DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAY 0 2 2014

J. Michael Nicholas, Ph.D.
Sr. Director, Strategic Regulatory Affairs
Teva Neuroscience, Inc.
901 E. 104th Street, Suite 900
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Re: Docket No. FDA-2013-P-1641

Dear Dr. Nicholas:

This letter responds to your citizen petition received on December 5, 2013 (Petition), in which you request that the Food and Drug Administration (FDA or Agency) not approve any abbreviated new drug application (ANDA) that references Copaxone (glatiramer acetate injection) unless and until the conditions specified in the Petition are satisfied. Specifically, you request that the Agency refrain from approving any ANDA that references Copaxone unless the ANDA contains:

1. information demonstrating that the proposed generic product contains the identical active ingredient as in Copaxone, not merely an active ingredient that is similar (or even highly similar) to Copaxone's;

2. the results of nonclinical 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. the results of comparative clinical investigations in relapsing-remitting multiple sclerosis (RRMS) patients using relevant safety and effectiveness endpoints demonstrating that the proposed generic drug is bioequivalent to Copaxone.[1]

You assert that the Agency cannot be assured that a purported generic product will be as safe and effective as Copaxone without these requirements because: (1) recent gene expression studies conducted by Teva suggest that purported generic glatiramer acetate products have structural and compositional differences from Copaxone that may affect safety and efficacy; (2) Copaxone is a highly complex mixture of polypeptides, and because its exact constituents cannot be completely characterized, no proposed generic can be found to have the "same" active ingredient; (3) Copaxone is highly immunogenic and comparative clinical testing is required to demonstrate that

[1] Petition at 5.

immunogenicity risks of a proposed generic are no greater than those associated with Copaxone; and (4) comparative clinical testing is necessary to show any proposed generic is bioequivalent to Copaxone and, therefore, as safe and effective.[2]

We have carefully considered the Petition. For the reasons stated below, the Petition is denied without comment on the approvability of any application for any glatiramer acetate injection drug product because it would be premature and inappropriate to do so at this time.

I. BACKGROUND

A. Copaxone

Teva Pharmaceuticals USA (Teva) is the holder of new drug application (NDA) 20-622 for Copaxone, 20 milligrams (mg)/milliliter (mL) and 20 mg/vial. This application was approved on December 20, 1996. Copaxone's active ingredient, glatiramer acetate, is a heterogeneous mixture of synthetic polypeptides synthesized from four naturally occurring amino acids — L-glutamic acid, L-alanine, L-tyrosine, and L-lysine.[3] Copaxone is indicated for the reduction of the frequency of relapses in patients with RRMS, including patients who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with multiple sclerosis.

B. Section 505(q) of the Federal Food, Drug, and Cosmetic Act

The Petition is subject to section 914 of the Food and Drug Administration Amendments Act of 2007, which amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) of the FD&C Act applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted,[4] and the 150-day period is not to be extended for any reason.

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[2] Petition at 2-5, 10.

[3] Teva Pharmaceutical, Inc., Citizen Petition FDA-2009-P-0555, dated November 13, 2009 (Second Teva Petition), at 10. For further physicochemical information about Copaxone, see FDA's May 11, 2010, denial of the Second Teva Petition at 2.

[4] Section 1135 of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 (Pub. L. No. 112-114) amended section 505(q) of the FD&C Act to change the time FDA has to take final Agency action from 180 days to 150 days from when the petition is submitted.

II. DISCUSSION

You state that you believe that "[b]ecause 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."[5] You also state that you have previously explained in prior Citizen Petitions[6] that, because of Copaxone's complexity and other unique characteristics, 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 FD&C Act.[7]

You maintain that even if FDA were to determine that a proposed generic product has the same active ingredient as Copaxone, "approval of an ANDA would be impermissible in the absence of data from *in vivo* studies demonstrating that the proposed generic product is bioequivalent to Copaxone" and that "a waiver of *in vivo* bioequivalence testing is not appropriate . . . because Copaxone is a colloidal suspension rather than a true solution . . . ."[8] As in your prior citizen petitions, you assert that "*in vivo* testing is necessary to ensure that any proposed generic product is bioequivalent to Copaxone," and that "bioequivalence can only be demonstrated via a well-controlled, comparative trial with clinical endpoints . . . ."[9] You assert that in vivo clinical investigations are warranted because Copaxone is a locally acting drug with largely unknown mechanisms of action and no validated pharmacodynamic markers of drug activity.[10] In addition, you state that as a condition of approval, "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" and "such testing must include an assessment of immunologic safety when the products are switched."[11] You assert that "a purported generic version of glatiramer acetate produced by a different manufacturing process and using a different starting material could have significant and unpredictable differences from Copaxone in its immunological mechanisms, raising major safety and efficacy concerns" such as "lack of efficacy, exacerbation of disease, immunotoxicity, and induction of additional autoimmune disorders."[12]

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[5] Petition at 2.

[6] The prior citizen petitions were docket no. FDA-2008-P-0529, received on September 26, 2008, and responded to on March 25, 2009; docket no. FDA-2009-P-0555, received on November 13, 2009, and responded to on May 11, 2010; docket no. FDA-2010-P-0642, received on December 10, 2010, and responded to on June 8, 2011; docket no. FDA-2012-P-0555, received on June 4, 2012, and responded to on November 30, 2012; and docket no. FDA-2013-P-1128, received on September 12, 2013, and withdrawn by Teva on January 6, 2014.

[7] Petition at 2-5.

[8] Id. at 3-4.

[9] Id. at 4.

[10] Id. at 2, 33-36, 49-50.

[11] Id. at 3.

[12] Id.at 3.

In its responses to your prior citizen petitions, the Agency has addressed your assertions regarding Copaxone's complexity, local action characteristics, insufficient knowledge of its method of action, immunogenicity, and purported lack of pharmacodynamic markers, and we therefore incorporate those responses by reference in our response to the Petition. In this petition, you have additionally submitted the results of certain gene expression studies you have performed comparing Copaxone to unapproved and foreign-approved glatiramer acetate products. You have also submitted certain conclusions based on these results regarding the approvability of ANDAs referencing Copaxone.

Your current Petition reports results of experimental studies that compared the effects of Copaxone to the effects of one unapproved and several foreign-approved glatiramer acetate products on gene expression in mice. These products are Glatimer (Natco Pharma, India), Escadra (Argentina), Probioglat (Mexico), Hangzhou (China), and TV-5010 (produced by Teva for research and not approved in any jurisdiction). During the studies, laboratory mice (type Balb/c x SJL) were injected with glatiramer acetate reference standard to induce reactive T-cells. Immune cells from their spleens were activated with either Copaxone or a foreign glatiramer acetate product after sacrifice. Microarrays were used to measure differential gene expression among the products.[13]

Your current Petition draws a number of conclusions from the reported results of these studies. According to the Petition, microarray testing identified 98 genes that are differentially expressed following exposure to Copaxone versus the foreign glatiramer acetate products. You assert that the foreign glatiramer acetate products were found to upregulate 30 genes associated with inflammatory responses, 20 genes related to immune cell adhesion, and an additional 39 genes associated with cell migration and chemotaxis. You identified the FOXP3 gene as particularly significant in the progression of multiple sclerosis. You claim that Copaxone acts on FOXP3 and promotes the production regulatory T-cells (Tregs) that induce tolerance more effectively than the generic products. You attribute the results concerning differential gene expression to differences in manufacturing processes. For example, you report that you produced TV-5010 by altering the manufacturing process for Copaxone to increase the molecular mass of TV-5010 and that these changes made the product toxic in animal studies.[14] You conclude that the foreign glatiramer acetate products "may upregulate inflammatory pathways that could increase the risk of adverse events and/or reduce the efficacy of treatment with glatiramer acetate."[15]

A second set of tests reported in your current Petition compared foreign glatiramer acetate samples produced by Escadra (Argentina), Probioglat (Mexico), and Hangzhou (China) to each other. You assert that "[n]umerous probes with potential links to safety and efficacy show differences in expression among purported 'generics' from different manufacturers."[16] More specifically, you claim that the Probioglat sample downregulated the production of progesterone

[13] Id. at 10-11.

[14] Id. at 19-21.

[15] Id. at 11.

[16] Id. at 18.

relative to Copaxone and the other two foreign glatiramer acetate products. You assert that progesterone is believed to be a neuroprotective agent that plays a role in myelin repair. You further claim that the Hangzhou sample did not significantly downregulate IL1B as compared to Copaxone or the other foreign glatiramer acetate products. You assert that this difference is significant because IL1B has been associated with late disability progression and neurodegeneration, and lower levels of IL1B slow the disease.

We have not yet determined the significance, if any, of the results of the gene expression studies described in the Petition to the approval of any ANDA that references Copaxone. The most significant differences in these comparisons were between Copaxone and TV-5010, a product that you created by deliberately altering Copaxone's molecular mass.[17] None of the foreign glatiramer acetate products used in these studies have been approved by FDA. Accordingly, FDA is not yet in a position to determine whether the results you have cited in the Petition would support a requirement of clinical trials, or other conditions of approval you suggest, on any current or future ANDA submitted to the Agency.[18]

In addition, although the Petition describes differences in gene expression between Copaxone and several foreign glatiramer acetate products following administration to mice, it does not provide sufficient evidence for FDA to conclude that these differences are clinically significant to the treatment of multiple sclerosis. The Petition does not provide references that characterize the genetic pathways that it postulates, nor does it seek to document those pathways itself, nor does it analyze research concerning any of the 98 genes that it identified in depth. FOXP3 is the only gene that is given more than a cursory discussion.

The Agency's position is that any decision regarding a requirement of clinical trials to demonstrate bioequivalence, or any other conditions of approval, will be informed by our review of a specific ANDA before us, and must be based on relevant scientific information specific to each product.[19] Therefore, any decision to implement any requirement for clinical trials to demonstrate bioequivalence or other conditions of approval would be taken on a per product basis, taking into account relevant physicochemical and other quality attributes of each specific product. Many products, including Copaxone, present unique challenges; thus it is reasonable and appropriate for the Agency to take into account each product's specific attributes in conjunction with other data provided in an ANDA as it assesses whether any additional information is necessary for approval of any specific ANDA.[20]

Accordingly, we deny the specific requests in the Petition regarding the approvability of an ANDA for a generic product referencing Copaxone because it would be premature and

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[17] Id. at 19.

[18] See Section 505(j) of the FD&C Act and 21 CFR 314.94 regarding the contents of an ANDA.

[19] This position is consistent with FDA's responses to Teva's previous citizen petitions regarding Copaxone.

[20] As this citizen petition (the sixth one you have filed over the course of six years) also demonstrates, scientific information regarding this complex drug continues to accumulate, which in turn means that FDA continues to update the information available to it in evaluating each ANDA before it.

inappropriate to definitively opine on this matter at this time. Such an action could, in effect, render a decision on a specific aspect of an ANDA before the Agency has had an opportunity either to fully consider specific data and information in such an application or to provide the procedural rights that accompany FDA actions on applications.[21] Were we, for example, to grant your requests to impose certain specific requirements for applications for glatiramer acetate, we could, in effect, be taking final action on the approvability of specific aspects of an application for a glatiramer acetate product before we have had an opportunity to fully review data and information submitted by an applicant or to provide the applicant with appropriate procedural protections.

As described above, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition, in this case, within 150 days of submission. Therefore, we must take action on the Petition at this time. However, FDA has made no final determination about whether, or on what basis, to approve or not approve any ANDA for a glatiramer acetate product. In addition, FDA continues to actively consider the issues you have raised and the information you have included in your Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved,[22] or may not be approved,[23] or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[24] In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[25] Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable and will provide a specific time frame and process should the applicant request such a hearing. These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

Therefore, we are denying your requests without comment on the specific requirements for approval of any generic version of Copaxone. The Agency intends to address the issues you have raised, if and when we approve a generic version of Copaxone.

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[21] We also note that under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the filing or approvability of any particular NDA or ANDA for a glatiramer acetate injection drug product unless we approve such application (or other grounds for disclosure apply).

[22] 21 CFR 314.105.

[23] Section 505(c) and 505(j) of the FD&C Act; 21 CFR 314.125 and 314.127.

[24] 21 CFR 314.110.

[25] Section 505(c)(1)(B) and 505(d) of the FD&C Act; 21 CFR 314.200.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.[26]

Sincerely,

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

[26] To the extent that this Petition revisits issues raised in your previous petitions, we reiterate our previous responses in which we have already explained that we would only be able to definitively address those issues after the Agency has had an opportunity to fully consider information and data in a specific ANDA.