

TEVA

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**CITIZEN PETITION REQUESTING THAT FDA
REFRAIN FROM APPROVING ANY
ABBREVIATED NEW DRUG APPLICATION
REFERENCING COPAXONE®
(GLATIRAMER ACETATE INJECTION)
UNTIL CERTAIN CONDITIONS ARE MET**

DECEMBER 5, 2013

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December 5, 2013

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”)¹ 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). 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 to assure that follow-on products are safe and effective. Teva manufactures and distributes Copaxone®, a treatment for the reduction of frequency of relapses in relapsing-remitting multiple sclerosis (“RRMS”).

I. Actions Requested

Copaxone® is a non-biologic complex drug (“NBCD”) and first-generation nanomedicine composed of an uncharacterized mixture of immunogenic polypeptides in a colloidal suspension. The active ingredient in Copaxone® – glatiramer acetate – is not a single molecular entity but

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®.

rather a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying lengths, some containing up to 200 amino acids, with structural complexity comparable to that of proteins. The complexity of glatiramer acetate is amplified by the fact that its exact mechanism of action is unknown, and the specific amino acid sequences (epitopes) responsible for efficacy and safety cannot be identified. Accordingly, like many biological products, glatiramer acetate is defined, in large part, by its well-controlled manufacturing process, which has been used by Teva for more than twenty years.

As part of its ongoing commitment to better characterize Copaxone®, Teva continues to evaluate the physicochemical and biological properties of Copaxone® using state-of-the-art technology. In a prior Petition, Teva submitted the results of traditional colloidal assessment experiments to confirm that Copaxone® is a colloidal suspension rather than a true solution.² In this Citizen Petition, Teva is submitting the results of new gene expression studies comparing Copaxone® and purported generic glatiramer acetate products. As discussed further below, the gene expression studies produced multiple lines of evidence suggesting that purported “generic” products have a significantly more variable biological impact than Copaxone®, particularly with respect to immune cells associated with inflammatory response and beneficial tolerance. The results from these recent tests thus raise significant concerns that proposed generic products manufactured via different processes and using different starting materials may have undetected structural and compositional differences from Copaxone® that could compromise safety, immunogenicity, and effectiveness.

In light of these new test results (together with the previously submitted data and information), Teva believes that the Food and Drug Administration (“FDA” or “the Agency”) should apply the statutory and regulatory requirements for approval of purported generic versions of Copaxone® in an extremely rigorous manner. In particular, because of the unique characteristics of both RRMS and Copaxone®, no ANDA should be approved by FDA in the absence of robust and convincing scientific evidence, including clinical studies, demonstrating that the proposed generic product (1) has the same active ingredient as Copaxone®; (2) does not entail an increased risk of immunogenicity (including when switched); and (3) is bioequivalent to Copaxone®. The following information expands on these three points.

Same Active Ingredient. 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 glatiramer acetate’s polypeptides, or to identify the specific epitopes 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. Where, like here, existing scientific methods are inadequate to characterize or identify a complex drug product’s active ingredient or ingredients, the Agency typically has refused to approve generic versions of the drug product, as evidenced by its refusal to approve ANDAs for pancreatic extract products and synthetic versions of Premarin® (conjugated estrogen tablets USP). The Agency instead has required competing products to seek approval via the 505(b)(2) pathway. See 21 U.S.C. § 355(b)(2).

² See Docket No. FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 1).

In some cases, however, FDA has permitted ANDA applicants for NBCDs to rely upon “overlapping criteria” of sameness to satisfy the statutory “same active ingredient” requirement. For example, the Agency recently approved an ANDA for enoxaparin, a naturally-sourced oligosaccharide mixture, based upon five criteria that addressed different aspects of “sameness.” For the reasons discussed below, however, this approach cannot be applied to Copaxone®, which is a synthetic product that is orders of magnitude more complex than enoxaparin (or any other naturally-sourced oligosaccharide). Indeed, Copaxone® has a complexity, including higher order structure, equal to or greater than many proteins. At best, then, an “overlapping criteria” approach can demonstrate only that a generic product contains an active ingredient that is *similar* to glatiramer acetate in its bulk physicochemical properties, such as molecular weight distribution and amino acid ratio; it cannot demonstrate that the generic product contains the *identical* active ingredient within the meaning of the FFDCA. In this way, Copaxone® is more like the protein and complex mixture products for which FDA has refused to approve ANDAs (e.g., synthetic versions of Premarin®) than the peptide products and naturally-sourced oligosaccharides that either can be adequately characterized by physicochemical testing alone (e.g., salmon calcitonin) or to which FDA has applied “overlapping criteria” to establish active ingredient sameness (e.g., enoxaparin, menotropins, heparin).

Immunogenicity. Copaxone® is a highly immunogenic mixture of uncharacterized polypeptides intended for chronic use in a patient population suffering from a serious autoimmune disease (i.e., RRMS). Given this combination of factors, the risk of immunogenicity for follow-on glatiramoids is particularly high. Because immunogenicity is notoriously unpredictable, a purported generic version of glatiramer acetate produced by a different manufacturing process and using a different starting material could have significant and unforeseeable differences from Copaxone® in its immunological mechanisms, raising major safety and efficacy concerns. Indeed, the new gene expression data discussed further below suggest that proposed generic products could have subtle but meaningful differences from Copaxone® in immunological effect that could affect both safety and effectiveness.

Among the potential risks associated with increased immunogenicity are lack of efficacy, exacerbation of disease, immunotoxicity, and induction of additional autoimmune disorders. Moreover, due to the nature of both RRMS and glatiramer acetate, these risks may not develop for months or years and, once apparent, may be irreversible. It is critical for FDA to ensure that any proposed generic product has an immunogenicity profile that is comparable to Copaxone®’s *before* approval. In particular, FDA should 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®. In addition, because Copaxone is intended to be used chronically, such testing must include an assessment of immunologic safety when the products are switched. If these types of immunogenicity studies are not permitted in an ANDA, FDA should require proposed generic products to utilize the 505(b)(2) approval pathway instead.

Bioequivalence. Finally, even if a generic applicant were able to demonstrate active ingredient “sameness” and a comparable immunogenicity profile within the confines of an ANDA, approval of the ANDA would be impermissible in the absence of data from *in vivo*

studies demonstrating that the proposed generic product is bioequivalent to Copaxone®. As discussed further below, a waiver of *in vivo* bioequivalence testing is not appropriate in this case for two independent reasons: (1) Copaxone® is a colloidal suspension rather than a true solution; and (2) the inevitable structural and compositional differences in any generic product's active ingredient, many of which may be undetected, could affect the bioequivalence of the proposed generic product, thereby resulting in decreased efficacy, increased toxicity, or both. 21 C.F.R. §§ 320.22(b)(1), (f). Under applicable FDA regulations, therefore, *in vivo* testing is necessary to ensure that any proposed generic product is bioequivalent to Copaxone®.

In this case, bioequivalence cannot be established by pharmacokinetic (“PK”) or pharmacodynamic (“PD”) testing due to, *inter alia*, the rapid hydrolysis of glatiramer acetate at the site of injection and its uptake by local antigen presenting cells, lack of information on the identity of glatiramer acetate’s active epitopes and metabolites, and the lack of validated PD markers of glatiramer acetate activity. Because PK and PD testing methods are infeasible, bioequivalence can only 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).

Teva previously has raised the above issues regarding active ingredient sameness, immunogenicity and bioequivalence with FDA in a series of Citizen Petitions dating back to 2008.³ 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 applications.⁴ Teva’s prior Petitions thus remain largely unanswered.

In order to facilitate the issuance of a comprehensive and substantive response by FDA to the important scientific, legal and public health issues raised in Teva’s prior Petitions, as well as to present new scientific data and information to support those arguments, Teva is hereby renewing and supplementing the arguments made in its prior Petitions regarding active ingredient sameness, immunogenicity and bioequivalence testing.⁵ At bottom, Teva believes it would be contrary to the public health for FDA to approve a purported generic glatiramer acetate product that, based on current analytical technologies, can only be shown to be similar, rather

³ The prior Citizen Petitions were submitted in 2008, 2009, 2010, 2012 and 2013, respectively, and are incorporated herein by reference. See FDA-2008-P-0529 (Sept. 26, 2008) (Exhibit 2); FDA-2009-P-0555 (Nov. 13, 2009) (Exhibit 3); FDA-2010-P-0642 (Dec. 10, 2010) (Exhibit 4); FDA-2012-P-0555 (June 4, 2012) (Exhibit 5); FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 1). 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 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).

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 6).

⁵ 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).

than identical, to Copaxone® – particularly without any clinical testing whatsoever to address residual uncertainty regarding immunogenicity, bioequivalence, safety or effectiveness.

Consequently, based upon the additional scientific information and data contained in this Petition, as well as the information and arguments set forth in Teva's prior Petitions, 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 *identical* active ingredient as Copaxone®, not merely an active ingredient that is similar (or even highly similar) to Copaxone®'s;
2. 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 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
3. Results of comparative clinical investigations in RRMS patients using relevant safety and effectiveness endpoints demonstrating that the proposed generic drug is bioequivalent to Copaxone®.

II. Statement of Grounds

A. Factual Background

1. Multiple Sclerosis

Multiple sclerosis ("MS") is a progressive, highly complex, immune-mediated disorder that affects the central nervous system ("CNS"). Most experts believe that MS is an autoimmune disease in which inflammatory cells attack myelin, a fatty tissue that surrounds and protects nerve axons in the brain, spinal cord, and optic nerves.⁶ Myelin enhances the rate of electrochemical signal conduction in the CNS. As myelin and the nerve fibers it protects are damaged or destroyed, the ability of the nerves to conduct electrical impulses to and from the brain is disrupted.^{7,8}

⁶ Myelin destruction involves several cell types, with extensive research indicating that subpopulations of antigen-specific T lymphocytes orchestrate a variety of pathogenic mechanisms. Myelin sheaths contain myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein, myelin oligodendrocyte basic protein, and oligodendrocyte specific protein. These proteins are thought to be the primary self-antigen targets of autoimmune T cells in MS.

⁷ Bjartmar C, Fox RJ. Pathological Mechanisms and Disease Progression of Multiple Sclerosis: Therapeutic Implications. Drugs Today 2002;38(1): 17-29.

While myelin degradation is common to all manifestations of MS, there are many forms of the disease, and patients experience its symptoms in different ways. The most common form of the disease is RRMS. People with this form of the disease experience acute attacks (also called relapses or exacerbations) of neurological dysfunction that can last days or weeks. Following these attacks, patients experience remission periods during which symptoms may decrease or disappear before recurring. Approximately 85% of MS patients have RRMS.⁹

MS is a progressive and highly debilitating disease. Early symptoms of MS include sensory disturbances, weakness, generalized fatigue, visual blurring, and dizziness.¹⁰ Cognitive impairment, depression, vertigo, sensory loss, sexual dysfunction, pain, and spasticity can develop. As the disease progresses, symptoms worsen and neurological disability increases; 50% of patients are unable to walk unassisted within 10 to 15 years of an RRMS diagnosis, and after 25 years, 50% are wheelchair-bound.¹¹

2. Copaxone® (glatiramer acetate injection)

Copaxone® is an injectable suspension containing glatiramer acetate as the active ingredient that is currently “indicated for reduction of the frequency in relapses in patients with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.”¹² The drug is used chronically and administered in a subcutaneous injection at a dose of 20 mg daily. Copaxone® is typically self-administered by patients in their homes.

Clinical studies of and extensive experience with Copaxone® in RRMS patients have demonstrated the beneficial effects of glatiramer acetate on clinical parameters and MRI indices of the disease. In clinical trials in RRMS patients, relapse rates were approximately one-third lower in patients receiving glatiramer acetate than in patients receiving placebo.¹³ Similarly, fewer patients receiving the drug experienced sustained disease progression than patients who

⁸ Noseworthy, JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple Sclerosis. N Engl J Med 2000;343:938-52.

⁹ National Multiple Sclerosis Society. Multiple Sclerosis: Just the Facts. 2013:9.

¹⁰ Noseworthy et al., 2000.

¹¹ Weinshenker BG. The natural history of multiple sclerosis. Mult Scler 1995;13:119-44.

¹² Copaxone® (glatiramer acetate injection) prescribing information. Teva Pharmaceuticals USA, Inc., North Wales, PA. Rev 8/2012 (Exhibit 7).

¹³ Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 1995;45:1268-76.

received a placebo.^{14,15} MRI scans show glatiramer acetate reduces both the number and size of lesions as well as the development of new lesions.^{16,17} The efficacy of the drug is sustained over long-term use (>10 years).¹⁸ The product also has an excellent safety profile with relatively modest clinical side effects.

a. **Copaxone® is a highly complex, heterogeneous mixture of synthetic, nano-sized polypeptides that cannot be completely characterized**

Unlike most active ingredients, glatiramer acetate is not a single molecular entity but rather a complex mixture of synthetic polypeptides of varying sizes constructed from four naturally occurring amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine. The average molar fraction of these four amino acids is 0.141, 0.427, 0.095, and 0.338, respectively, and the average molecular weight of the polypeptide mixtures comprising glatiramer acetate ranges from 5000-9000 Daltons. 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.¹⁹ Moreover, due to their size and specific conformation of the polypeptide chains, the Copaxone® constituents have a complex, characteristic conformation in solution, with a structural complexity comparable to many proteins.

The glatiramer acetate in Copaxone® is not just *structurally* complex; it also is highly complex *compositionally*. Copaxone® is prepared using a well-controlled, proprietary polymerization process in which large chains of amino acids are formed, followed by a well-controlled cleavage reaction in which these large chains are broken down into a mixture of smaller (but still quite large) polypeptide chains. This process creates a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides.

¹⁴ Boneschi FM, Rovaris M, Johnson KP, et al. Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled trials. *Multiple Sclerosis* 2003; 9: 349-55.

¹⁵ Bornstein MB, Miller A, Slagle S, et al. A pilot trial of Cop 1 in exacerbating remitting multiple sclerosis. *N Engl J Med* 1987; 317: 408-14.

¹⁶ Comi G, Filippi M, Wolinsky JS, et al. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann. Neurol* 2001; 49:290-27.

¹⁷ Fillipi M, Rovaris M, Rocca MA, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes." *Neurology* 2001;57:731-33.

¹⁸ Ford CC, Johnson KP, Lisak RP, et al. A prospective open-label study of glatiramer acetate: over a decade of continuous use in MS patients. *Mult Scler* 2006;12:309-20.

¹⁹ 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).

The amino acid sequences and polypeptide chain lengths, however, are not entirely random, and extensive quality testing by Teva demonstrates excellent batch-to-batch consistency. To date, however, Teva has been unable to fully characterize the array of polypeptides in glatiramer acetate due to their number, structural complexity, and the current limitations of analytical technologies. Indeed, current analytical methods are not capable of separating and fully characterizing the polypeptides in the Copaxone® mixture. Like many biological products, therefore, the glatiramer acetate in Copaxone is defined, in large part, by its well-controlled manufacturing process.

Teva has, however, been able to glean a partial picture of glatiramer acetate by evaluating the drug's "bulk" properties, *i.e.*, general properties of the entire glatiramer acetate mixture across batches of Copaxone®, using an array of proprietary analytical methods.²⁰ It is crucial to note that these characterization tests do not identify specific amino acid sequences that form glatiramer acetate's many protein-like polypeptides; nor the frequency with which they occur in the mixture; nor the higher order structures of these polypeptides; nor which of glatiramer acetate's polypeptides provide or contribute to the product's proven therapeutic effects. These tests help ensure that Teva's carefully controlled manufacturing process generates a consistent product and can be used to identify *differences* between batches of Copaxone®, but they cannot demonstrate that the clinically relevant polypeptide sequences in two glatiramoid products manufactured by different processes are *identical*.

Finally, Teva has been able to separate certain polypeptide subsets (or fractions) from the rest of the glatiramer acetate mixture using various chromatographic techniques. Each of these fractions contains many thousands of different polypeptides, and the bulk properties of each of these broad fractions in turn differs significantly from every other fraction (as well as from the unfractionated glatiramer acetate mixture as a whole) along multiple tested parameters.²¹ Recent testing, in fact, has revealed two distinct populations of stable, solvated glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase.²² The first population is comprised of spherical nanoparticles with sizes of 4±2 nanometers ("nm"). The second population is comprised of string-like polypeptides with lengths of ~60 to 300 nm. The detection of two distinct populations of particles 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, however, has been fully characterized, and their clinical relevance is unknown at this time.

²⁰ These analytical tests include (but are not limited to): Gel Filtration Chromatography Test for Molecular Weight Distribution; Coomassie Brilliant Blue ("CBB") Test; Edman Degradation Profile; Peptide Mapping Profile; Fluorescent Dye Binding Test; Western Blot Test; Cytokine Profiling; Acid Digestion; Experimental Autoimmune Encephalomyelitis Blocking Test; and a Potency Test.

²¹ Data on file, Teva Pharmaceuticals, Inc. 2012.

²² See Docket No. FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 1).

In sum, Teva believes that Copaxone®'s complexity and the limitations of current analytical technologies make it impossible to definitively characterize the chemical composition and distinct structures of each of the polypeptides that comprise glatiramer acetate.

b. Copaxone® is Highly Immunogenic

Glatiramer acetate is a highly immunogenic antigen-based therapy that acts as a therapeutic vaccine and elicits cellular and humoral responses in virtually all treated subjects. As an immunomodulator, glatiramer acetate is intended to achieve its therapeutic effects by interacting with and modulating a patient's immune system over an extended period of time. For this reason, Copaxone®'s package insert warns that chronic use has the potential to alter healthy immune function as well as induce pathogenic immune mechanisms, although no such effects have been observed with Copaxone®.²³

Following treatment with Copaxone®, anti-glatiramer acetate antibodies are detected in all treated patients and animals.²⁴ These antibodies, however, do not neutralize biological activity or clinical efficacy and are not associated with local or systemic adverse effects in RRMS patients receiving chronic treatment.^{25,26,27,28} In fact, some evidence suggests that anti-glatiramer acetate antibodies may enhance the biological activity of Copaxone®.²⁹

The anti-glatiramer acetate antibody profile (titers and isotypes) changes with repeated glatiramer acetate administration, resulting in a unique response profile over time. In RRMS patients, anti-glatiramer acetate antibody levels peak between 3 and 6 months of treatment initiation and then gradually decline.³⁰ Anti-glatiramer acetate antibodies are mainly of the IgG class, with consistent shifts in predominant subclasses over time (i.e., IgG-2 shifting to IgG-1).

²³ Copaxone® prescribing information, § 5.4 (Exhibit 7).

²⁴ Brenner T, Arnon R, Sela M, et al. Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone®. *J Neuroimmunol* 2001;115:152-60.

²⁵ Brenner et al (2001).

²⁶ Teitelbaum D, Brenner T, Abramsky O, et al. Antibodies to glatiramer acetate do not interfere with its biological functions and therapeutic efficacy. *Mult Scler* 2003;9:592-99.

²⁷ Karussis D, Teitelbaum D, Sicsic C, et al. Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. *J Neuroimmunol* 2010;220:125-30.

²⁸ Farina C, Vargas V, Heydari N, et al. Treatment with glatiramer acetate induces specific IgG4 antibodies in multiple sclerosis patients. *J Neuroimmunol* 2002;123:188-92.

²⁹ Ure DR, Rodriguez M. Polyreactive antibodies to glatiramer acetate promote myelin repair in murine model of demyelinating disease. *FASEB J* 2002;16:1260-62.

³⁰ Copaxone® prescribing information, § 5.4 (Exhibit 7).

Despite Copaxone®'s excellent safety profile, there long have been general concerns regarding glatiramer acetate's immunogenic potential. While extremely rare, there have been reports of anti-glatiramer acetate IgE antibodies that have been associated with late-occurring anaphylactic reactions that can arise up to one year after beginning treatment, with no symptomology beforehand to signal hypersensitivity. As a result, Copaxone®'s package insert specifically warns about the potential risk of anaphylaxis.³¹ In light of these serious risks, the immunogenic profile of an unknown glatiramoid warrants extensive scrutiny.

B. New Gene Expression Studies Suggest That Proposed Generic Glatiramer Acetate Products May Have Structural and Compositional Differences From Copaxone® That Affect Safety and Efficacy

As part of its ongoing commitment to better characterize Copaxone®, Teva has conducted high throughput gene expression analysis studies. As discussed further below, these studies raise significant concerns that proposed generic glatiramer acetate products manufactured via a different process and using a different starting material could have undetectable structural and compositional differences from Copaxone® that compromise the safety and/or effectiveness of the product. These tests thus underscore the importance of applying rigorous standards with respect to active ingredient sameness, immunogenicity and bioequivalence testing before FDA approves any purported generic versions of Copaxone®.

Gene expression studies measure the amount of ribonucleic acid ("RNA") in a sample at a given time. Because RNA plays a critical role in building the proteins that carry out many biological functions, gene expression studies provide a highly informative snapshot of the biological processes occurring in a sample. Microarray technology enables the simultaneous measurement of RNA expression levels for tens of thousands of genes. By using microarray data to identify genes with altered expression in samples exposed to different conditions, it is often possible to gain insight into the biological impact of the different conditions.

In the new studies, mice of the (Balb/c x SJL) F1 variety were injected with glatiramer acetate reference standard ("GA-RS") in order to induce glatiramer acetate-reactive T cells. After 3 days, the mice were sacrificed and immune cells from their spleens (splenocytes) were isolated. The isolated splenocytes were then activated *ex vivo* with either GA-RS, Copaxone®, or other glatiramoids, including a purported foreign-sourced "generic" (Glatimer®, Natco Pharma, Ltd., Hyderabad, India),³² and TV-5010, a developmental glatiramoid that has been discontinued because of unexpected safety problems.

³¹ Copaxone® prescribing information, § 5.4 (Exhibit 7).

³² Glatimer® is a purported "generic" version of Copaxone® that is marketed by Natco Pharma in India and the Ukraine. Although Glatimer® is not currently approved or marketed in the United States, Mylan Pharmaceuticals has publicly announced an agreement with Natco to distribute a generic version of Copaxone® in the United States. See Press Release Announcing Collaboration (June 10, 2008), available at <http://www.prnewswire.com/news-releases/mylan-inc-natco-pharma-ltd-to-collaborate-on-worldwide-marketing-and-distribution-of-generic->

For each sample, total RNA was extracted from activated splenocytes using PerfectPure RNA Cultures CEKK kit 50 (5Prime GmbH, Hamburg, Germany). RNA quality was assessed using the absorbance ratio at 260/280 nm and gel electrophoresis (Experion, Bio-Rad, Hercules, CA, USA). Gene expression was then measured using Illumina WG-6_V2 microarrays, a commonly used and well-validated technology capable of measuring more than 45,000 transcripts. Samples were randomized on the chips to avoid batch effects. Illumina's BeadStudio software was utilized for image processing, quantification of signal intensity per bead, and background signal correction. For the initial analyses multiple probes for a given gene were averaged, while the advanced analyses were conducted on individual probes.

1. Findings From Initial Analyses³³

Testing initially identified 75 genes differentially expressed between Copaxone® and the purported “generic” using a one-way ANOVA analysis (FDR-adjusted p < 0.05). Further analyses indicated that the “generic” clustered into two groups, the first including three samples from two manufacturing batches, and the second including eight samples from three manufacturing batches. These differences are likely due to variability in the manufacturing processes for the purported “generic” as discussed further below. When we compared Copaxone® specifically to the eight “generic” samples from the three manufacturing batches, we identified 98 genes as being differentially expressed by one-way ANOVA analysis (FDR-adjusted p < 0.05 and fold change ≥ 1.3).

Pathway analyses were performed on these 98 genes using Ingenuity Pathway Analysis (IPA) software. Inflammatory response genes were found to be significantly upregulated by the purported “generic” relative to Copaxone® (30 genes, p < 8.67 x 10⁻¹⁹), along with genes associated with immune cell adhesion (20 genes, p < 7.57 x 10⁻¹⁷), and cell movement (39 genes, p < 9.55 x 10⁻¹⁵) as well as various other pathways associated with cell migration and chemotaxis. Taken together, these pathway analyses suggest that the “generic” may upregulate inflammatory pathways that could increase the risk of adverse events and/or reduce the efficacy of treatment with glatiramer acetate.

Among the 98 genes that are differentially expressed between Copaxone® and the purported “generic” product, there are four general patterns (**Figure 1**).³⁴ Some of the genes are expressed at lower levels following treatment by “generic” than by Copaxone®, as indicated by portions of clusters B and C. Genes meeting this description include IFIT3 (interferon-induced protein with tetratricopeptide repeats 3). IFIT3 is an antiviral adaptor protein that facilitates the activation of TBK1 and phosphorylation of the transcription factor IRF3, which subsequently

[copaxoner-57430927.html](#). The results of tests on the foreign-sourced Natco product thus are particularly relevant to potential generic copies in the U.S.

³³ Published in: Bakshi, S. et al. Gene expression analysis reveals functional pathways of glatiramer acetate activation. Expert Opinion on Therapeutic Targets 17, 351–362 (2013) (Exhibit 9).

³⁴ References in the Figures to GA, GA-RS, and GA-DP stand for “glatiramer acetate,” “GA reference standard,” and “GA drug product” (i.e., Copaxone®), respectively.

activates antiviral genes.³⁵ IFIT3 has been proposed to be a key mediator of the activity of interferon-alpha,³⁶ through its influence on IRF3.³⁷ Interferon-alpha, and type I interferons more generally, are cytokines believed to play a beneficial role in MS. In addition, patients with lower expression of IFIT3 may be less likely to respond to glatiramer acetate.³⁸ Because lower levels of IFIT3 may be associated with non-response, the lower expression of IFIT3 following stimulation by the purported “generic” raises concerns for its efficacy.

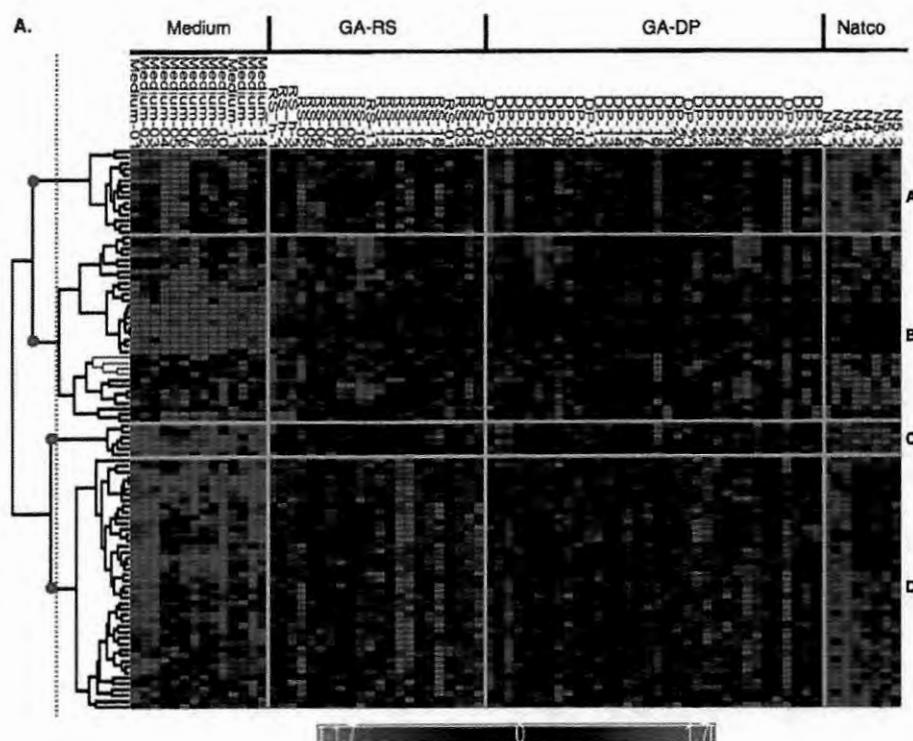


Figure 1: Genes differentially expressed between Copaxone® (GA-RS and GA-DP) and purported “generic” (Natco) follow four general patterns.

³⁵ Zhou, X. et al. Interferon Induced IFIT Family Genes in Host Antiviral Defense. *Int J Biol Sci* **9**, 200–208 (2013).

³⁶ Schmeisser, H. et al. Identification of Alpha Interferon-Induced Genes Associated with Antiviral Activity in Daudi Cells and Characterization of IFIT3 as a Novel Antiviral Gene. *J. Virol.* **84**, 10671–10680 (2010).

³⁷ Solis, M. et al. Distinct functions of IRF-3 and IRF-7 in IFN-alpha gene regulation and control of anti-tumor activity in primary macrophages. *Biochem. Pharmacol.* **72**, 1469–1476 (2006).

³⁸ Comabella, M. et al. Gene expression profiling study in multiple sclerosis patients responders and non-responders to treatment with glatiramer acetate. in *ECTRIMS* (2012).

2. Findings From Advanced Analyses³⁹

a. *Variability Analysis: Copaxone® is significantly more consistent than “generic”*

In comparing medicines produced by different manufacturing processes, it is important to assess if they are equally consistent in their biological impacts. We sought to examine differences in global variability across all relevant probes in order to address the question of whether the biological impact of a purported foreign “generic” was as consistent (across five batches) as Copaxone® (across 30 batches). Defining relevant probes as those with variability induced specifically by activation (as opposed to experimental noise such as the variability seen in samples exposed only to medium), we found that 4-fold more probes had significantly higher variability across the “generic” batches than across the Copaxone® batches (**Figure 2**). In other words, the purported generic’s inconsistency from batch-to-batch causes it to have a variable impact on 4 times as many genes as Copaxone®, which is highly consistent from batch to batch.

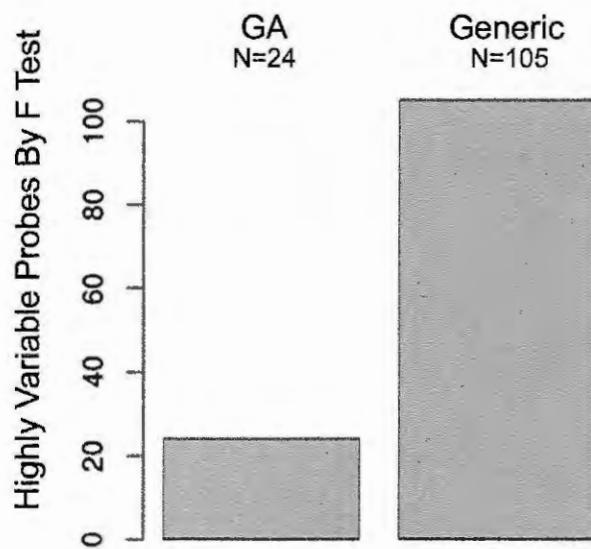


Figure 2: The biological impact of Copaxone® is significantly more consistent than that of “generic.” Among probes with variability induced by activation, 4-fold more probes had significant variation by F-test across 11 generic-activated samples from 5 batches, when compared to the number of probes with significant variation by F-test across 34 Copaxone®-activated samples from 30 batches.

It is important not only to identify differences in variability, but also to explore the potential biological impact of these differences. Thus, we calculated for each probe the ratio of the variance in “generic” to the variance in Copaxone®. The highest ranked probe by variability in “generic” relative to its variability in Copaxone® was for *FOXP3* (ILMN_2635132, ratio 4.17,

³⁹ To be published in: Towfic, F. et al. Comparing the Biological Impact of Glatiramer Acetate with the Biological Impact of a Generic. PLOS ONE. (2013) (will be submitted as Exhibit 10 upon publication).

forkhead box P3), a transcription factor that acts as the key marker of tolerance-inducing regulatory T cells (“Tregs”). Tregs, which normally counteract the actions of effector T cells (“Teffs”) in order to prevent autoimmune damage, are not only important in the pathology of MS but also affected by treatment with glatiramer acetate.^{40,41,42,43} Consistent with its role as a key Treg marker, FOXP3 expression is significantly reduced in MS patients relative to healthy controls, and FOXP3 expression is highly correlated with expression in functional assays.⁴⁴ The probe with the second highest ratio of variance in “generic” to variance in Copaxone® was for *GPR83* (ILMN_2707941, ratio 4.14, G-protein coupled receptor 83), which is also an established Treg marker⁴⁵ and may be a transcriptional target of FoxP3. Moreover, transduction of GPR83 was shown to induce immunosuppressive FoxP3+ Tregs under inflammatory conditions.⁴⁶

b. Comparing Impact on Key Immune System Genes: Copaxone® induces Treg markers FoxP3 and Gpr83 more effectively than “generic”

To systematically examine the differential expression of a particular gene in response to different medicines, we applied multiple methods including both parametric and non-parametric testing. Not only did Copaxone® induce expression of the key marker of tolerance-inducing Tregs *FOXP3* more consistently than the purported “generic,” but Copaxone® also induced significantly higher expression as determined by 4 parametric methods: ANOVA (adjusted p < 1.37 x 10⁻³), LIMMA with background subtraction (adjusted p < 6.14 x 10⁻⁴), comparative marker selection using signal-to-noise (adjusted p < 1.34 x 10⁻²) and t-test (adjusted p < 2.12 x 10⁻²), and a non-parametric Wilcoxon rank-sum test (adjusted p < 4.62 x 10⁻² (**Figure 3(Top)**)).

Applying the same methods to another marker of tolerance-inducing Tregs, *GPR83*, we found that Copaxone® induced significantly higher levels of expression than generic: ANOVA (adjusted p < 4.75 x 10⁻⁸), LIMMA with background subtraction (adjusted p < 8.67 x 10⁻¹⁰), comparative marker selection using signal-to-noise (adjusted p < 1.34 x 10⁻²) and t-test (adjusted

⁴⁰ Kasper, L. H., Haque, A. & Haque, S. Regulatory mechanisms of the immune system in multiple sclerosis. T regulatory cells: turned on to turn off. *J Neurol* **254**, 110–114 (2007).

⁴¹ Costantino, C. M., Baecher-Allan, C. & Hafler, D. A. Multiple sclerosis and regulatory T cells. *J. Clin. Immunol.* **28**, 697–706 (2008).

⁴² Haas, J. et al. Glatiramer acetate improves regulatory T-cell function by expansion of naive CD4(+)CD25(+)FOXP3(+)CD31(+) T-cells in patients with multiple sclerosis. *J. Neuroimmunol.* **216**, 113–117 (2009).

⁴³ Venken, K., Hellings, N., Liblau, R. & Stinissen, P. Disturbed regulatory T cell homeostasis in multiple sclerosis. *Trends Mol Med* **16**, 58–68 (2010).

⁴⁴ Huan, J. et al. Decreased FOXP3 levels in multiple sclerosis patients. *J. Neurosci. Res.* **81**, 45–52 (2005).

⁴⁵ Sugimoto, N. Foxp3-dependent and -independent molecules specific for CD25+CD4+ natural regulatory T cells revealed by DNA microarray analysis. *International Immunology* **18**, 1197–1209 (2006).

⁴⁶ Hansen, W. et al. G protein-coupled receptor 83 overexpression in naive CD4+CD25- T cells leads to the induction of Foxp3+ regulatory T cells in vivo. *J. Immunol.* **177**, 209–215 (2006).

$p < 1.49 \times 10^{-2}$), and a non-parametric Wilcoxon rank-sum test (adjusted $p < 3.45 \times 10^{-4}$, **Figure 3(Bottom)**). *GPR83* is also in the top 20 probes by fold change from Copaxone® compared to the purported “generic.”

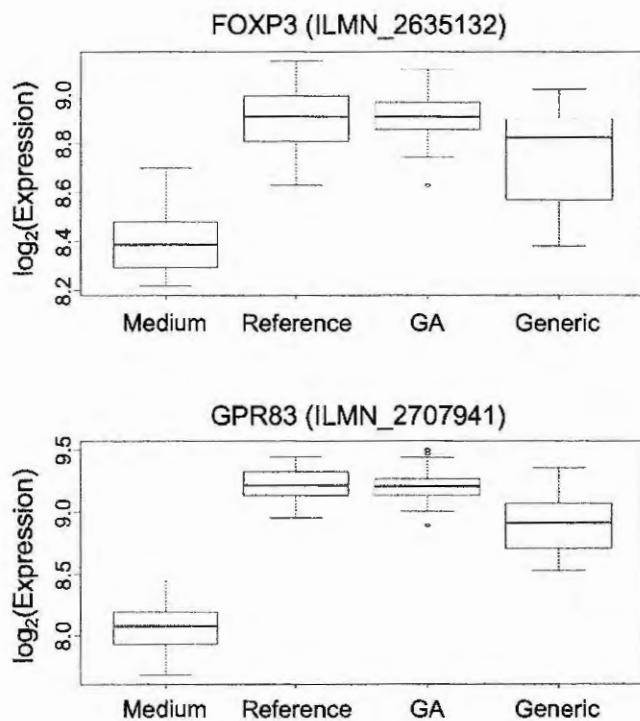


Figure 3: Copaxone® induces Tregs more effectively than “generic.” (Top) Copaxone® induces significantly higher expression of FoxP3 than “generic.” FoxP3 is a key marker of Tregs, and (Bottom) another key Treg marker, Gpr83, shows a similar pattern of expression.

When the genes differentially expressed in response to different medicines are also transcription factors (e.g. *FOXP3*), we can further test the observation by examining the expression of genes known to be targets of that transcription factor. In this case, we sought to determine whether genes downstream of FoxP3 are upregulated following activation by Copaxone® as compared to “generic.” Through Gene Set Enrichment Analysis (GSEA),⁴⁷ we found that FoxP3 target genes were enriched in Copaxone® samples compared to medium (FDR-adjusted $q = 0.008$) to a more significant degree than in “generic” samples compared to medium (FDR-adjusted $q = 0.036$). Taken together, these findings emphasize that Copaxone® upregulates FoxP3+ Tregs more consistently and to a higher level than “generic.” This finding has implications for efficacy.

⁴⁷ Subramanian, A. et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* **102**, 15545–15550 (2005).

c. ***Comparing Potential Safety-related Impacts on Key Immune System Cell Types: “Generic” may upregulate myeloid lineage cells to a greater extent than Copaxone®***

Using an ANOVA-based pattern analysis, we identified a list of genes that are significantly upregulated only by the purported “generic” compared to medium, and not by Copaxone® or glatiramer acetate reference standard compared to medium. Cell type enrichment yielded a variety of stromal cells, macrophages, and monocytes. Similarly, genes that were significantly downregulated by Copaxone® and the glatiramer acetate reference standard relative to medium, but not by “generic” relative to medium were most enriched for macrophages, monocytes, and granulocytes. Finally, genes that have significantly higher expression in samples activated by “generic” than in samples activated by Copaxone® by four different parametric methods were enriched primarily in macrophages and monocytes.



Figure 4: Cell-type specific differences in the biological impact of Copaxone® and “generic.” Copaxone® induces higher expression of Treg-associated genes than “generic,” while “generic” induces higher expression of macrophage and monocyte-associated genes.

To illustrate the cell-type specificity among the genes differentially expressed between Copaxone® and the purported “generic,” we created a heat map of the differentially expressed genes showing the relative expression of Treg-specific genes, macrophage-specific genes, and monocyte-specific genes in samples activated by Copaxone® compared to samples activated by “generic” (**Figure 4**). Applying a cell-type enrichment algorithm, we determined that the list of genes upregulated by “generic” relative to Copaxone® was significantly enriched in genes associated with macrophages and monocytes (for example, MPO (myeloperoxidase), PRTN3 (proteinase 3), C3 (complement component 3), and TGFB1 (transforming growth factor, beta-

induced)). Macrophages and monocytes are known to play a role in neuroinflammation in MS.⁴⁸ By contrast, the list of genes downregulated by generic relative to Copaxone® was significantly enriched in genes associated with T cells including Tregs. This suggests Copaxone® and “generic” may have significantly different impacts on a variety of key immune cell types, with implications for both safety and efficacy.

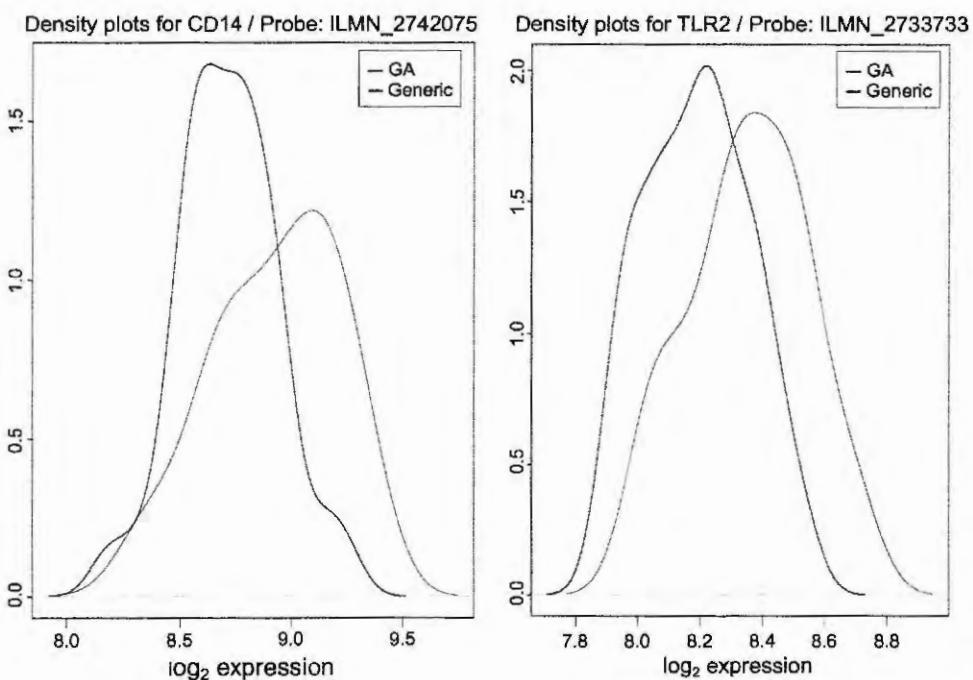


Figure 5: The “generic’s” impact on monocytes may differ from Copaxone®’s impact. “Generic” induces significantly higher expression of CD14 and TLR2, as determined by a Wilcoxon rank sum test and depicted as kernel density plots, which can be likened to a smoothed histogram.

To further investigate discrepant cell type activation between the Copaxone® and “generic,” we utilized the non-parametric Wilcoxon rank-sum test to determine which genes had significantly higher expression from “generic” than from Copaxone®. We then sought to determine if this list was enriched in genes for any specific pathways, by performing an enrichment using the Broad Institute’s molecular signature database, MSigDB.⁴⁹ The TLR signaling pathway was significantly enriched (adjusted p < 1.27 x 10⁻⁶). Among the overlap genes significant by Wilcoxon and present in this pathway were *CD14* (adjusted p < 4.77 x 10⁻²), a monocyte marker, and *TLR2* (adjusted p < 3.65 x 10⁻²). Kernel density plots (**Figure 5**), which can be likened to a smoothed histogram and effectively illustrate differences identified by non-

⁴⁸ Bar-Or, A. *et al.* Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. *Brain* **126**, 2738–2749 (2003).

⁴⁹ Subramanian, A. *et al.* (2005).

parametric tests such as the Wilcoxon, show the differences in expression between “generic” and Copaxone® for these two genes.

d. Generics vs. Generics Comparison

In addition to comparing Copaxone® to a purported foreign “generic” version, we also sought to compare purported generics from various manufacturers to each other. Using the same mouse splenocyte procedure described above, we generated expression data in response to activation with proposed generic glatiramer acetate samples from Escadra (Argentina), Probioglat (Mexico), and Hangzhou (China; API, unknown expiration date).

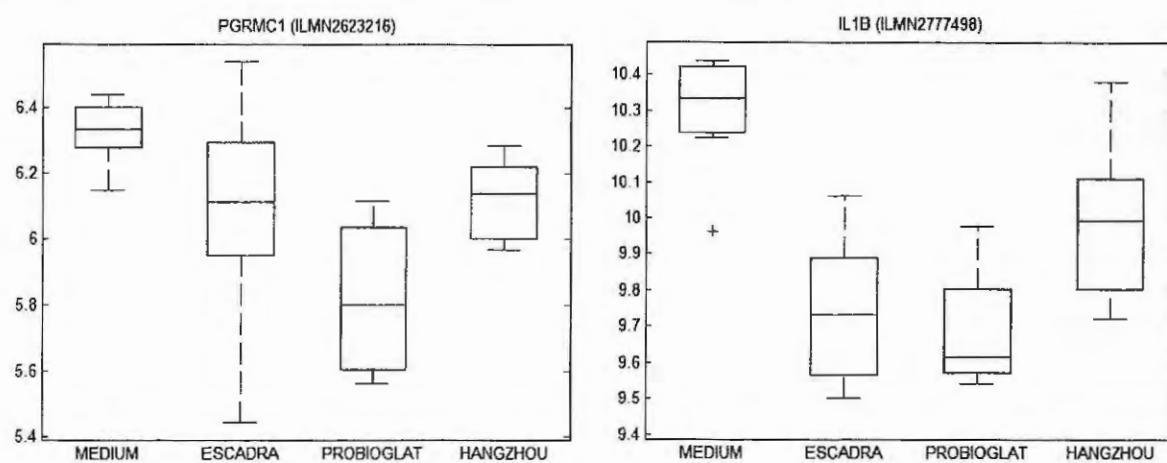


Figure 6: The expression of PGRMC1 and IL1B shows significantly different expression following stimulation with proposed “generics” from different manufacturers.

Numerous probes with potential links to safety and efficacy show differences in expression among purported “generics” from different manufacturers. For instance, the progesterone receptor membrane component 1 (PGRMC1) is significantly downregulated by Probioglat relative to medium (adjusted $p < 0.0103$), but not by Hangzhou or Escadra relative to medium (adjusted $p < 0.283$ and 0.205 respectively) (**Figure 6**). This is particularly relevant to MS patients, because progesterone is believed to be neuroprotective and may play a role in myelin repair^{50,51} as well as affect the balance between Tregs and Teffs.⁵² This implies that the altered expression of PGRMC1 could reduce the efficacy of Probioglat in several possible ways (e.g. by restricting neuroprotection). In contrast, Copaxone® does not downregulate PGRMC1 significantly relative to medium (adjusted $p < 0.231$).

⁵⁰ Kipp, M., Amor, S., Krauth, R. & Beyer, C. Multiple sclerosis: neuroprotective alliance of estrogen-progesterone and gender. *Front Neuroendocrinol* **33**, 1–16 (2012).

⁵¹ Schumacher, M., Guennoun, R., Stein, D. G. & De Nicola, A. F. Progesterone: therapeutic opportunities for neuroprotection and myelin repair. *Pharmacol. Ther.* **116**, 77–106 (2007).

⁵² Hughes, G. C., Clark, E. A. & Wong, A. H. The intracellular progesterone receptor regulates CD4+ T cells and T cell-dependent antibody responses. *J Leukoc Biol* **93**, 369–375 (2013).

Another relevant gene for MS, interleukin 1 beta (IL1B), is significantly downregulated by Probioglat and Escadra relative to medium (adjusted p < 0.00267 and 0.000134 respectively), but not by Hangzhou relative to medium (adjusted p < 0.159) (**Figure 6**). IL1B is a cytokine that stimulates a variety of immune system cells, and may contribute to the development of MS by promoting T_H17 cell development.⁵³ Consistent with these observations, IL1B has also been found to be associated with late disability progression and neurodegeneration in MS,⁵⁴ and glatiramer acetate has been found to significantly reduce interleukin-1beta levels under chronic inflammatory conditions *in vitro* in human monocytes with p = 0.028.⁵⁵ In light of these findings, the reduced effectiveness of Hangzhou in downregulating IL1B could negatively impact its efficacy. In contrast, Copaxone® is extremely effective in downregulating IL1B relative to medium (adjusted p < 5.72 x 10⁻⁷).

Purported “generics” are not only different from Copaxone® in many ways, but also different from each other, causing differential effects in a variety of pathways modulating immunological processes that could have clinical and biological significance. The differences among “generics” highlight the importance of the manufacturing process for glatiramer acetate, and demonstrate that even slight changes in the manufacturing process can alter the biological properties of the resulting medicine.

e. ***TV-5010 experience demonstrates link between gene expression and findings in animal safety studies***

Having identified genes differentially expressed in response to Copaxone® versus purported “generics” (and among purported “generics” from different manufacturers), including genes that raised concern about safety risks from purported “generics,” we sought to further investigate the applicability of gene expression to the prediction of toxicity issues. An important test case for doing so was provided by TV-5010 (Protiramer).

Teva developed TV-5010 by making slight changes to the manufacturing process for Copaxone® in order to produce a higher average molecular mass (in the range of 13,500-18,500 daltons) and investigate whether such a change in molecular mass would be beneficial.⁵⁶ Surprisingly, TV-5010 proved toxic in long-term animal studies, inducing fibrosis, nephropathy, increases in eosinophil counts, and severe injection site lesions including subcutaneous necrosis, vascular necrosis, cavity formation, and inflammation; in some cases these lesions were associated with mortality in both rats and monkeys, possibly related to vascular damage,

⁵³ Sims, J. E. & Smith, D. E. The IL-1 family: regulators of immunity. *Nat Rev Immunol* **10**, 89–102 (2010).

⁵⁴ Rossi, S. *et al.* Early CSF detection of IL1b predicts late disability progression and neurodegeneration in relapsing remitting multiple sclerosis. in *ECTRIMS* (2013).

⁵⁵ Burger, D. *et al.* Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1β in human monocytes and multiple sclerosis. *Proceedings of the National Academy of Sciences* **106**, 4355–4359 (2009).

⁵⁶ Varkony H, Weinstein V, Klinger E, et al. The glatiramoid class of immunomodulator drugs. *Expert Opin Pharmacother* 2009;10:657-68 (Exhibit 11).

hemorrhage, thrombus formation, and septicemia.⁵⁷ These toxicities were never seen in any of the development programs for Copaxone®, and led to the termination of TV-5010's development. Some patients treated with TV-5010 showed injection site reactions and/or developed anti-drug antibodies, but the clinical studies were terminated in time to prevent any of the chronic toxicities observed in long-term animal studies from occurring in humans.⁵⁸

Because Copaxone® and TV-5010 had many similarities, with the two key differences that (1) TV-5010 had a higher molecular mass than Copaxone®, and (2) Copaxone® was safe while TV-5010 induced toxicity in long-term animal studies, we sought to determine if there were genes differentially expressed in response to the two medicines that could have predicted toxicity prior to the initiation of long-term animal studies.

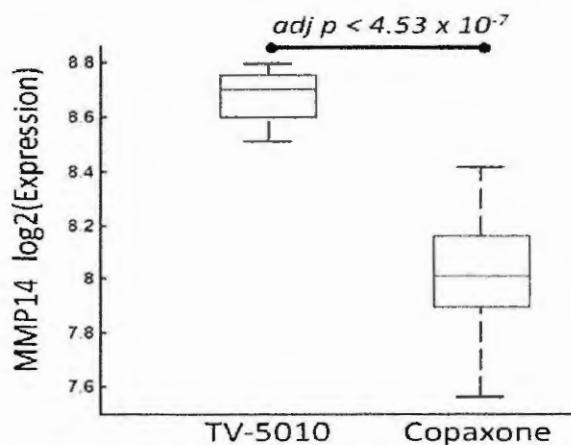


Figure 7: MMP14 expression is significantly elevated by TV-5010 relative to Copaxone®, and literature indicates that MMP14 is consistently associated with fibrosis: the same toxicity seen in animals following long-term exposure to TV-5010.

Having generated gene expression profiles for TV-5010-stimulated splenocytes using the same procedures described above, we applied LIMMA to create a ranked list of genes with significantly different expression levels in response to TV-5010 compared to Copaxone®, with both analyzed relative to medium. Among the genes with fold changes greater than 1.5, the gene with the lowest (best) p-value was MMP14. MMP14 expression was significantly higher in response to TV-5010 than in response to Copaxone® as determined by both ANOVA ($\text{adj } p < 4.53 \times 10^{-7}$) and LIMMA ($\text{adj } P < 1.07 \times 10^{-5}$) (Figure 7).

The observed upregulation of MMP14 was striking because MMP14 has been associated with fibrosis and eosinophil-related disorders in literature, the very same toxicities seen in

⁵⁷ Ramot, Y. et al. Comparative Long-Term Preclinical Safety Evaluation of Two Glatiramer Compounds (Glatiramer Acetate, Copaxone(R), and TV-5010, Protiramer) in Rats and Monkeys. *Toxicologic Pathology* **40**, 40–54 (2011).

⁵⁸ Varkony, H. et al. (2009) (Exhibit 11).

animals following long-term treatment with TV-5010. MMP14 levels increase to over 250% of control as fibrosis is induced in rats,⁵⁹ and MMP14 activity is chronically elevated in a mouse model of dermal fibrosis.⁶⁰ In patients with the eosinophil-related disorder eosinophilic esophagitis (EoE), MMP14 is expressed at a 5.3-fold higher level than in controls.⁶¹

In addition to MMP14, another gene (STAT3) which has been linked to fibrosis⁶² also showed significantly elevated expression in response to TV-5010 relative to Copaxone®. It is also noteworthy that IFIT3 is expressed at lower levels following stimulation with TV-5010 versus Copaxone®, especially given that this gene is also expressed at lower levels following stimulation with proposed “generic” and may have links to glatiramer acetate efficacy as discussed above. Overall, our findings with TV-5010 lend further support to the utility of mouse splenocyte gene expression studies for predicting drug safety issues.

3. Discussion

Our gene expression studies produced multiple lines of evidence suggesting that purported “generic” products have a significantly more variable biological impact than either Copaxone® reference standard or Copaxone®. For instance, 34 samples representing 30 different Copaxone® batches were found to be highly consistent and similar to glatiramer acetate reference standard. In contrast, more probes have higher variability in expression following stimulation with eleven samples representing five different “generic” batches. This variability itself is cause for concern, since the batch-to-batch variability of “generic” could manifest itself in ways that are harmful to patients. One possibility is that a patient could experience benefit from a particular batch but not from a subsequent batch, preventing the patient from achieving the maximum benefit possible. Another, more disconcerting, possibility is that the variability could lead to a particular batch of “generic” causing adverse events. Due to the generic’s heterogeneity, such adverse events could be intermittent and therefore difficult to detect, monitor, and report. The specific design of these gene expression studies, in which glatiramer acetate-primed splenocytes are re-activated with generic product, is equivalent to a human situation in which a patient is initially treated with Copaxone® and later switched to a generic.

Our analyses also identified specific genes and immune cell types that are upregulated significantly more by Copaxone® than by the “generic” product. In this case, there is a preponderance of evidence suggesting that Copaxone® upregulates FoxP3+ Tregs more

⁵⁹ Zhou, X. *et al.* Expression of matrix metalloproteinase-2 and -14 persists during early resolution of experimental liver fibrosis and might contribute to fibrolysis. *Liver Int.* **24**, 492–501 (2004).

⁶⁰ Sounni, N. E. *et al.* Stromal regulation of vessel stability by MMP14 and TGFbeta. *Dis Model Mech* **3**, 317–332 (2010).

⁶¹ Beppu, L., Anilkumar, A. A., Dohil, R., Broide, D. H. & Aceves, S. S. MMP-14 Is Elevated in Pediatric Subjects with Eosinophilic Esophagitis. *Journal of Allergy and Clinical Immunology* **131**, AB132–AB132 (2013).

⁶² Prêle, C. M., Yao, E., O’Donoghue, R. J. J., Mutsaers, S. E. & Knight, D. A. STAT3: a central mediator of pulmonary fibrosis? *Proc Am Thorac Soc* **9**, 177–182 (2012).

consistently and more effectively than “generic.” We have shown that the expression of FoxP3 itself, genes downstream of FoxP3, other known Treg markers, and Treg specific genes are all enriched from activation by Copaxone® relative to “generic.” This dramatic difference in biological impact on Tregs is certainly of note. It is well established that FoxP3+ Tregs induce beneficial tolerance in MS patients by suppressing harmful myelin reactive T cells,⁶³ so the more variable and reduced Treg induction raises questions about the potential efficacy of the purported generic, especially given recent findings demonstrating Copaxone®’s impact on Tregs⁶⁴ and linking Tregs to clinical response in MS patients.⁶⁵

Our studies also identified specific genes and immune cell types that are upregulated significantly more by the purported “generic” product than by Copaxone®. In this case, the “generic” had a significantly higher impact on cells of the myeloid lineage such as monocytes and macrophages than Copaxone® did. The list of genes with significantly higher expression in “generic” than in Copaxone® includes key monocyte markers such as CD14, is enriched in genes associated with macrophage and monocyte cell types, and is enriched in genes associated with TLR signaling as determined using the molecular signature database.⁶⁶ CD14 activates NF-kappa-B and leads to cytokine secretion and an inflammatory response, and higher levels of soluble CD14 have been observed in MS patients relative to controls (mean values of 4862 ± 663 ng/mL for 20 RRMS patients versus 4213 ± 529 ng/mL for 19 healthy controls, p value 0.002).⁶⁷ The stronger upregulation of monocyte-specific genes warrants further investigation by physicians and regulators, especially given that monocytes are “prominent contributors” to neuroinflammation in MS⁶⁸ and given recent reports that one of Copaxone®’s mechanisms of action involves its impact on monocytes.^{69,70} Given the strong links between monocytes and neuroinflammation, the increased expression of CD14 and other monocyte-related genes with “generic” raises serious concerns about the potential for adverse events and/or decreased efficacy with “generic.”

⁶³ Nylander, A. & Hafler, D. A. Multiple sclerosis. *Journal of Clinical Investigation* **122**, 1180–1188 (2012).

⁶⁴ Hong, J., Li, N., Zhang, X., Zheng, B. & Zhang, J. Z. Induction of CD4+CD25+ regulatory T cells by copolymer-I through activation of transcription factor Foxp3. *Proc Natl Acad Sci U S A* **102**, 6449–6454 (2005).

⁶⁵ Dhib-Jalbut, S., Boppana, S., Valenzuela, R., Khan, O. & Ito, K. Clinical response to glatiramer acetate correlates with an increase in activated and memory CD45RA-Foxp3+CD4+ T-cells. in *ECTRIMS* (2012).

⁶⁶ Subramanian, A. *et al.* (2005).

⁶⁷ Brettschneider, J. *et al.* The macrophage activity marker sCD14 is increased in patients with multiple sclerosis and upregulated by interferon beta-1b. *J. Neuroimmunol.* **133**, 193–197 (2002).

⁶⁸ Bar-Or, A. *et al.* Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. *Brain* **126**, 2738–2749 (2003).

⁶⁹ Burger, D. *et al.* Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1β in human monocytes and multiple sclerosis. *Proceedings of the National Academy of Sciences* **106**, 4355–4359 (2009).

⁷⁰ Carpintero, R. *et al.* Glatiramer acetate triggers PI3K /Akt and MEK/ERK pathways to induce IL-1 receptor antagonist in human monocytes. *Proceedings of the National Academy of Sciences* **107**, 17692–17697 (2010).

There are clear differences in biological impact of Copaxone® and “generic.” Our study design sought to model the situation in which a patient is initially treated with Copaxone®, and later switched to a generic. A variety of other experimental designs could be explored in future studies, including priming *in vivo* with generic and reactivating with generic, then comparing the resulting transcription profiles to those that result from priming *in vivo* with Copaxone® and reactivating with Copaxone®. Such studies may demonstrate even more dramatic differences between Copaxone® and a purported “generic” version. Given the batch-to-batch variability that we identified in the “generic,” such studies should explore priming and reactivating with the same batch of “generic,” as well as priming and reactivating with different batches of “generic.” Further studies could also be conducted in human cell lines or PBMC, and could build upon the previously identified physiochemical differences between Copaxone® and “generic”⁷¹ by assaying for mechanistically relevant immunological processes such as Treg activity, binding affinity to HLA class II molecules, Th1 to Th2 shift, and TCR modulation.

Teva’s experience with TV-5010 provides a dramatic illustration that even small changes in the manufacturing of glatiramer acetate can lead to serious toxicities, and that gene expression studies may predict these toxicities. It is therefore extremely concerning from a patient safety perspective that the purported foreign “generic” shows significant differences in gene expression compared to Copaxone®, particularly since Mylan may be using this foreign-sourced active ingredient in its proposed generic product. In these studies, we found higher variability in gene expression following activation by “generic” compared to Copaxone®, and the significant differences in impact on key biological processes including Tregs and monocytes. These differences raise questions the safety and efficacy of purported “generic” Copaxone® for treatment of MS patients, and suggest that clinical studies are warranted, using appropriate safety and efficacy endpoints to compare generic to Copaxone®.

⁷¹ See Teva’s Second Copaxone Petition, FDA-2009-P-0555, at 24-35 (Nov. 13, 2009) (Exhibit 3).

C. **ACTIVE INGREDIENT SAMENESS: FDA Should Not Approve An ANDA For A Purported Generic Product That Cannot Be Conclusively Demonstrated To Have The Identical Active Ingredient or Ingredients As Copaxone®**

Because Copaxone® is a highly complex mixture of synthetic, nano-sized polypeptides, its 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 discussed below, FDA cannot overcome these scientific and 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. Accordingly, like synthetic versions of Premarin®, FDA should refuse to approve ANDAs for purported generic versions of Copaxone® until the state of the science is adequate to demonstrate active ingredient sameness for this complex mixture of polypeptides.

1. **The “Sameness” Standard**

Pursuant to the FFDCA and applicable FDA regulations, an ANDA applicant for a proposed generic drug must demonstrate, among other things, that its product contains the “same” active ingredient as the RLD.⁷² This requirement plays an essential role in the ANDA approval process because it helps to ensure that any approved generic drug product will be as safe and effective as the RLD upon which it relies for approval. As FDA has explained, “[b]ecause generic drug manufacturers do not have to repeat the clinical studies used to develop the original drug, assurance that generic copies have the same active ingredients as the [RLD] is a *crucial aspect* of the scientific basis for their approval for marketing.”⁷³

By regulation, FDA has defined “same” to mean that the proposed generic drug must have the “identical” active ingredient or ingredients as the RLD.⁷⁴ Despite this categorical language, however, FDA does not require complete chemical identity in all cases.⁷⁵ Rather, FDA typically considers two active ingredients to be “identical” if they meet the same standards of identity, which often are described in the United States Pharmacopeia (“USP”), although FDA can impose additional requirements, if necessary.⁷⁶ The burden of proving sameness falls

⁷² 21 U.S.C. §§ 355(j)(2)(A)(ii), (j)(4)(C); 21 C.F.R. §§ 314.94(a)(5), 314.127(a)(3).

⁷³ FDA Backgrounder on Conjugated Estrogens, p. 1 (May 5, 1997) (emphasis added) (Exhibit 12).

⁷⁴ 21 C.F.R. § 314.92(a)(1).

⁷⁵ For example, different polymorphic forms of an active ingredient may be considered the “same” by FDA in some circumstances. See *Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism*, at 5 (July 2007).

⁷⁶ 57 Fed. Reg. 17958 (April 28, 1992).

squarely on the ANDA applicant,⁷⁷ and FDA is appropriately rigid in putting ANDA applicants to their proof in order to avoid the severe harms that could result from the approval of an alleged generic drug that is not as safe or as effective as the RLD whose underlying clinical studies formed the basis for the purported generic drug's approval.⁷⁸

For most drugs, the determination of active ingredient sameness is not complicated. This is because most drug substances subject to the ANDA approval process, including most small molecule drugs and many therapeutic peptides, have a relatively simple chemical structure that lends itself to physicochemical characterization. Once the structure of a particular molecule has been characterized, an ANDA applicant typically can demonstrate fairly easily using basic analytical tools that the active ingredient in its product is identical to the active ingredient in the RLD. This allows an ANDA applicant to demonstrate directly and unequivocally that two drug products contain the same active ingredient.

For other molecules, however, the chemical identity of the active ingredient in the RLD has not been, and in some cases cannot be, fully characterized using physicochemical analytical tools, and therefore is not known.⁷⁹ These drugs, which typically include proteins and protein-like polypeptides, usually are substantially larger, more structurally complex, may exhibit significant secondary or tertiary structure, may consist of mixtures of indistinct active and inactive entities, and may exhibit minor or major degrees of structural batch-to-batch variability. Because the active ingredient or ingredients in these products cannot be characterized and, in fact, may not be known, it may be difficult or, in some cases, impossible for the manufacturer of a purported generic product to demonstrate that the active ingredient in its product is "identical" to the active ingredient in the RLD.

Over time, FDA has adopted a case-by-case approach to evaluating active ingredient sameness for these types of complex drug products that cannot be fully characterized.⁸⁰ In some cases, FDA has determined that a particular molecule or active ingredient is so complex that it is

⁷⁷ 21 U.S.C. § 355(j)(2)(A)(ii); 21 C.F.R. § 314.127(a)(13); *see also Edison Pharmaceutical Co. v. FDA*, 513 F.2d 1063, 1065 (D.D.C. 1975).

⁷⁸ Memorandum from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research ("CDER") to Douglas L. Sporn, Director, Office of Generic Drugs, Regarding Approvability of Synthetic Generic Version of Premarin, at 1 (May 5, 1997) ("Premarin Decision") (Exhibit 13).

⁷⁹ Premarin Decision at 6; *see also* Letter from Steven K. Galson, M.D., M.P.H., Director, CDER Re: Docket No. 2005P-0134/CP1, at 9 (Oct. 25, 2005) (hereinafter "Hyaluronidase Decision") ("Because hyaluronidase products have never been fully characterized with respect to the[ir] chemical structure[s], it is not possible to know whether one hyaluronidase product is the same as another."); FDA Guidance for Industry, Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs, at 2 (Apr. 2006) (hereinafter "Exocrine Decision") ("Because of the complexity of pancreatic extract products, it is unlikely that currently available physicochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same.") (Exhibit 14).

⁸⁰ Letter from Janet Woodcock, M.D., Director, CDER, Regarding Docket No. FDA-2005-P-0367, at 3 (Nov. 17, 2008) ("Salmon Calcitonin Decision").

not possible using existing scientific technology for an ANDA applicant to demonstrate that its active ingredient is identical to the RLD. As FDA has explained, the ANDA pathway is available only where “the state of the science is adequate to demonstrate that the active ingredient [in a proposed generic drug] is the same as the active ingredient of the RLD.”⁸¹ For example, FDA has taken the position that protein molecules typically cannot be approved via the ANDA pathway:

Because of the complexity of protein molecules and limitations of current analytical methods, it would be difficult for manufacturers of proposed protein products to demonstrate that the active ingredient in their proposed product is identical to the active ingredient in an already approved product. Therefore, the [ANDA] approval pathway, which is predicated on a finding of the “same active ingredient, will not ordinarily be available for more structurally complex molecules.⁸²

Likewise, FDA has refused to accept ANDAs for pancreatic extract products because, due to their complexity, “it is unlikely that currently available physicochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same.”⁸³

In other cases, however, FDA has permitted ANDA applicants for complex products to rely upon “overlapping criteria” to satisfy the statutory “same active ingredient” requirement. In essence, this approach allows ANDA applicants to rely upon a variety of surrogate markers to prove indirectly what they cannot demonstrate directly through physicochemical testing. Even then, however, substantial certainty regarding the active ingredient’s composition is required.⁸⁴ And because any residual uncertainty or differences between the respective products’ active ingredients create a risk that the follow-on product will not be as safe or effective as the RLD, FDA has further required a clear understanding of the RLD’s mechanisms of action and relied on knowledge gained from past clinical experience to rule out the possibility that such differences are clinically relevant.⁸⁵

⁸¹ Letter to Sarfaraz K. Niazi, Ph.D., FDA-2009-P-0004, at 4 (Feb. 24, 2012) (Exhibit 15).

⁸² *Id.*

⁸³ Exocrine Decision, at 2 (Exhibit 14).

⁸⁴ Letter from Janet Woodcock, M.D., Director of CDER, Regarding Docket No. 92-0487, at 10-13 (June 17, 1997) (hereinafter “Menotropins Decision”) (Exhibit 16); *see also* Premarin Decision at 7-17.

⁸⁵ Testimony by Janet Woodcock, M.D., Before the Subcommittee on Health of the Committee on Energy and Commerce, House of Representatives (Serial No. 110-40), 33 (May 2, 2007) (hereinafter “Woodcock Testimony”) (“When the mechanism of action is well understood and there is a significant amount of clinical experience with a product, it may be easier to make a scientific assessment of the ability to rely on conclusions about safety and efficacy from a prior application.”); *see also* Menotropins Decision at 12-13 (Exhibit 16).

For example, the Agency recently determined that it would be possible to demonstrate sameness in the context of generic enoxaparin products despite the fact that the RLD (Lovenox®) was not fully characterized.⁸⁶ It did so by developing and applying five criteria, each of which captured different aspects of the generic active ingredient's sameness. More specifically, the Agency required generic applicants to provide substantial, though not complete, demonstrations of physicochemical sameness; sameness of source material and the key manufacturing method; and sameness in effect as measured by biological, biochemical, and pharmacodynamic activity. Together, the satisfaction of these criteria provided “overlapping evidence” demonstrating the generic active ingredient's sameness to the brand manufacturer's product.

The Agency was able to take advantage of its long experience with similar products in gauging whether proposed generic enoxaparin products are equivalent to Lovenox®. To that end, the Agency had extensive experience with both heparin (the source material for enoxaparin), and various members of the low molecular weight heparin class of drugs (of which enoxaparin is a member).⁸⁷ In addition, the Agency had an excellent understanding of enoxaparin's mechanism of action, which enabled it both to describe the pharmacological activity of the class and develop a multifaceted approach to proving sameness that “worked” for that unique product.⁸⁸ And the Agency was able to draw from its accumulated knowledge of the depolymerization process in the context of low-molecular-weight molecules (which presumably does not cause any rearrangement in the sequences),⁸⁹ and to rely on the availability of clinically relevant pharmacological markers of efficacy and safety in animals and in humans to assess and rule out the risk of adverse immune responses associated with product impurities.⁹⁰ Against this backdrop, and in light of the Agency's extensive experience with the class of drug at issue, the Agency's five sameness criteria thus provided reasonable assurance that the pharmaceutical composition and therapeutic activity of generic enoxaparin and Lovenox® would be equivalent even though the composition of Lovenox® is not fully elucidated.

To Teva's knowledge, FDA has used this “overlapping criteria” approach only when both the proposed, complex generic product and the RLD are *naturally-sourced* (rather than synthetic). In its Lovenox® decision, for instance, FDA was careful to clarify that the five overlapping criteria could be used only for purposes of approving generic enoxaparin products that, like Lovenox®, are “*naturally sourced*.⁹¹ Likewise, in its decision to approve generic

⁸⁶ Letter to Peter O. Safir and Scott L. Cunningham, FDA Docket No. FDA-2003-P-0273, at 3 (July 23, 2010) (hereinafter “Enoxaparin Decision”) (Exhibit 17).

⁸⁷ *Id.* at 5-6 (“Currently, there are eleven approved NDAs and six approved ANDAs for heparin sodium injection, which are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).”).

⁸⁸ *Id.* at 3 n.8.

⁸⁹ *Id.* at 13.

⁹⁰ *Id.* at 41-42.

⁹¹ *Id.*, at 3 (emphasis added).

menotropins, a naturally-sourced drug extracted from human post-menopausal urine, FDA stated that, to be considered to have the same active ingredient as the RLD, a generic product must have the same protein backbone and amino acid sequence, which could be “assured by using *the same natural source material.*”⁹²

This reliance upon natural sourcing as a surrogate marker for “sameness” makes sense in the context of complex drug products: if one does not know the exact constituents that comprise a complex mixture like enoxaparin or menotropins, one way to ensure that a purported generic product nevertheless contains all of those same constituents is to use the same natural source material, which can be *presumed* to contain those same constituents (including, for example, the same amino acid sequences). Although additional testing, such as biochemical and biological assays and pharmacodynamic testing, may be necessary to confirm a finding of sameness by showing that the active ingredient in the generic product behaves the same way as the active ingredient in the RLD and to rule out safety concerns, these additional tests are, at bottom, corroborative.

If either the RLD or the proposed, complex generic product is *synthetic*, however, this critically important surrogate marker is no longer available, and its absence may preclude a finding of active ingredient sameness. Indeed, in the enoxaparin decision, FDA stated that all five factors – including the use of the same natural source material – were required to support a finding of active ingredient sameness. Presumably, then, if either Lovenox® or a proposed generic product were synthetic, FDA would have refused to approve the ANDA on the basis that active ingredient sameness could not be established.

This, in fact, is precisely the conclusion FDA reached in its seminal decision regarding generic versions of Premarin® (conjugated estrogens), which highlights and explains the important distinction between naturally-sourced and synthetic products. Premarin is a complex mixture of various estrogens derived from the urine of pregnant mares. As with many complex drugs, Premarin’s active ingredients had neither “been adequately characterized” nor “definitively identified” and the specific features of the drug that made “clinically meaningful contributions to the drug’s therapeutic effects” were at that time unknown.⁹³ The Agency thus held that it could not make a finding of active ingredient sameness for *synthetic* versions of Premarin® because the Premarin® active ingredient had not been adequately characterized.⁹⁴ The Agency instead required synthetic conjugated estrogen products to seek approval via the 505(b)(2) pathway.

By contrast, FDA indicated that it would be willing to approve an ANDA for a *naturally-sourced* generic version of Premarin®. The Agency explained its reasoning as follows:

⁹² Menotropins Decision at 12 (emphasis added) (Exhibit 16).

⁹³ Premarin Decision at 1-2 (Exhibit 13).

⁹⁴ *Id.* at 16-17.

Despite the fact that at this time Premarin is not adequately characterized, the Agency could approve generic copies of Premarin *that originate from the same natural source material (pregnant mares' urine)* before the active ingredients are defined, provided that detailed chemical composition of the product is known. This is because Premarin is manufactured and controlled using certain methods, and *there could be confidence that generic copies using the same source materials and controlled in the same manner, based on the known composition of Premarin, would have the same level of assurance that the same active ingredients are in the generic product as are in Premarin.*⁹⁵

In other words, the Agency concluded that although it could not make a finding of active ingredient sameness for a *synthetic* version of Premarin given the gaps in knowledge regarding the identity and structure of the relevant active ingredients, it could do so for a *naturally-sourced* version that used the same natural starting material and critical manufacturing steps.

The above Agency decisions thus reflect the scientific understanding that it typically is not possible to “reverse engineer” a complex drug product that cannot be fully characterized, particularly a heterogeneous mixture like Premarin or enoxaparin, or to re-create a generic version synthetically in the laboratory. In such cases, if both the proposed generic product and the RLD are naturally-sourced, FDA may be able to rely upon this fact to support a finding of active ingredient sameness, provided the generic product uses the same natural source material as the RLD. This option, however, is not available if either the RLD or the proposed generic product is *synthetic*. Moreover, even if two products are shown to use the same, natural source material, they often will need to be manufactured using the same critical process steps. Even then, additional physicochemical, biological, biochemical, pharmacokinetic, pharmacodynamic and immunogenicity testing may be necessary to corroborate active ingredient sameness given other differences in the manufacturing process.

2. Lack of Adequate Characterization of Copaxone® Precludes A Determination of Sameness

Because glatiramer acetate’s unique mixture of protein-like polypeptides has not been fully characterized, and because the specific polypeptide sequences and structures that generate glatiramer acetate’s proven therapeutic effects remain unidentified, it is not currently possible for an ANDA applicant to establish that the active ingredient in a proposed generic version of Copaxone® is “the same” as the glatiramer acetate in Copaxone®.

There are a number of reasons why the chemical composition of Copaxone® is so difficult to determine. First, the protein-like polypeptides that comprise glatiramer acetate are quite large and complex, ranging in average molecular weight from 5,000 to 9,000 daltons, with some as large as 20,000 daltons. Many of these polypeptides are composed of between 20 and 200 amino acids, with many (so far as their structure is known) evidencing the sort of higher order structure typically observed in proteins. Consequently, characterizing even a single, large

⁹⁵ *Id.* at 17 (emphasis added).

polypeptide (assuming it could be isolated) would present technological difficulties similar to characterizing a protein. An ANDA applicant would need to demonstrate that its proposed generic product has the same (1) primary structure (i.e., amino acid sequence), (2) amino acid modifications (e.g., terminal ends), and (3) higher order structure as an individual glatiramer acetate molecule. FDA, however, has indicated that because of the limitations of current analytical technology it usually will be not possible to demonstrate that one protein product is structurally identical to a RLD across these parameters.⁹⁶

Glatiramer acetate, of course, is not a single molecular entity like acetaminophen or, even, salmon calcitonin, but rather is composed of perhaps millions of distinct molecular entities. Indeed, it has been estimated that glatiramer acetate likely contains more than 10^{12} different polypeptides and theoretically could contain more than 10^{29} possible primary polypeptide sequences.⁹⁷ For comparison purposes, there are fewer stars in the sky.⁹⁸ This molecular diversity presents significant, additional scientific barriers to the full characterization of glatiramer acetate and thus a demonstration of active ingredient sameness. In addition to demonstrating sameness of primary structure, amino acid modifications, and higher order structure for each of the potentially millions of individual polypeptides in the glatiramer acetate mixture, ANDA applicants would need to demonstrate that their proposed generic active ingredient is *compositionally* identical to Copaxone®, i.e., that it contains the same components in the same quantities as the RLD.

Given the limitations of current analytical technology, however, this task simply is not feasible. Indeed, merely separating and isolating individual molecules from this vast number of polypeptides to determine precisely how many are present and in precisely what quantities would be an impossible task. Many of the polypeptides in Copaxone® appear to be similar in size, charge, and hydrophobicity. Even state-of-the-art separation methods, including multi-dimensional separation methods combined with mass spectrometry, do not have the ability to discriminate, separate, or quantitate each and every one of the peptide sequences in such a complex mixture.⁹⁹ And even if the individual polypeptides could be separated, determining the precise sequence of each polypeptide's amino acids and the higher-order structural features of each one of these polypeptides, as discussed above, would be immensely difficult.

In addition, recent testing has revealed that, far from being a random collection of polypeptides, glatiramer acetate is in fact composed of two distinct populations of stable,

⁹⁶ Letter to Sarfaraz K. Niazi, Ph.D., FDA-2009-P-0004, at 4 (Feb. 24, 2012) (Exhibit 15); *see also* Woodcock Testimony, at 32 (“Although the primary sequence of a separated polypeptide/protein can usually be determined, “[C]onclusive analysis of other aspects of a protein’s structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself.””).

⁹⁷ Krull and Cohen. Letter. 2009 (Exhibit 8).

⁹⁸ CNN, Star survey reaches 70 sextillion, July 23, 2003 (last visited Nov. 6, 2009), available at <http://www.cnn.com/2003/TECH/space/07/22/stars.survey/>.

⁹⁹ Varkony et al. 2009. (Exhibit 11).

glatiramer acetate nanoparticles dispersed in the aqueous mannitol phase.¹⁰⁰ The first population is comprised of spherical nanoparticles with sizes of 4±2 nm. The second population is comprised of string-like polypeptides with lengths of ~60 to 300 nm. The detection of two distinct populations of particles 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. However, in order to be regarded as having the same active ingredient as Copaxone®, an ANDA applicant would need to demonstrate that its generic product contains the same unique micro-structure of stable particulate populations as Copaxone®.

The scientific challenges associated with establishing active ingredient sameness are compounded by the fact that the specific molecule or molecules responsible for glatiramer acetate's clinical effects are unknown. Consequently, like Premarin, it currently is not possible for an ANDA applicant to identify which of the components in glatiramer acetate are "active ingredients" and which are merely inert constituents. In order to identify the particular sequences and structures of the polypeptides in glatiramer acetate responsible for Copaxone®'s proven therapeutic benefits, one would need to synthesize a sufficient quantity of each polypeptide and screen it for activity—presuming it would be possible to screen the individual polypeptides for potential therapeutic activity. Yet even that activity would not be completely informative, since studies of Copaxone® indicate that no single molecular entity accounts completely for the drug's overall level of activity¹⁰¹ and since the product's therapeutic efficacy may vary from patient to patient, based on differences in the patients' genetic backgrounds and antigen exposures. As a result, there could be many patient-dependent active polypeptide sequences in glatiramer acetate. It is even possible that every polypeptide sequence in the glatiramer acetate mixture makes a therapeutically relevant contribution by affecting different components of the immune system that collectively produce the clinical effect.

Even if the above scientific hurdles could be overcome, and (at least for now) they cannot, additional hurdles remain. In particular, a proposed generic product manufactured by a different process undoubtedly will have structural and compositional differences from Copaxone®, some of which may be impossible to detect by current analytical methods. In this case, however, there is no clinical trial experience—and no published literature—with a previously approved Copaxone® variant that would allow the Agency to reliably determine that potential differences are clinically insignificant. To the contrary, and as discussed in Teva's prior Petitions, other purported generic versions of glatiramer acetate have failed multiple chemical, biological and immunological tests used to assure the consistency of Copaxone®'s bulk properties—conclusively demonstrating that these products are not even similar (much less identical) to Copaxone®'s glatiramer acetate at the molecular level.¹⁰²

¹⁰⁰ See Teva's Fifth Copaxone Petition, FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 1).

¹⁰¹ Data on File. Teva Pharmaceuticals Inc.

¹⁰² See Teva's Second Copaxone Petition, FDA-2009-P-0555, at 24-35 (Nov. 13, 20019) (Exhibit 3).

Moreover, when similarities in bulk physicochemical properties are found among glatiramoids, they do not guarantee similarities in biological or immunological activity—and vice versa. Indeed, the new gene expression data discussed above underscores this point. Despite bulk physicochemical similarities between Copaxone® and a purported, foreign generic version in broad parameters such as size distribution of the polypeptide components and the molar ratio of the amino acids, the products exhibit significant differences when they are tested using more sensitive chemical or biological analyses. These parameters have an impact on key biological processes, particularly immune responses associated with regulatory T cells and neuroinflammation. These differences in expression patterns could signal important differences in the safety, immunogenicity and/or efficacy between the products.

Finally, although Teva uses several analytical tests to ensure batch-to-batch consistency, these proprietary analytical methods are incapable of determining whether an ANDA's proposed active ingredient is the same as the glatiramer acetate in Copaxone®.¹⁰³ This is because they only provide information on Copaxone®'s bulk properties and do not elucidate the specific sequences and structures that constitute the active ingredient. Indeed, as FDA has long cautioned, “[t]he tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to characterize it.”¹⁰⁴ Even assuming that a different manufacturer was capable of making a product that met all of Teva's rigid, proprietary specifications with respect to the drug's bulk properties, the actual product could still vary significantly at the molecular level from the Copaxone® produced by Teva.¹⁰⁵

In sum, until the chemical composition of Copaxone®'s glatiramer acetate has been fully characterized, or unless enough is learned about the features of Copaxone® to both identify which of its features generate its therapeutic effects and rule out the possibility that other

¹⁰³. These controls include, but are not limited to: (1) measures of molecular weight distribution; (2) identification of components and impurities through chromatographic profiles; (3) peptide mapping (by reversed phase chromatography after enzymatic hydrolysis) which can discriminate between batches made using different manufacturing processes; and (4) analyses of polypeptide primary, secondary, and tertiary structures using a variety of analytical techniques. Additional (non-routine) tests include assays to detect characteristic order of amino acids in the N-terminal region of peptides (which have been demonstrated consistently in batches of product dating back to 1989) and fractionation studies comparing the chemical, biological, and immunological properties of fractions of glatiramer acetate to those of the whole mixture. Immunochemical and biological tests are also performed to demonstrate consistency of antigenic determinants in different batches, and correlations among the immunoreactivity, chemical properties, an *in vitro* biological activity and potency of the drug.

¹⁰⁴. FDA/ICH Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, 8-9 (June 2005) (hereinafter “Q5 Guidance”). Although this Guidance was written regarding biotechnology products, the complexity of the process used to make glatiramer acetate, and the resulting complex polypeptide product, makes the Guidance relevant to this synthetic product.

¹⁰⁵. Q5 Guidance, 3 (“The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar . . .”)

variances undermine the drug's proven clinical safety and efficacy profile, FDA cannot approve an ANDA with Copaxone® as the RLD because sameness cannot be demonstrated.

3. The “Overlapping Criteria” Approach Used For Enoxaparin Is Not Feasible For ANDAs Referencing Copaxone®

Given the fact that glatiramer acetate cannot be adequately characterized, the Agency has indicated that it may be considering the possibility of developing “overlapping” criteria for purposes of establishing sameness between Copaxone® and a purported generic glatiramer acetate product, as it did with enoxaparin.¹⁰⁶ Teva fully agrees with the Agency’s position that the sameness of complex drugs and their putative generic equivalents must be evaluated on a case-by-case basis. Although an “overlapping criteria” approach was possible and appropriate for naturally-sourced products like enoxaparin and menotropins, Teva respectfully submits that there are no “overlapping criteria” capable of demonstrating active ingredient “sameness” for purported generic versions of Copaxone®. This is because:

- glatiramer acetate is synthetic rather than naturally-sourced and is manufactured using a carefully-controlled, proprietary process;
- glatiramer acetate is orders of magnitude more complex than enoxaparin or any other NBCD to which the “overlapping criteria” approach has been applied;
- glatiramer acetate’s mechanisms of action are not well understood; and
- there are no clinically relevant bioassays or validated biomarkers to assess biological activity or the safety or effectiveness of the product.

Accordingly, ***none*** of the five criteria that provided reasonable assurance of sameness between generic enoxaparin and Lovenox® are viable in the Copaxone® context, and Teva is not aware of different or additional criteria that would provide such assurance.¹⁰⁷ Consequently, while an “overlapping criteria” approach might be able demonstrate that the active ingredient in a purported generic product is *similar* to glatiramer acetate, it cannot demonstrate that the active ingredients are *identical*.

First, and perhaps most significantly, Copaxone® is a *synthetic* product that is manufactured from a proprietary source material to which no other generic applicant has access. Consequently, FDA cannot rely upon a generic’s use of the “same source material” as a

¹⁰⁶ See, e.g., FDA Response to Fourth Copaxone Petition, FDA-2009-P-0555, at 10 (“For instance, given the complexity of Copaxone, we may require that any ANDA sponsor demonstrate active ingredient sameness through a multi-criteria test or series of tests, each criterion of which captures different aspects of the active ingredient’s ‘sameness,’ and which together would provide overlapping evidence by which an ANDA applicant could demonstrate active ingredient sameness within the meaning of the Act and FDA regulations.”) (Exhibit 6).

¹⁰⁷ Additional information explaining why the five criteria used to support the development of generic enoxaparin are not applicable to glatiramer acetate is set forth in Teva’s Third Copaxone Petition, FDA-2010-P-0642 (Dec. 10, 2010) (Exhibit 4).

surrogate marker of sameness. This, in and of itself, should preclude any determination of sameness. It is important to clarify that the relevant “source material” in this case is not the amino acid building blocks (L-glutamic acid, L-alanine, L-lysine, and L-tyrosine), which generally are available for bulk purchase, but rather the high-molecular weight, protected polypeptide mixture created by Teva’s proprietary polymerization process. It is this “source material,” rather than the bulk amino acid building blocks, that ultimately determines the primary structure (amino acid sequences) of the polypeptides that comprise the glatiramer acetate active ingredient. Teva’s protected polypeptide source material thus performs the same function for Copaxone® that heparin performs for Lovenox®.

Unlike heparin, however, Teva’s source material is completely proprietary and not available for use by third-party manufacturers. Thus, unless a generic company could replicate Teva’s proprietary manufacturing process – despite the fact that third parties have no direct access to or knowledge of it –ANDA applicants could not obtain and use the “same source material” as Copaxone®. This is because the primary structure and identity of the high-molecular weight, protected polypeptide mixture that forms the Copaxone® “source material” are highly dependent upon both the ratios and purity of the starting materials and upon polymerization reaction conditions, which are carefully controlled by Teva. Even slight changes in the process for polymerizing the glatiramer acetate source material—for example, differences in the quality of the starting monomers or in the precise ratio of monomers to the initiator, neither of which is standardized in a USP monograph—yield differences in the arrangement of amino acid sequences in the source material (*i.e.*, its primary structure). Yet this intermediate production process yields consistent non-random amino acid sequences in the source material *only* when performed under stringent and strictly controlled manufacturing processes; even minor differences in inputs produce significant deviations in the source material outputs yielded by the solution polymerization process.

Similar problems make it difficult for a generic applicant to use the same downstream production steps employed for Copaxone®. In the context of Copaxone®, the de-protection/depolymerization process applied to the glatiramer acetate source material is highly sensitive to reaction conditions. Because there are no analytical methods that can completely characterize Copaxone®, Teva has rigorously maintained and not altered the only production method proven to provide a safe and effective drug product. Even if it were possible for a generic applicant to follow Teva’s proprietary process to the letter, applying that process to a slightly different source material would yield a complex mixture of polypeptides with primary structures that are completely different from those that comprise glatiramer acetate. Moreover, any slight changes in the reaction process would amplify the difference by yielding a different distribution of the polypeptide chains. Accordingly, and in direct contrast to enoxaparin, it is not possible for a generic applicant using a different manufacturing process to reliably demonstrate that it uses the “same source material” or critical manufacturing steps as Copaxone®. And in the absence of this showing, as explained in the Premarin decision, there can be no assurance that any synthetic generic product contains the identical active ingredient or ingredients as Copaxone®.

Second, glatiramer acetate is orders of magnitude more complex than enoxaparin, both structurally and compositionally. Indeed, FDA has determined that “[t]he structural

characteristics of enoxaparin required for activity are much less complex and more stable than those of most proteins” and that “no significant higher order structure [i.e., secondary or tertiary three-dimensional structure] has been found” for enoxaparin.¹⁰⁸ By contrast, many of the polypeptides in glatiramer acetate exhibit significant higher order structure and have a structural complexity akin to that of many proteins.¹⁰⁹ Moreover, although both glatiramer acetate and enoxaparin are composed of complex, heterogeneous mixtures, the former is far more complex than the latter in terms of both the possible number of amino acid sequences on each polypeptide strand in the mixture and of the number of combinations of active sequences (“epitopes”) in the mixture. Thus, while it has been estimated that any of $>10^{29}$ different potential polypeptide sequences could be found in Copaxone®,¹¹⁰ similar estimates indicate that there are no more than 1.6×10^{12} possible sequences in enoxaparin¹¹¹—meaning that Copaxone® and enoxaparin belong to completely distinct and separate categories of molecular entities in terms of their complexity.

Moreover, the less complex composition of enoxaparin has enabled the isolation of many pure components that can be fully characterized by comparing them to an authentic synthetic reference. This approach is not, however, remotely feasible for glatiramer acetate because none of the components of glatiramer acetate are present in sufficient quantity to allow its isolation, identification, and characterization. In the best case scenario, only fractions of the glatiramer acetate mixture can be separated based on broad physicochemical parameters, including size, hydrophobicity, and charge, using size exclusion chromatography, reverse-phase liquid chromatography, and ion-exchange chromatography.¹¹² Each of these fractions, however, contains many thousands of different polypeptides, and the bulk properties of each of these broad fractions in turn differs significantly from every other fraction (as well as from the unfractionated glatiramer acetate as a whole) along multiple tested parameters.¹¹³ Accordingly, any comparison of broad physicochemical characteristics between Copaxone® and a purported generic product will be far less informative – and thus far less supportive of active ingredient sameness – than a similar comparison between Lovenox® and generic enoxaparin products.

Third, the mechanisms by which glatiramer acetate exerts its therapeutic effects in MS are not fully elucidated despite extensive research by Teva and many other research laboratories over many years. Consequently, there are no reliable, accurate, reproducible, well-established,

¹⁰⁸ FDA Memorandum in Opposition to Plaintiff’s Motion for a Temporary Restraining Order and a Preliminary Injunction, Civil Action No. 10-1255, at 33 (Aug. 4, 2010) (quoting from an internal FDA memorandum from Dr. Keith Webber, Deputy Director of the Office of Pharmaceutical Science) (Exhibit 18).

¹⁰⁹ Data on File, Teva Pharmaceutical Industries, Ltd.

¹¹⁰ Krull and Cohen. Letter. 2009 (Exhibit 8).

¹¹¹ Data on file, Teva Pharmaceutical Industries, Ltd.

¹¹² See Teva’s Second Copaxone Petition, FDA-2009-P-0555, at 10-13 (Nov. 13, 2009) (Exhibit 3).

¹¹³ Data on file, Teva Pharmaceutical Industries, Inc.

or testable biological or biochemical markers of Copaxone®'s therapeutic activity in reducing the frequency of clinical relapse in MS patients. This is in direct contrast to enoxaparin, for which established *in vitro* measures of activated partial thromboplastin time (aPTT) and heptest prolongation time provide relevant markers of the product's anticoagulant activity.¹¹⁴

Although multiple *in vitro* biological assays have been developed for glatiramer acetate over the years that have helped demonstrate the drug's immunomodulatory effects on different immune cells, these assays cannot reliably be used to support a determination of pharmaceutical equivalence because glatiramoids that are demonstrably non-equivalent to glatiramer acetate can and often do yield identical results to Copaxone® in many of these tests. At bottom, the use of *in vitro* biological and biochemical assays is not likely to guarantee similar effects in other biological systems, because different sequences in the glatiramer acetate mixture appear to be responsible for different biological outcomes in different systems. While Teva maintains that it is important to evaluate a generic glatiramer acetate product using *in vitro* biological and biochemical assays, these tests simply cannot provide proof of sameness between a putative generic product and Copaxone® in the absence of established, validated biomarkers of Copaxone®'s clinical efficacy.

Finally, there are no well-established, validated pharmacodynamic markers to account for the clinical efficacy of glatiramer acetate. FDA's enoxaparin response required generic applicants to demonstrate the equivalence of their product's *in vivo* pharmacodynamic profile to Lovenox®.¹¹⁵ That approach worked for enoxaparin because it is well established that different FDA-approved low molecular weight heparin products have different pharmacodynamic profiles, based on anti-Xa and anti-IIa profiles *in vivo*. Because there are no similar pharmacodynamic markers for glatiramer acetate, comparable pharmacodynamic characteristics between generic glatiramer acetate and the RLD would not demonstrate, or even support, active ingredient sameness.

In the absence of any criteria that could conclusively demonstrate that a purported generic product has the identical active ingredient or constituents as Copaxone® – and particularly given Copaxone®'s status as a *synthetic* drug product – the most an ANDA applicant could achieve by relying upon “overlapping criteria” would be a demonstration that its proposed generic product is *similar* to glatiramer acetate. Even a finding that the generic product is *highly similar* to glatiramer acetate, however, would not satisfy the statutory and regulatory requirements that the two active ingredients must be the same, i.e., identical.

On the contrary, Congress adopted the “highly similar” standard for biosimilar biological products, rather than the “sameness” standard used for non-biological generic drugs, because it recognized that it would be impossible for an applicant to show that a follow-on biological product contained the identical active ingredient as the innovator product due to the complexity of biological products. *See* 42 U.S.C. § 262(k)(2)(A)(i)(I)(aa). This statutory provision indicates

¹¹⁴ Enoxaparin Decision, at 21 (Exhibit 17).

¹¹⁵ *Id.* at 22.

that the “highly similar” and “sameness” standards are different and that a determination of active ingredient “sameness” in the context of the FFDCA, in fact, requires a higher showing than merely that two products are *highly similar*. Indeed, FDA has specifically recognized that, even in the 505(b)(2) context, “a finding of *similarity* . . . does not imply a finding of *sameness* as that term is used in section 505(j) of the Act.”¹¹⁶

Based upon the above, Copaxone® thus is more like a biological product regulated under the Public Health Service Act – or one of the other NBCDs for which FDA has refused to approve ANDAs, such as synthetic versions of Premarin® and pancreatic extract products – than it is to peptide products that can be adequately characterized by physicochemical testing alone (e.g., salmon calcitonin) or naturally-sourced products for which FDA has applied “overlapping criteria” to establish active ingredient sameness (e.g., enoxaparin, menotropins, heparin). Because of the extreme complexity of these protein and NBCD products and the limitations of current analytical technologies, it is not possible to definitively characterize the composition or structure of the relevant active ingredients or demonstrate more than that one NBCD’s active ingredient is highly similar to another’s – even using “overlapping criteria.” Accordingly, FDA should treat Copaxone® in the same way it treats NBCDs like synthetic versions of Premarin® and refuse to approve any ANDA that seeks to rely upon “overlapping criteria” of sameness. As discussed above, no such criteria exist that can conclusively demonstrate that the active ingredient in a purported generic product is *identical* to the glatiramer acetate in Copaxone®.

D. IMMUNOGENICITY: 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

1. Comparative Clinical Testing Must Include Endpoints Examining the Effect of a Generic Product on Immune Function and Immunogenicity

Copaxone® is a highly immunogenic mixture of uncharacterized polypeptides intended for chronic use in a patient population suffering from a serious autoimmune disease (i.e., RRMS). Given this combination of factors, the risk of immunogenicity for follow-on glatiramoids is particularly high. Because immunogenicity is notoriously unpredictable, a purported generic version of glatiramer acetate produced by a different manufacturing process and using a different starting material could have significant and unforeseeable differences from Copaxone® in its immunological mechanisms, raising major safety and efficacy concerns. Accordingly, FDA should require ANDA applicants to conduct non-clinical and clinical immunogenicity studies *before approval* demonstrating that the risk of an untoward immune response is not greater for a proposed generic product than for Copaxone®.

There are several factors that create a particularly high risk of immunogenicity for purported generic versions of Copaxone®. First, *glatiramer acetate is an immunomodulator*. In other words, the drug is intended to achieve its therapeutic effects by interacting with and

¹¹⁶ FDA Response to Omnitrope Petition, Docket No. 2004P-0231, at 9 n. 23 (May 30, 2006).

modulating a patient's immune system over an extended period of time. For this reason, Copaxone®'s package insert warns that chronic use has the potential to alter healthy immune function as well as induce pathogenic immune mechanisms, including serious, life-threatening adverse reactions.¹¹⁷ Because Copaxone® acts as an antigen-based therapeutic vaccine, the development of anti-drug antibodies occurs in all treated patients and animals.¹¹⁸ Although anti-drug antibodies are mainly of the IgG class, there have been rare but serious reports of patients developing anti-drug IgE antibodies that have been associated with late-occurring anaphylactic reactions that can arise up to one year after beginning treatment, with no symptomology beforehand to signal hypersensitivity. As a result, Copaxone®'s package insert specifically warns about the potential risk of anaphylaxis.¹¹⁹

Second, the intended patient population for generic glatiramer acetate products is at particularly high risk for developing adverse immunogenic reactions. Among the many patient-related factors that can influence drug immunogenicity are immune status, disease, and previous exposure to a drug. According to a recent FDA guidance document, patients with an activated immune system caused by, *inter alia*, autoimmune disease, may have "augmented responses" to immunogenic drugs.¹²⁰ As noted above, RRMS is believed to be caused by autoimmune attack on self myelin and non-myelin antigens. Moreover, because glatiramer acetate is a chronic treatment, patients who are administered a purported generic product likely will have been previously exposed to Copaxone®, which may result in sensitization, thus predisposing patients to adverse clinical consequences upon exposure to a purported generic glatiramoid.

Third, glatiramer acetate is intended to be administered subcutaneously, a route of administration known to increase the risk of sensitization. Indeed, FDA has explained that, in general, "intradermal, subcutaneous, and inhalational routes of administration are associated with increased immunogenicity compared to the intramuscular and intravenous (IV) routes."¹²¹

The fact that Copaxone® is a synthetic drug does not significantly mitigate the risks of immunogenicity. On the contrary, immunogenicity is notoriously difficult to predict and is associated with both naturally-sourced and synthetic complex drug products. The recent recall of Omontys (peginesatide acetate) clearly illustrates this point. Omontys is a synthetic peptide product and NBCD that was approved in 2012 via a New Drug Application ("NDA"). Less than a year later, on February 2013, the manufacturer voluntarily recalled all lots of the drug to the user level as a result of new postmarketing reports regarding serious hypersensitivity reactions,

¹¹⁷ Copaxone® prescribing information, § 5.4 (Exhibit 7).

¹¹⁸ Brenner et al (2001).

¹¹⁹ Copaxone® prescribing information, § 5.4 (Exhibit 7).

¹²⁰ [Draft] *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products*, at 8-9 (Feb. 2013) (hereinafter "Draft Immunogenicity Guidance") (Exhibit 19).

¹²¹ Draft Immunogenicity Guidance , at 9.

including life-threatening and fatal anaphylaxis.¹²² At the time, fatal reactions were reported in approximately 0.02% of patients following the first dose of intravenous administration. Although clinical studies were conducted prior to approval of Omontys, they do not appear to have been designed to specifically assess the immunogenicity risks of Omontys (including when switched with other erythropoiesis stimulating agents) and, in fact, did not identify any such immunogenicity risks.¹²³ The risks of life-threatening anaphylaxis only became obvious following introduction of the product into widespread use in a high-risk patient population.

For proposed generic glatiramer acetate products, the risk of unwanted immunogenicity likewise is significant. A purported generic product manufactured by a different process could have significant and unpredictable differences from Copaxone® in its immunological mechanisms, raising major safety and efficacy concerns. Indeed, as discussed in detail above, the active ingredient in proposed generic products almost certainly will differ from the glatiramer acetate in Copaxone® in structure and composition because it will be made using a different source material and manufacturing process from that used by Teva.

Even if a generic glatiramer acetate product has very similar bulk properties to Copaxone® and is produced by a method that is basically similar to the Teva process, the efficacy, safety, and immunogenicity of the generic product can still differ markedly from those of Copaxone®.¹²⁴ Several product-related factors can influence the immunogenicity profile. Even minute or inadvertent deviations from the validated Copaxone® synthesis protocol can result in unwanted moieties in a glatiramoid, such as altered amino acid sequences, impurities (*e.g.*, aggregates), and degradation products. Alterations to amino acid sequences and conformations or impurities in a proposed generic glatiramer acetate product can alter cellular and humoral immune responses to it, and may generate antibody repertoires with different specificities and activities from those of anti-glatiramer acetate antibodies, with variable consequences on safety and patient response to therapy. Even if the primary structures of the protein-like polypeptides in Copaxone® could be identified and matched by a proposed generic product, properties such as protein folding cannot be controlled, potentially leading to differences in how the proposed generic interacts with cell receptors. As FDA has explained, “Both the primary sequence and the higher-order structure of therapeutic protein products are important factors that contribute to immunogenicity.”¹²⁵

The new gene expression data submitted herein underscores the heightened risk of immunogenicity in this case. As discussed above, the testing identified 98 genes differentially

¹²² Press Release: Affymax and Takeda Announce a Nationwide Voluntary Recall of All Lots of OMONTYS® (pgenesatide) Injection (Exhibit 20), available at, <http://www.fda.gov/Safety/Recalls/ucm340893.htm>

¹²³ See Medical Review for OMONTYS (Feb. 29, 2012), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202799Orig1s000MedR.pdf

¹²⁴ Varkony et al (2009) (Exhibit 11).

¹²⁵ Draft Immunogenicity Guidance, at 12 (Exhibit 19).

expressed between Copaxone® and a purported foreign generic product, many of which may have a profound impact on immune response. In particular, the analyses indicate that (1) Copaxone® upregulates genes associated with beneficial immune processes in MS patients more consistently and more effectively than a foreign “generic” product; (2) the purported “generic” product differentially upregulates genes associated with inflammatory pathways compared to Copaxone®; and (3) Copaxone® is significantly more consistent in its biological effects than the purported generic. This suggests that, despite broad physicochemical similarities, Copaxone® and the purported “generic” may have significantly different impacts on a variety of key immune cell types, with important implications for immunogenicity, safety and effectiveness.

Among the potential risks associated with increased immunogenicity are lack of efficacy, exacerbation of disease, anaphylaxis, immunotoxicity, and induction of additional autoimmune disorders. Moreover, due to the nature of both RRMS and glatiramer acetate, these risks may not develop for months or years and, once apparent, may be irreversible. It is thus critical for FDA to ensure that any proposed generic product has an immunogenicity profile that is comparable to Copaxone®’s *before* approval. In particular, FDA should 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®.

In a related context, FDA has recognized that immunogenicity testing generally is an essential requirement for approving one protein product based, in part, on the safety and effectiveness information generated for a different protein product. Because of the complexity of both proteins and the immune system, FDA has determined that “[s]tructural, functional, and animal data are generally not adequate to predict immunogenicity in humans.”¹²⁶ Consequently, FDA has taken the position that it typically will require “at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product.”¹²⁷ Because glatiramer acetate is highly complex and immunogenic, and thus entails similar immunogenicity risks to therapeutic proteins, FDA should apply the same clinical trial requirement before approving purported generic glatiramer acetate drug products.

2. FDA Should Require Clinical Testing Demonstrating That The Risks Of Switching Between A Proposed Generic Glatiramer Acetate Product And Copaxone® Are Not Greater Than The Risks of Using Copaxone® Without Such Switching

Finally, the potential for the development of cross-reactive neutralizing antibodies must be assessed before FDA approves any generic glatiramer acetate product intended to be used interchangeably with Copaxone®. Switching between two complex polypeptide products with subtle differences in structure and/or composition may increase the chance of cross-reactivity, a

¹²⁶ *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product [Draft]*, at 14 (Feb. 2012) (Exhibit 21).

¹²⁷ *Id.* at 14.

phenomenon that has been observed with interferon beta products.¹²⁸ Upon switching from Copaxone® to a proposed generic product or using them interchangeably, antibodies formed against Copaxone® may neutralize the activity of the proposed generic product and *vice versa*. If this were the case, patients would be left without any effective treatment. Again, there is no evidence that progression of neurologic disability associated with untreated MS can ever be reversed.

Recent legislation governing the approval of follow-on biological products requires FDA to assess the risks of switching therapies before designating a follow-on product as “interchangeable” with a previously-approved biological product. In particular, the Biologics Price Competition and Innovation Act (“BPCIA”) requires FDA to determine that “the risk in terms of safety or diminished efficacy of alternating or switching between use of the [follow-on] biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.” 42 U.S.C. § 262(k)(4)(B). This requirement is applicable specifically to biological products that, like Copaxone®, are intended to be “administered more than once to an individual.” *Id.*

Although Copaxone® is not currently regulated as a “biological product” as defined by the BPCIA, it nevertheless shares many of the same characteristics as biological products, including a large and complex molecular structure, some higher order structure, and concomitantly complex interactions with the immune system. Consequently, the same scientific justifications for requiring data on the risks of switching “interchangeable” biological products apply equally to proposed generic glatiramer acetate products that are intended to be used interchangeably with Copaxone®. Indeed, because Copaxone® is intended to be used chronically, and because its effects on the immune system appear to evolve over time, there is no way to predict the effect of a “switch” or, for that matter, multiple switches on safety or effectiveness without conducting adequate and well-controlled clinical trials.

Consequently, 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. If these types of safety-related tests are not appropriate or permissible for NDAs, FDA should require proposed generic glatiramer acetate products to utilize the 505(b)(2) approval pathway instead.¹²⁹

¹²⁸ Bertolotto A, Malucchi S, Milano E, et al. Interferon beta neutralizing antibodies in multiple sclerosis: neutralizing activity and cross-reactivity with three different preparations. *Immunopharmacology* 2000;48:95-100.

¹²⁹ Teva previously raised this argument in its fourth Citizen Petition. Although FDA indicated that it would specifically address Teva’s contention that “switching” clinical studies are appropriate to assess immunologic safety,” FDA’s November 20, 2012 decision letter does not, in fact, contain any discussion of this issue. See FDA Response to Fourth Copaxone Petition, FDA-2012-P-0555 (Nov. 30, 2012) (Exhibit 6).

E. BIOEQUIVALENCE: Comparative Clinical Testing Using Appropriate Safety and Efficacy Endpoints Is Necessary to Ensure That Proposed Generic Glatiramer Acetate Products Are Bioequivalent To, And Thus As Safe and Effective As, Copaxone®

Even if a generic applicant were able to demonstrate active ingredient sameness using “overlapping criteria” and a comparable immunogenicity profile within the confines of an ANDA, approval of the ANDA would be impermissible in the absence of data from *in vivo* studies demonstrating that the proposed generic product is bioequivalent to Copaxone®. As discussed further below, a waiver of *in vivo* bioequivalence testing is not appropriate because, among other reasons, Copaxone® is a colloidal suspension rather than a true solution. Because PK and PD methods are infeasible in this case, a well-controlled, comparative trial with clinical endpoints is the most accurate, sensitive, and reproducible approach to determine whether structural or 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 of action, *e.g.*, the immune system.

1. Statutory and Regulatory Requirements Applicable to the Demonstration of Bioequivalence

In order to obtain approval of an ANDA, an applicant must demonstrate, *inter alia*, that its proposed generic product is “bioequivalent” to a RLD. 21 U.S.C. § 355(j)(2)(iv). The FFDCA provides that a generic drug is bioequivalent to a RLD 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 [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .

Id. § 355(j)(8)(B)(i). The FFDCA imposes bioequivalence requirements on all drugs, even those that are not systemically absorbed. 54 Fed. Reg. 28872, 28882 (July 10, 1989). For a drug that is not intended to be absorbed into the bloodstream, the statute provides that “[FDA] may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the [RLD] in safety and therapeutic effect.” 21 U.S.C. § 355(j)(8)(C).

FDA’s regulation defining “bioequivalence” does not distinguish between drugs that are systemically absorbed and those that are not. According to FDA, “bioequivalence” is defined (in relevant part) as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” 21 C.F.R. § 320.1(e).

Bioequivalence can be demonstrated through a variety of *in vivo* and/or *in vitro* tests depending upon the purpose of the study, the analytical methods available, and the nature of the

drug product. *Id.* § 320.24(a). FDA regulations describe the following acceptable test methods in descending order of accuracy, sensitivity, and reproducibility: (1) *in vivo* PK test in humans measuring absorption into the bloodstream; (2) *in vivo* test in humans measuring urinary excretion; (3) *in vivo* PD tests in humans; (4) comparative clinical trials with safety and effectiveness endpoints; (5) *in vitro* studies, and (6) any other approach deemed adequate by FDA. *Id.* § 320.24(b). ANDA applicants generally are required to use the “most accurate, sensitive, and reproducible approach available” among those specified in the regulations. *Id.*

As is clear from the above list, FDA’s regulations provide that *in vivo* studies typically are the “preferred method” to demonstrate bioequivalence.¹³⁰ Nevertheless, the requirement for *in vivo* studies may be waived in certain circumstances. For example, FDA considers bioequivalence to be “self-evident” – and thus will waive *in vivo* testing – for a “parenteral solution” intended solely for injection if the proposed generic drug product contains the same active and inactive ingredients in the same concentrations as the RLD. 21 C.F.R. § 320.22(b)(1). FDA also can waive *in vivo* bioequivalence testing “for good cause” if such a waiver is “compatible with the protection of the public health.” *Id.* § 320.22(e).

On the other hand, FDA may require *in vivo* bioequivalence testing for any product, even one otherwise eligible for a waiver (*e.g.*, parenteral solutions), if “the agency determines that any difference between the drug product and [the RLD] may affect the bioavailability or bioequivalence of the drug product.” *Id.* § 320.22(f). Likewise, FDA may require *in vivo* bioequivalence testing at any time if the agency has evidence that a proposed generic product: (1) may not produce comparable therapeutic effects to the RLD; (2) may not be bioequivalent to the RLD; or (3) has greater than anticipated potential toxicity related to PK or other characteristics. *Id.* § 320.24(c).

2. FDA Should Require *In Vivo* Bioequivalence Testing for Proposed Generic Glatiramer Acetate Products

FDA should require *in vivo* bioequivalence testing for generic glatiramer acetate drug products. Such testing is necessary to assess whether unavoidable and, perhaps, undetectable, structural and compositional differences between the proposed generic product and Copaxone® have clinical effects on bioequivalence.

a. Biowaivers Are Not Granted For Colloidal Suspensions

Generic glatiramer acetate drug products are not eligible for a waiver of *in vivo* bioequivalence testing pursuant to 21 C.F.R. § 320.22 because Copaxone® is a colloidal suspension. Although FDA regulations at 21 C.F.R. § 320.22(b)(1) require the agency to waive *in vivo* bioequivalence testing for certain “parenteral solutions,” this regulation applies only to true solutions, not colloidal suspensions like Copaxone®. FDA historically has considered “parenteral colloidal solutions . . . to be a problem and waivers of *in vivo* bioequivalence studies

¹³⁰ Letter to William A. Rakoczy, FDA-2007-P-0418, at 4 (May 7, 2008).

are not granted on them.”¹³¹ In this way, FDA treats colloidal solutions similarly to injectable suspensions, which are deemed to have potential bioequivalence problems “because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption.”¹³² For example, FDA recently refused to grant a waiver of *in vivo* bioequivalence testing for proposed generic products referencing Ferrlecit® (sodium ferric gluconate complex in sucrose injection) as the RLD because Ferrlecit® is considered to be a colloidal suspension.¹³³

Copaxone® is an injectable product comprising nano-sized particles of glatiramer acetate suspended in an aqueous solution with mannitol that, under FDA guidelines, is considered to be a “colloidal” suspension. The FDA defines a “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), that do not settle out under the influence of gravity; the particles may be in emulsion or in suspension.¹³⁴

Copaxone® meets this definition because it is composed of glatiramer acetate molecules in sizes ranging from 1.5 nm to 550 nm suspended in a continuous medium (*i.e.*, a solution of mannitol and water), maintaining a homogenous appearance, *i.e.*, the suspended particles do not settle out under the influence of gravity.¹³⁵ See Declaration of Raj Bawa, M.S., Ph.D. ¶¶ 13, 20, 21, 35 (“Bawa Decl.”) (Exhibit 26).

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

¹³¹ See ANDA 40-024, FDA Review of Pharmacokinetics and Iron Utilization Studies, November 28, 1995 (Exhibit 22).

¹³² *Approved Drug Products With Therapeutic Equivalence Evaluations*, p. xix (33rd ed. 2013) (“the Orange Book”) (Exhibit 23).

¹³³ FDA Response to Ferrlecit Petition, FDA-2004-P-0494, p. 13-14 (March 31, 2011) (Exhibit 24). FDA concluded that “because iron colloid injection products are not solutions and may differ in rate and extent of iron availability, *in vivo* bioequivalence studies will be required as FDA’s Office of Generic Drugs (OGD) routinely does for other nonsolution parenteral products.” Likewise, FDA recently issued a revised draft bioequivalence guidance that requires *in vivo* bioequivalence testing for injectable iron sucrose drug products, apparently on the basis that such products also are considered to be colloidal solutions. See *Draft Guidance for Iron Sucrose* (Nov. 2013) (Exhibit 25).

¹³⁴ See FDA Response to Ferrlecit Petition, FDA-2004-P-0494, p. 4, n. 13 (Exhibit 24).

¹³⁵ Data on file, Teva Pharmaceuticals, Inc. 2012.

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,¹³⁶ thus, Copaxone® is stable under these conditions.

In a letter 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,¹³⁷ demonstrates that Copaxone® is a colloidal suspension.¹³⁸ In order to address FDA’s questions and substantiate that Copaxone® is, in fact, a colloidal suspension, Teva conducted additional tests evaluating the physicochemical properties of Copaxone® using several sophisticated analytical techniques. These tests, which include traditional colloidal assessment experiments such as ultracentrifugation, particle size and zeta potential,¹³⁹ conclusively demonstrate that Copaxone® is a stable colloidal suspension rather than a true solution. *See* Bawa Decl. ¶ 13 (Exhibit 26). In particular, these state-of-the-art tests 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 these studies complement each other and, together, confirm that Copaxone® is a stable, lyophilic colloidal suspension. *See* Bawa Decl. ¶ 35 (Exhibit 26). A description of the specific tests conducted and the results obtained is presented in more detail in Teva’s Fifth Copaxone Petition (Exhibit 1) as well as in the attached Declaration of Raj Bawa, M.S., Ph.D. (Exhibit 26).

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

¹³⁶ Data on file, Teva Pharmaceuticals, Inc. 2012.

¹³⁷ Teva previously submitted the results of DLS and AFM testing of Copaxone® to FDA in a letter dated May 31, 2012.

¹³⁸ FDA Response to Fourth Copaxone Petition, FDA-2012-P-0555, at 9 (Nov. 30, 2012) (Exhibit 6).

¹³⁹ 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 27).

(“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.”¹⁴⁰ 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.”¹⁴¹ 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. *See* Bawa Decl. ¶ 28 (Exhibit 26). 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. *See* Bawa Decl. ¶ 35 (Exhibit 26). Based upon the “relevant scientific evidence specific to [Copaxone®],” therefore, FDA should refuse to grant biowaivers to proposed generic versions of Copaxone®.

b. The Inevitable Structural and Compositional Differences In Active Ingredients Due to Different Manufacturing Processes Preclude A Biowaiver

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 resulting in decreased efficacy, increased toxicity, or both.¹⁴² FDA regulations provide that the agency may require *in vivo* bioequivalence testing if differences between the proposed generic product and the RLD could affect bioequivalence, regardless of whether the proposed generic product otherwise qualifies for a waiver. 21 C.F.R. § 320.22(f).¹⁴³

¹⁴⁰ *United States Pharmacopeia and National Formulary* (USP 32-NF 27). Vol. 1. Rockville, MD: United States Pharmacopeia Convention; 2010:672 (Exhibit 28).

¹⁴¹ *United States Pharmacopeia and National Formulary* (USP 32-NF 27). Vol. 1. Rockville, MD: United States Pharmacopeia Convention; 2010:670 (Exhibit 28).

¹⁴² Teva previously raised this argument in its fourth Citizen Petition. Although FDA indicated that it would specifically address this argument, FDA’s November 30, 2012 decision letter does not, in fact, contain any discussion of this issue.

¹⁴³ Moreover, *in vivo* bioequivalence testing can be required if there is evidence that the proposed generic product may not have a comparable therapeutic effect or risk profile. 21 C.F.R. § 320.24(c). The data from the gene expression studies described above provide such evidence.

The Agency has explained that this provision may be triggered if the generic applicant uses “a manufacturing process (including a formulation change) different from that used by the manufacturer of the listed drug, a difference that may affect the proposed product’s bioavailability.” 54 Fed. Reg. 28872, 28912 (July 10, 1989).

Although bioequivalence often is affected more by formulation differences (*e.g.*, different excipients) than active ingredient characteristics, FDA has recognized that, in some cases, structural and compositional differences in the active ingredient can affect bioequivalence, particularly for complex drugs like Copaxone® that interact with the immune system. Indeed, FDA regulations recognize that pharmaceutically equivalent drug products may present actual or potential bioequivalence problems justifying *in vivo* testing if, among other things, “the particle size and/or surface area of the *active drug ingredient* is critical in determining its bioavailability.” 21 C.F.R. § 320.33(e)(3) (emphasis added). In this case, of course, the uptake of Copaxone® by the immune system is directly related to both the particle size and surface characteristics (*i.e.*, epitopes and higher order structure) of its active drug ingredient, glatiramer acetate.

Because of the complexity of glatiramer acetate, the use of a different polymerization and/or depolymerization process by an ANDA applicant inevitably will result in the manufacture of an active ingredient with structural and compositional differences from Copaxone®, such as polypeptide chains with different amino acid sequences (primary structure), lengths, and conformations. Although some of these differences may be identified and controlled through analytical tests, given the limitations of current analytical test methods, many relevant differences will not be identified.¹⁴⁴ Since glatiramer acetate’s mechanism of action is not well understood, and since there is no way to predict whether differences between Copaxone® and a proposed generic product will result in different clinical effects, FDA should conclude that these differences “may affect” the bioequivalence of the proposed generic drugs for purposes of 21 C.F.R. § 320.22(f). Indeed, this appears to be exactly the type of situation envisioned by FDA when it promulgated this regulation.

Given the complexity of glatiramer acetate and its interactions with the immune system, there is a possibility that a purported generic product will differ from Copaxone® in terms of drug uptake, effectiveness, and immunogenicity. This, in fact, is demonstrated by the results of preclinical and clinical studies suggesting that differences in glatiramoids could have significant effects on safety and effectiveness.^{145,146,147} It also is demonstrated by the results of the gene

¹⁴⁴ See *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product [Draft]*, at 5 (“current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins.”) (Exhibit 21).

¹⁴⁵ Ramot Y, Rosenstock M, Klinger E, et al. Comparative long-term preclinical safety evaluation of two glatiramoid compounds (glatiramer acetate, Copaxone®, and TV-5010, protiramer) in rats and monkeys. *Toxicol Pathol* 2012;40:40-54.

¹⁴⁶ Varkony et al. 2009 (Exhibit 11).

expression studies discussed above, which suggest that Copaxone® and a purported foreign “generic” may have significantly different impacts on a variety of key immune cell types, with implications for safety, immunogenicity, and efficacy.

In a very similar situation, FDA recently required *in vivo* bioequivalence testing for generic versions of Ferrlecit®, in part, because of questions regarding the effect of particle size and surface characteristics of the active ingredient on bioavailability. In particular, FDA was concerned that differences in the “gluconate/sucrose shell” of the active ingredient could have an effect “on drug uptake by the reticuloendothelial system (RES) (such as through phagocytosis by macrophages).”¹⁴⁸ Significantly, FDA did not require the differences in shell structure to be identified or characterized as a necessary condition to ordering *in vivo* testing. In fact, it was precisely because FDA lacked data on the surface properties of the carbohydrate shell and the effect of the shell surface on iron uptake that the Agency required *in vivo* testing. This is consistent with FDA’s position that “[t]he burden of showing that a new product is . . . bioequivalent rests with the applicant.” 57 Fed. Reg. 17950, 17976 (April 28, 1992). Although FDA concluded that differences in the gluconate/sucrose shell were “unlikely” to have a “significant effect” on drug uptake, it nevertheless required *in vivo* testing “as a conservative measure,” consistent with FDA’s duty to protect the public health. In another recent example that also involves a NBCD, FDA recognized that a biowaiver “would not be appropriate for generic versions of Doxil *given the complexity of the drug.*”¹⁴⁹

Given Copaxone®’s high degree of complexity, a biowaiver is similarly inappropriate here. Consequently, FDA should refrain from approving any ANDA for a generic glatiramer acetate product unless it contains acceptable results from *in vivo* bioequivalence studies. Such studies should be required not as a “conservative measure” but rather as a necessary prerequisite to ensure that differences in active ingredient composition resulting from unique polymerization processes do not significantly affect drug uptake or compromise patient health and safety.

3. Pharmacokinetic Studies Are Not Capable of Establishing the Bioequivalence of Proposed Generic Glatiramer Acetate Products and Copaxone®

For drug products whose primary mechanism of action depends on systemic absorption, the determination of bioequivalence generally rests on PK studies; *i.e.*, “a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.”¹⁵⁰

¹⁴⁷ De Stefano N, Filippi M, Confavreux C, et al. The results of two multicenter, open-label studies assessing efficacy, tolerability and safety of protieramer, a high molecular weight synthetic copolymeric mixture, in patients with relapsing-remitting multiple sclerosis. Mult Scler 2009;15:238-43.

¹⁴⁸ See FDA Response to Ferrlecit Petition, FDA-2004-P-0494, p. 15 (March 31, 2011) (Exhibit 24).

¹⁴⁹ FDA Response to Doxil Petition, FDA-2009-P-0216, p. 12 n. 62 (Feb. 4, 2013) (emphasis added) (Exhibit 29).

¹⁵⁰ See Letter to Izumi Hara and Jeffrey Jonas, M.D., FDA-2010-P-0111, at 5 (Aug. 20, 2010) (Exhibit 30); *see also* 21 C.F.R. §§ 320.24(b)(1), (2).

PK studies, however, often are inadequate to demonstrate bioequivalence for drug products that act locally, like Copaxone®. This is because such drugs may not produce measurable concentrations of the active ingredient, active moiety, or metabolites in an accessible biological fluid, and even when measurable concentrations are produced, there is a lack of evidence of “any correlation between these systemic concentrations and concentrations at the site of drug action.”¹⁵¹

Because Copaxone®’s primary mechanism of action is not fully understood, it is unclear whether Copaxone® depends to any degree on systemic absorption to achieve its pharmacological effects. That being said, it is assumed that glatiramer acetate initiates its immunomodulatory effect at the site of injection by the uptake of the peptides by the local antigen presenting cells and by activating a cascade of events at the site of injection. Therefore, systemic concentrations of glatiramer acetate are not indicative of its activity. Furthermore, upon subcutaneous injection, Copaxone® degrades into smaller peptides and free amino acids locally, resulting in low or undetectable serum concentrations of the drug or its metabolites. Results of PK studies in healthy volunteers indicate that a substantial fraction of the glatiramer acetate dose is hydrolyzed locally. According to the approved Copaxone® package insert, “[s]ome fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.”¹⁵²

Consequently, PK studies are incapable of demonstrating bioequivalence for at least three reasons: (a) Copaxone® is at least partially a locally acting drug product, (b) neither the active components of Copaxone® nor its metabolites can be identified or measured in any accessible biological fluid, and (c) even if they could be identified and measured, there is a lack of evidence of any correlation between systemic concentrations of Copaxone® or its metabolites and concentrations at the site of drug action. Accordingly, PK studies are not appropriate for demonstrating bioequivalence because they would not be expected “to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect.” 21 U.S.C. § 355(j)(8)(C).

4. Pharmacodynamic Parameters Have Not Been Validated to Serve As Markers of Bioequivalence

When PK testing is not informative, alternative measures may be sought to demonstrate bioequivalence. One such alternative is PD testing; *i.e.*, measuring an appropriate acute pharmacological effect of the active moiety or, when appropriate, active metabolites, as a function of time. 21 C.F.R. § 320.24(b)(3). FDA considers this approach to be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution. *Id.* Under the statute and FDA regulations, however, the choice of

¹⁵¹ See Docket No. FDA-2010-P-0111, at 5 (Exhibit 30).

¹⁵² Copaxone® prescribing information, §12 .2 (Exhibit 7).

study design to demonstrate bioequivalence must be based upon the ability of the study “to compare the drug delivered by the two products at the particular site of action of the drug.”¹⁵³

In this case, PD testing is of limited utility in demonstrating bioequivalence because, although there are some PD effects with Copaxone® administration, none have been validated to correlate with the availability of the active moiety or moieties at the site of drug action. For example, most RRMS patients treated with Copaxone® develop glatiramer acetate-reactive antibodies; concentrations of these antibodies peak at approximately 3 months after initiation of treatment, decrease beginning at approximately 6 months to 12 months, and remain low thereafter.¹⁵⁴ Additionally, Copaxone® proteins and polypeptides stimulate peripheral blood lymphocytes (“PBLs”) in RRMS patients and in healthy donors. Upon repeated exposure to Copaxone®, the specific proliferative response of PBLs decreases, and glatiramer acetate-specific T cells shift from a Th1 to a Th2 phenotype. These PD parameters, however, have not been validated to serve as markers of bioavailability of Copaxone®, or as markers of bioequivalence between Copaxone® and other proposed generic glatiramer acetate products.

In addition, it is important to note that immune responses to glatiramer acetate are time-dependent; cytokine secretion, peripheral blood mononuclear cell (PBMC) proliferation, and anti-glatiramer acetate antibody levels all have a unique time-response profile during treatment with Copaxone®. The immunomodulatory responses to Copaxone® develop and change over time with chronic daily injections; therefore, measurement of an immunological response at a single time point (snapshot) would be scientifically unsound. For example, utilizing the Th1/Th2 cytokine ratio as a potential biomarker for clinical response would require long-term follow-up, because ratios observed after 1 month of treatment are different from those observed after 1 year of treatment. Therefore, a purported generic glatiramer acetate product will require evaluation over time to determine whether it has time-dependent immunomodulatory effects comparable to those of Copaxone®.

More importantly, evidence of immunoavailability (development of anti-glatiramer acetate antibodies) or of an immune response (proliferation of glatiramer acetate-specific T cells) does not necessarily correlate with availability of the active moiety at the site of action or with clinical efficacy. There appears to be a cascade of events after subcutaneous injection of Copaxone® that leads to clinical efficacy; antibody formation and proliferation of PBLs are early steps in the cascade but no correlation between these steps and clinical efficacy has been established. Moreover, any subtle shifts in the amino acid sequences of glatiramer acetate polypeptides can lead to immunological responses that could alter the safety and efficacy of the drug (for example, lead to the development of neutralizing antibodies). Such antibodies could block the efficacy of the approved dose, requiring higher dosing levels of the generic product to achieve the same level of immunopotentiation.

¹⁵³ Letter to William A. Rakoczy, FDA-2007-P-0418, p. 4.

¹⁵⁴ Brenner T, Arnon R, Sela M, et al. Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone®. J Neuroimmunol 2001;115:152-60.

Finally, because the mechanisms of action of Copaxone® are not fully understood, it is not possible to exclude the possibility that PD testing measuring the above-described parameters will fail to capture critical information about the availability of glatiramer acetate's active components at other important sites of action. In other words, given the complexity of glatiramer acetate and the lack of information regarding its mechanisms or sites of action, PD testing is not an accurate or sensitive method for measuring the availability of glatiramer acetate's active components at the site or sites of drug action, many of which may be unknown. Because PD testing would not be expected "to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect," 21 U.S.C. § 355(j)(8)(C), it, too, is not an appropriate method for demonstrating bioequivalence between Copaxone® and proposed generic glatiramer acetate drug products.

5. A Comparative Clinical Trial Using Appropriate Safety and Effectiveness Endpoints Is the Most Sensitive, Accurate, and Reproducible Method for Demonstrating the Bioequivalence of Proposed Generic Glatiramer Acetate Products to Copaxone®

Although comparative clinical studies generally are not considered to be as sensitive, accurate, and reproducible in determining bioequivalence as PK or PD studies, FDA has recognized that well-controlled clinical studies are acceptable when, as here, PK and PD approaches are "infeasible."¹⁵⁵ Indeed, FDA regulations provide that comparative trials with appropriate clinical endpoints may be considered "sufficiently accurate for . . . demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally." 21 C.F.R. § 320.24(b)(4). Further, FDA officials have stated that "most" locally acting drugs "require clinical endpoint studies" to demonstrate bioequivalence.¹⁵⁶

Because Copaxone® is intended to be administered and act locally following subcutaneous injection, comparative clinical trials are an acceptable method for demonstrating bioequivalence. In fact, given the complexity of Copaxone®'s active ingredient and the uncertainty regarding its active amino acid sequences (*i.e.*, epitopes) and mechanisms of action, a comparative trial with clinical endpoints is the *only* study method capable of "compar[ing] the drug delivered by the two products at the particular site of action of the drug."¹⁵⁷ In other words, it is the most sensitive, accurate, and reproducible method for demonstrating the bioequivalence of proposed generic glatiramer acetate products to Copaxone®.

¹⁵⁵ See Docket No. FDA-2010-P-0111, at 6 (Exhibit 30); see also *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (hereinafter BA/BE Guidance), at 9-10 (March 2003).

¹⁵⁶ See *Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs*, Dena Hixon, M.D., Assoc. Dir. Medical Affairs, FDA Office of Generic Drugs, presented at the Pharmaceutical Science Advisory Committee (March 12, 2003) (Exhibit 31), available at http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S1_18_Hixon.ppt.

¹⁵⁷ Letter to William A. Rakoczy, FDA-2007-P-0418, p. 4.

In a situation with striking similarities to Copaxone®, FDA required ANDA applicants seeking approval of generic sucralfate products to conduct a “clinical safety and efficacy trial” to demonstrate bioequivalence to Carafate®, the RLD. Sucralfate, like Copaxone®, is a locally-acting drug product with a variety of mechanisms of action that are not well-understood. Given this complexity, generic applicants were not able to correlate the chemical properties of their proposed drugs with all of the postulated modes of action of the RLD. The Agency explained that, “[g]iven the number and complexity of [the RLD’s] postulated modes of action and in the absence of data that demonstrates equivalence of formulations in producing each of these effects,” a comparative clinical trial with safety and effectiveness endpoints would be required to demonstrate bioequivalence.¹⁵⁸ More recently, in November 2011, FDA issued a recommendation that proposed generic rifaximin drug products demonstrate bioequivalence through an *in vivo* study using primary and secondary clinical endpoints, *i.e.*, clinical cure of traveler’s diarrhea at the test of cure visit on study day 5 and time to last unformed stool, respectively.¹⁵⁹

Prior correspondence from FDA to Teva sharply underscores the need for comparative trials with meaningful clinical endpoints. More specifically, FDA recently denied approval of an NDA supplement (“sNDA”) in which Teva sought approval for a new formulation of Copaxone®, holding instead that a clinical trial would be necessary to demonstrate the proposed product’s efficacy. Of particular note here, the proposed product contained the very same glatiramer acetate contained in Copaxone®, but presented the active ingredient in a higher concentration/lower volume formulation (*i.e.*, 20 mg per 0.5 mL of water rather than 20 mg per 1 mL of water).¹⁶⁰ Nonetheless, FDA required clinical efficacy studies for this formulation of Copaxone® based on the Agency’s acceptance of the uncertainty regarding Copaxone®’s mechanism(s) of action:

The 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. While [your] study provides reasonable short-term safety information, it is inadequate to support efficacy of the new formulation [A]n adequate and well-controlled efficacy study will be needed to support efficacy of this new formulation.

In other words, FDA would not approve an sNDA for a different formulation of Copaxone® that used the very same amount of the very same active ingredient because the lack

¹⁵⁸ See ANDA No. 70-848, Response to Consultation re Biocraft Submission of April 27, 1988 (May 2, 1988) (Exhibit 32), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/070848.PDF.

¹⁵⁹ *Draft Guidance on Rifaximin* (Nov. 2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281455.pdf>.

¹⁶⁰ Anderson G, Meyer D, Herrmann CE, et al. Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection an open-label, multicenter, randomized comparative study. *J Neurol* 2010;257:1917-23.

of understanding regarding the product's mechanism(s) of action would not permit the Agency to rule out the possibility that the absence of an inactive ingredient – just 0.5 mL of water – might compromise the product's efficacy. If 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.

Finally, the need for comparative clinical trials is further underscored by the Agency's recent experience with generic versions of colloidal iron products, which, like Copaxone, are complex, nanoparticle-based drug products that have not been fully characterized. In that case, although FDA required *in vivo* bioequivalence studies for proposed generic products, it did not require comparative studies with clinical endpoints. Instead, the Agency approved generic products on an assumption that "physicochemical characterization tests . . . would ensure compatible tissue distribution and no more iron leakage from generic formulations than that from RLD."¹⁶¹ Because of recently identified concerns that generic versions of these NBCDs were not, in fact, performing in a similar manner to the RLDs, FDA took the highly unusual step on April 19, 2013 of initiating a process to solicit a third-party contractor to conduct a rigorous three-year evaluation of whether the approved generic product, Nulecit, is in fact therapeutically equivalent to the RLD (Ferrlecit).¹⁶² On July 16, 2013, FDA took the additional step of issuing a formal solicitation for such studies.¹⁶³ Although the generic product has not yet been withdrawn from the market, this development raises significant questions about the adequacy of FDA's approval criteria for generic copies of NBCDs like iron colloidal products and its failure to require comparative clinical endpoint studies to establish bioequivalence.

6. Comparative Clinical Studies Should Use Appropriate Clinical Endpoints, Not Surrogate Endpoints Such as MRI Outcomes

The comparative clinical studies required by FDA to demonstrate bioequivalence should utilize appropriate safety and effectiveness endpoints based upon the endpoints used in the clinical studies supporting approval of Copaxone®, not surrogate endpoints such as MRI outcomes. Specifically, FDA should require ANDA applicants to conduct clinical studies in RRMS patients that are adequately powered to demonstrate comparable safety and efficacy between the proposed generic product and Copaxone®. This likely will require well-controlled clinical studies comparable in size and duration to those for a new molecular entity. FDA officials previously have explained that the trial design and efficacy and safety endpoints of a "clinical endpoint" bioequivalence study are similar to those required for an NDA.¹⁶⁴

¹⁶¹ Solicitation No. FDA-SOL-1120929 (July 16, 2013) (Exhibit 33).

¹⁶² Therapeutic Equivalence of Generic Iron Complex Product, Solicitation No. FDA-SS-1116099 (Apr. 19, 2013) (Exhibit 34), available at <https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SS-1116099/listing.html>.

¹⁶³ Solicitation No. FDA-SOL-1120929 (July 16, 2013) (Exhibit 33).

¹⁶⁴ See *Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs*, Dena Hixon, M.D. (Exhibit 31).

Sponsors typically are required to conduct a 3-arm comparative trial comparing the proposed generic product versus the RLD versus placebo. The endpoints should be similar to those required for an NDA and should include outcomes of drug effects on the approved indication in a comparable patient population according to the labeled dosing of the RLD. Moreover, both the generic and RLD must be statistically superior to placebo ($p<0.05$) in order to assure that the study is sensitive enough to show a difference between products, and the endpoints must meet established bioequivalence limits (e.g., a difference of $\pm 20\%$ in a 90% confidence interval).

For glatiramer acetate, ANDA applicants should be required to conduct one or more well-controlled clinical investigations of their proposed generic products compared against both Copaxone® and placebo in patients with RRMS. Moreover, given the difficulty of demonstrating efficacy in an RRMS population, a minimum duration of 2 years is necessary to attain valid efficacy results. The clinical trial or trials should be designed so that one of the clinical endpoints is reduction of the frequency of relapses in patients with RRMS; *i.e.*, the approved indication for Copaxone®. Other clinical endpoints, including safety endpoints, also may be appropriate. In addition, sufficient numbers of patients should be included to surmount potential biases related to the inter- and intra-patient variability of RRMS disease activity and, as discussed further below, to thoroughly characterize the immunogenicity of the proposed generic product.

FDA should not permit ANDA applicants to use surrogate endpoints, such as MRI outcomes, to demonstrate bioequivalence to Copaxone®. Although various MRI techniques capture different aspects of MS disease pathology and lesion evolution over time, there is general agreement that no single MRI measure will have sufficient predictive value to act as a valid surrogate for clinical outcomes.¹⁶⁵ Together, the complex immunomodulatory mechanisms of glatiramer acetate, considerable heterogeneity of MS disease pathology and symptoms, and the variable response to Copaxone® therapy render a short-term clinical trial using only conventional MRI as a primary endpoint insufficient to establish the safety or efficacy of a proposed generic product or to demonstrate bioequivalence to Copaxone®.

A short-term MRI study also is inappropriate because it may fail to detect potential safety risks associated with the longer-term use of a proposed generic product. Copaxone® is associated with potential risks that may have onset several months after the initiation of therapy. For example, post-injection reactions and lipoatrophy have been reported to develop for the first time several months after the initiation of treatment.¹⁶⁶ Likewise, RRMS patients treated with Copaxone® develop glatiramer acetate-reactive antibodies that rise and fall over a period of a year or more. Although this does not appear to adversely affect the safety or efficacy of

¹⁶⁵ McFarland HF, Barkhof F, Antel J, et al. The role of MRI as a surrogate outcome measure in multiple sclerosis. *Mult Scler* 2002;8:40-51.

¹⁶⁶ Edgar CM, Brunet DG, Fenton P, et al. Lipoatrophy in patients with multiple sclerosis on glatiramer acetate. *Can J Neurol Sci* 2004;31:58-63.

Copaxone[®], the same cannot be said for proposed generic products in the absence of clinical trials of at least 2 years duration. Indeed, the long-term consequences of continued alteration of immune function due to chronic treatment with a proposed generic product will not be known if approval is based solely upon results of short-term MRI studies. Such studies, therefore, are not appropriate to demonstrate bioequivalence or ensure that a generic product is as safe and effective as Copaxone[®] for chronic use.

F. 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. Because of the extreme complexity of Copaxone[®], current analytical technologies can demonstrate, at most, that a proposed generic product is highly similar to Copaxone[®], not that it is *identical*, as required by Congress. This means that a generic, if approved via the ANDA pathway without clinical trials in man, could have undetected differences from Copaxone[®] that make it less safe or effective, including differences that could trigger variable immune responses in patients. The scientific data provided demonstrates that Copaxone[®] is far more complex than ever imagined. Obviously, the interaction at the cellular level, as measured by gene expression, indicates that clinical trials are the only way to assure patients and physicians that the product as approved will be safe. No amount of reverse engineering can assure patients that the purported "generic" product they are taking for such a serious disease as MS is effective and safe without the demonstration in man in clinical studies. While Teva firmly supports the benefits of generic competition, in this case, Teva does not believe it is in the public interest for patients to be subjected to purported "generic" versions of Copaxone[®] without any clinical testing whatsoever to address residual uncertainty regarding immunogenicity, bioequivalence, safety and effectiveness.

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: September 30, 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

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