeta potential of 3 Batches of Copaxone®



As shown in **Table 2**, these zeta potentials are approximately 34-37mV, indicating the stability of the colloidal solution through strong electrostatic repulsion of Copaxone® moieties, which prevents their flocculation. Zeta potential results confirm the physical stability of the Copaxone® suspension. Bawa Decl. ¶ 32 (Exhibit 12).

Table 2: Summary of Zeta Potential Results

Sample	Batch	Zeta potential (mV)	
		Average	STDV
Copaxone	1	36.5	2.3
	2	37.4	2.0
	3	34.5	1.0
Placebo	-	5.5	3.3

Notably, in its response to Teva's most recent Citizen Petition, the FDA stated that "Ferrlecit®'s thermodynamic stability in particular is indicative of its state as a true colloidal suspension, making *in vivo* bioequivalence studies necessary for the approval of generic versions of this

product."[27] As reported, the zeta potential of Ferrlecit® is -13mV[28], which fails to cross the -30 mV "dividing line" typically used to indicate colloidal stability. Indeed, the repulsive force between the suspended particles in Ferrlecit® appears to be considerably weaker than the repulsive forces operating in Copaxone®, which (unlike Ferrlecit®) has a zeta potential that crosses the dividing line for colloidal stability. Based upon these data and data published for Ferrlecit®, Copaxone® appears to be more stable than Ferrlecit® and thus likewise should be classified as a colloidal suspension.

6. Summary of Test Results

The results of these studies – ultracentrifugation and reconstitution, DLS, AFM, Cryo-TEM, and zeta potential – complement each other and, together, confirm that Copaxone® is a stable, lyophilic colloidal suspension. Bawa Decl. ¶ 35 (Exhibit 12). These studies show that under adequate centrifugal force, Copaxone® can be separated into layers exhibiting different concentrations that are easily re-dispersed back to the original concentration upon vortexing. They demonstrate the presence of solvated, stable, nano-sized molecules and associations dispersed homogenously within the aqueous mannitol solution. The sufficiently high zeta potential values attest to the stability of the colloidal suspension caused by electrostatic forces in the product. The dual population of small and large nanoparticles observed in the analysis is supportive of the unique and distinct microstructure of the Copaxone® product.

B. FDA Should Not Approve Any ANDA that Relies Upon Copaxone as the RLD Unless It Contains Information Demonstrating That the Proposed Generic Product Contains the Same Active Ingredient as Copaxone®

Based on the data provided herein and previously submitted to FDA, it is clear that Copaxone® is a highly complex mixture of polypeptides whose exact constituents cannot be individually and completely characterized. Therefore, it currently is not technologically possible for an ANDA applicant to synthesize a generic version of glatiramer acetate that is structurally and compositionally *identical* to the active ingredient or ingredients in Copaxone®. Moreover, for the reasons described in Teva's third Petition, FDA cannot overcome these regulatory hurdles by applying the type of "overlapping" criteria of sameness used for other complex drug products (e.g., oligosaccharides) to satisfy the statutory "same active ingredient" requirement.

The above-described data provide new evidence of Copaxone®'s complexity that further underscores the need for FDA to apply a rigorous standard with respect to active ingredient "sameness" to ANDAs for purported generic versions of glatiramer acetate. First, Teva's testing and data conclusively demonstrate that Copaxone® is a colloidal suspension rather than a true solution, a physical characteristic of the product that was not previously recognized. Second, and perhaps more significantly for purposes of active ingredient sameness, the testing revealed

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[27] FDA's Response to Fourth Copaxone Petition, FDA-2012-P-0555 (Nov. 30, 2012) (Exhibit 5).

[28] Yang Y, Shah RB, Faustino PJ, Raw A, Yu LX, Khan MA.. Thermodynamic stability assessment of a colloidal iron drug product: sodium ferric gluconate. *J Pharm Sci* 2010; 99(1):142-53 (Exhibit 11).

two distinct populations of stable, solvated glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase. The first population is comprised of spherical nanoparticles with sizes of 4±2nm. The second population is comprised of string-like polypeptides with lengths of ~60 to 300nm. The detection of two distinct populations of particles shows that Copaxone® is more complex than a mere suspension of agglomerated particles and is actually comprised of a unique micro-structure of two, stable particulate populations. Neither of these populations of polypeptides has been fully characterized, and their clinical relevance is unknown at this time.

Consequently, based upon this additional scientific information, as well as the information and arguments in its prior petitions (which are incorporated herein by reference), Teva respectfully requests that FDA refuse to approve any ANDA relying upon Copaxone® as the RLD unless and until one of the following sameness standards has been satisfied:

1. The glatiramer acetate in Copaxone® has been fully characterized (i.e., every potentially active polypeptide sequence of the drug has been identified and quantified, and its structure fully elucidated) and an ANDA applicant has met the burden of proving that its product contains exactly the same polypeptide sequences, in the same amounts and with the same structures, as the fully characterized glatiramer acetate in Copaxone®; OR

2. All polypeptide sequences which contribute to the therapeutic effects of Copaxone®'s glatiramer acetate have been identified, the ANDA applicant has met the burden of proving that its product contains exactly the same clinically relevant polypeptide sequences, in the same amounts and with the same structures, as Copaxone®'s glatiramer acetate; and the ANDA applicant further has proven that any differences between the non clinically active polypeptides in its product and those in Copaxone®'s glatiramer acetate do not undermine the clinically active polypeptide's safety, efficacy, toxicology, and immunology profiles.

C. Comparative Clinical Testing Using Appropriate Safety and Efficacy Endpoints Is Necessary to Ensure That Any Proposed Generic Glatiramer Acetate Product Is Bioequivalent To Copaxone®

The above-described test results also provide additional support for Teva's prior request that FDA refuse to waive *in vivo* bioequivalence testing requirements pursuant to 21 C.F.R. § 320.22(b)(1) because Copaxone® is a colloidal suspension rather than a true solution. Those test results, taken together, provide strong confirmation that Copaxone® is a stable colloidal system composed of two distinct populations of polypeptide nanoparticles (disperse phase) uniformly suspended in an aqueous mannitol solution (continuous phase). As such, Copaxone® meets the regulatory definition of "colloid" adopted by FDA for purpose of its bioequivalence regulations[29] as well as the more rigorous, scientific definition proposed by Teva in section II.A above.

[29] As noted above, FDA defines the term "colloid" as "a chemical system composed of a continuous medium (continuous phase) throughout which are distributed small particles, 1 to 1000 nanometers in size (disperse phase),

Copaxone®'s classification as a colloidal "suspension" rather than a true "solution" is further supported by reference to the definitions adopted in the United States Pharmacopeia ("USP"). The USP defines "suspensions" as "liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble."[30] By contrast, "solutions" are defined as "liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents."[31] The above-described test results demonstrate that glatiramer acetate is not dissolved in the aqueous mannitol solution but is instead well solvated because, among other things, ultracentrifugation was able to separate larger and smaller particles, which is not possible for a true solution. Bawa Decl. ¶ 28 (Exhibit 12). The testing instead confirmed that glatiramer acetate is dispersed throughout the aqueous mannitol solution (liquid phase) as two nanoscale populations of solid particles (solid phase solvated by the solvent molecules). As such, it is more appropriately treated as a "suspension" for purposes of FDA's biowaiver regulations than a "solution."

Teva acknowledges that FDA's biowaiver decisions "must be based on relevant scientific information specific to each active ingredient" and that FDA has treated some peptide and large molecule drug products, such as heparin sodium injection and oxytocin injection, as "solutions" that are eligible for biowaivers. In this case, however, Teva has presented conclusive scientific evidence from traditional colloidal assessment experiments that Copaxone®, like Ferrlecit®, is a colloidal suspension rather than a true solution. Bawa Decl. ¶ 35 (Exhibit 12). Based upon the "relevant scientific evidence specific to [Copaxone®]," therefore, FDA should refuse to grant biowaivers to proposed generic versions of Copaxone®. In a recent similar example, FDA recognized that a biowaiver "would not be appropriate for generic versions of Doxil *given the complexity of the drug*."[32] Given Copaxone®'s high degree of complexity and established colloidal properties, a biowaiver is similarly inappropriate here.

In addition, in its most recent prior Petition, Teva argued that even if Copaxone® were considered to be a true solution, FDA nevertheless should require *in vivo* bioequivalence testing because the inevitable structural and compositional differences in any proposed generic product's active ingredient could affect the bioequivalence of that product, thereby potentially resulting in decreased efficacy, increased toxicity, or both. Teva notes that FDA did not address this specific argument in its November 30, 2012 response letter. Teva thus renews its request for

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that do not settle out under the influence of gravity; the particles may be in emulsion or in suspension." Letter to David Zuchero, M.S., J.D., *et al.*, FDA-2004-P-0494, p. 4, n. 13 (March 31, 2011) (Exhibit 9).

[30] *United States Pharmacopeia and National Formulary* (USP 32-NF 27). Vol. 1. Rockville, MD: United States Pharmacopeia Convention; 2010:672 (Exhibit 16).

[31] *United States Pharmacopeia and National Formulary* (USP 32-NF 27). Vol. 1. Rockville, MD: United States Pharmacopeia Convention; 2010:670 (Exhibit 16).

[32] FDA Response to Doxil Petition, FDA-2009-P-0216, p. 12 n. 62 (Feb. 4, 2013) (emphasis added) (Exhibit 17).

in vivo bioequivalence testing based upon this argument, which is incorporated herein by reference.

In sum, based upon the additional scientific information discussed above, as well as the information and arguments set forth in its most recent prior Citizen Petition (which is incorporated herein by reference), Teva respectfully requests that FDA refuse to approve any ANDA that relies upon Copaxone® as the RLD unless it contains the results of comparative clinical investigations in RRMS patients using relevant safety and effectiveness endpoints that demonstrate the proposed generic drug is bioequivalent to Copaxone®. Given the general uncertainty regarding Copaxone®'s active components and mechanism(s) of action as well as current analytical limitations, a comparative clinical trial with appropriate clinical endpoints is the most accurate, sensitive, and reproducible approach to determine whether compositional differences between a proposed generic product and Copaxone® have an impact on the rate and extent to which glatiramer acetate becomes available at the sites the action, e.g., the immune system.

D. FDA Should Require Comparative Clinical Testing Demonstrating That the Immunogenicity-Related Risks Associated With a Proposed Generic Product Are No Greater than Those Associated With Copaxone®, Including With Respect to Switching

In its most recent prior Petition, Teva requested that FDA require ANDA applicants to conduct non-clinical and clinical immunogenicity studies demonstrating that the risk of an untoward immune response is not greater for a proposed generic product than for Copaxone®, including an assessment of immunologic safety when the products are switched. Although FDA indicated that it would specifically address Teva's contention that "'switching' clinical studies are appropriate to assess immunologic safety," FDA's decision letter does not, in fact, contain any discussion of this issue.

The above-described test results further underscore the need for immunological safety testing, including switching studies. Those test results indicate that Copaxone® is a colloidal suspension that has a complex and unique micro-structure of two particulate populations of glatiramer acetate polypeptides. It currently is not known how these distinct particulate populations, either alone or together, are responsible for Copaxone®'s immunomodulatory activity. Consequently, based upon the additional scientific information discussed above, as well as the information and arguments in its most recent prior Citizen Petition (which is incorporated herein by reference), Teva renews is request that before approving any proposed generic glatiramer acetate product, FDA should require the ANDA applicant to conduct clinical tests demonstrating that the risk in terms of safety or diminished efficacy of switching between use of a proposed generic glatiramer acetate product and Copaxone® is not greater than the risk of using Copaxone® alone.

E. Conclusion

For the foregoing reasons, no ANDA application that references Copaxone® as the RLD should be approved unless and until the conditions set forth above have been satisfied.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

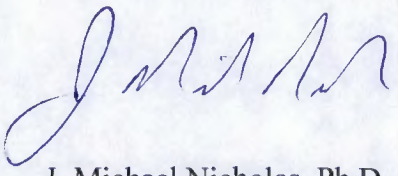
IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: March 1, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organization: my employer, Teva. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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

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

Robert Temple, M.D.
Deputy Center Director for Clinical Science
Acting Deputy Director, Office of Drug Evaluation I

Russell G. Katz, M.D.
Director, Division of Neurology Products

Kathleen Uhl, M.D., Acting Director
Office of Generic Drugs