TEVA CNS

March 10, 2014

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BY HAND DELIVERY

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

Re: Docket No. FDA-2013-P-1641;
Supplemental Information and Response to Mylan, Inc.'s Comment Submitted to Docket No. FDA-2013-P-1128

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva") is hereby submitting comments in opposition to the comments submitted by Mylan, Inc., on February 6, 2014, to Docket No. FDA-2013-P-1128. On January 6, 2014, Teva withdrew the Citizen Petition on which Mylan commented. Teva took this action because of the submission of a subsequent, comprehensive Citizen Petition on December 5, 2013 (Docket No. FDA-2013-P-1641) that incorporates the new data and arguments addressed in the prior petition. Although Mylan's comments were submitted after withdrawal of the prior Citizen Petition and, to the best of Teva's knowledge, have not yet been submitted to the new Citizen Petition under this docket, Teva nevertheless believes it is appropriate to address Mylan's comments here because the arguments in the prior Citizen Petition have been incorporated into the currently docketed Citizen Petition.

In its February 6, 2014 comments, Mylan asserts that the Food and Drug Administration ("FDA") has already rejected Teva's arguments that Copaxone® (glatiramer acetate injection) is colloidal suspension and thus that purported generic products should not be granted a biowaiver.[1] In particular, Mylan argues that Teva's purported definition of a colloid is overly simplistic and focuses primarily on size; that FDA has discretion to grant a biowaiver to "lyophilic colloidal systems" like Copaxone®; and that FDA in fact has granted biowaivers to peptide products like oxytocin, leuprolide acetate, and desmopressin. Finally, Mylan asserts that Teva is abusing the Citizen Petition process by "simply reassert[ing] arguments previously denied by FDA."[2] For the reasons discussed below, Mylan assertions are specious and should be summarily rejected by the Agency. Instead, for the reasons specified in Teva's prior Citizen Petitions, FDA should grant the relief requested in Teva's December 5, 2013 Petition.

[1] Mylan Comments, Docket No. FDA-2013-P-1128 (Feb. 6, 2014) (Exhibit 1).
[2] Mylan Comments, Docket No. FDA-2013-P-1128, at 6.

Teva Pharmaceuticals
11100 Nall Avenue | Overland Park, KS 66211 | Tel. 800.22[illegible]4026 | www.tevapharm[illegible]a.com

First, Mylan mischaracterizes the applicable definition of the term "colloid" as a creation of Teva's that incorrectly focuses predominantly on the size of the suspended particles. In fact, the definition of "colloid" relied upon by Teva was adopted by FDA itself in a prior petition response in which the Agency refused to grant a biowaiver to a colloidal suspension like Copaxone®.[3] In addition, the definition is not primarily size-based but also focuses on the stability of the system and whether suspended particles precipitate out under the influence of normal gravitational forces. For this reason, the additional testing submitted by Teva to establish that Copaxone® is a colloidal suspension included not just analytical techniques such as dynamic light scattering ("DLS") and atomic force microscopy ("AFM"), which establish that the glatiramer acetate particles in Copaxone® are within the appropriate colloidal size range, but also techniques such as ultracentrifugation and resuspension and zeta potential testing, which establish that Copaxone® is thermodynamically and/or kinetically stable but is not a true solution. In other words, the testing establishes that Copaxone® is a colloidal suspension under the applicable regulatory definition adopted by FDA. Indeed, even Mylan appears to accept this conclusion, describing Copaxone in its comments as "a lyophilic colloidal system."[4]

Second, Mylan misconstrues Teva's argument that FDA should deny a biowaiver for purported generic versions of glatiramer acetate. Contrary to Mylan's claim, the fact that FDA previously asserted it has broad discretion to grant or deny biowaivers in specific situations is immaterial to this case. In its prior petition, Teva specifically acknowledged 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.[5] 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. Teva thus has argued that, *in this specific case based upon the scientific evidence presented*, FDA should refuse to grant biowaivers to proposed generic version of Copaxone®. In other words, Teva is not arguing about whether or not FDA has some discretion, as a general matter, to grant or deny biowaivers; only that FDA should base its decision to deny a biowaiver in this case based upon the "relevant scientific evidence specific to [Copaxone®]." Although Mylan asserts that FDA has granted biowaivers to similar peptide products, such as oxytocin and leuprolide acetate, Teva is not aware of any similar scientific evidence being submitted to FDA for these products, particularly information derived from traditional colloidal assessment experiments like those performed on glatiramer acetate.[6]

Third, Mylan's assertion that Teva is abusing the Citizen Petition process is specious and should be summarily rejected. Although Mylan contends that Teva "simply reasserts arguments previously denied by FDA," Teva in fact has performed and submitted extensive, new scientific data that specifically addresses the issues identified in FDA's November 30, 2012 petition response. This is precisely the function that the Citizen Petition process is intended to perform:

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[3] Letter to David Zuchero, M.S., J.D., *et al.*, FDA-2004P-0494, p. 4, n. 13 (March 31, 2011).
[4] Mylan Comments, Docket No. FDA-2013-P-1128, at 4 (Feb. 6, 2014).
[5] Teva Citizen Petition, Docket No. FDA-2013-P-1128, at 19 (Sept. 12, 2013).
[6] Teva also notes that the active ingredients identified by Mylan as subject to biowaivers appear to be much smaller and less complex than glatiramer acetate.

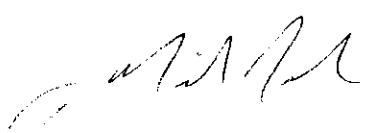
to make FDA aware of new scientific data and information that is relevant to and should inform its regulatory decisions. Although this new scientific information was submitted to FDA in a new Citizen Petition (thus fueling Mylan's misguided allegations regarding serial petitioning), this in fact was mandated by FDA's own regulations.[7] Accordingly, Teva's submission represents an appropriate and *bona fide* use of the Citizen Petition process because it presents relevant, new, scientific data to FDA to guide its regulatory decision-making.

Finally, it is important to remember that the ultimate goal of Teva's request for clinical studies of purported generic products, including bioequivalence studies with clinical endpoints, is to protect patient welfare and safety. Mylan and others are seeking approval of purported generic versions of an immensely complicated drug product based upon chemistry, manufacturing, and control ("CMC") data alone without any clinical studies in patients. Mylan apparently believes that analytical comparisons alone are enough to predict safety and efficacy in the clinical setting. For a product like glatiramer acetate, however, which is so complex it is impossible to adequately characterize, it likewise is impossible to predict whether or not it will have its intended effect in patients based solely upon a comparison using current analytical techniques. For the reasons set forth in Teva's prior petitions, including its pending petition, Teva believes doing so would present an unacceptable risk to multiple sclerosis patients. It is pubic knowledge that Synthon has performed a clinical trial where a follow-on glatiramoid was examined versus placebo and Copaxone®. It would be in the best interest of patients and regulatory decision makers to examine the results of the Synthon trial prior to making a decision on a pending ANDA. We believe the trial results are imminent.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about February 7, 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.

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

Respectfully submitted,



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

[7] *See* 21 C.F.R. § 10.33(e) (requiring new scientific information to be submitted as a separate Citizen Petition rather than a Petition for Reconsideration).

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

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

Billy Dunn, M.D.
Acting Director, Division of Neurology Products

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