DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JUN 15 2015

Frank Casty, M.D.
Mylan Specialty, L.P.
1000 Mylan Blvd.
Canonsburg, PA 15317

Re: Docket No. FDA-2015-P-0181

Dear Dr. Casty:

This letter responds to your citizen petition dated January 16, 2015 (Petition) and supplement dated April 28, 2015. In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take certain actions with respect to abbreviated new drug application (ANDA) 090589, submitted by Teva Pharmaceuticals, for an epinephrine auto-injector (hereafter Teva application or product). Among other things, you ask that the Commissioner refrain from approving the Teva application unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the Agency concludes that the proposed product is the "same as" the EpiPen auto-injector. You state that this includes the request that patients, caregivers, and other relevant user groups trained in the use of the EpiPen auto-injector who face an emergency situation be able to safely and effectively use the proposed product in accordance with the EpiPen auto-injector instructions for use, without additional physician interaction or training.

We have carefully considered the Petition and supplement. For the reasons stated below, the Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. EpiPen

Mylan Specialty, L.P., holds approved new drug application (NDA) 019430 for EpiPen (epinephrine auto-injector). The product is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis of various origins. It is available in two strengths, 0.3 milligram (mg)/delivery (0.3 mg/0.3 mL) (the EpiPen auto-injector) (yellow carrier cap and label) and 0.15 mg/delivery (0.15 mg/0.3 mL) (the EpiPen Jr auto-injector) (green carrier cap and label). EpiPen was initially approved on December 22, 1987.

B. Section 505(q) of the FD&C Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, 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 (21 U.S.C. 355(b)(2) or (j)) 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. The 150-day period is not to be extended for any reason.

II. DISCUSSION

In the Petition, you request that FDA:

1. Refrain from approving the Teva application unless the Agency affirmatively finds that the proposed generic product is the same as the EpiPen auto-injector such that:

    a. Patients, caregivers, and other relevant user groups who were trained in the use of the EpiPen auto-injector and who face an emergency situation are able to safely and effectively use the Teva product in accordance with the instructions for the EpiPen auto-injector without additional retraining or physician interaction;

    b. No human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use by patients or their caregivers who were trained in the use of the EpiPen auto-injector, or such that the Teva product has the same safety and effectiveness profile as the EpiPen auto-injector;

    c. The instructions for use and related aspects of the label and labeling of the Teva product do not differ from the EpiPen auto-injector label and labeling beyond differences permitted by the statute and applicable regulations, which require that a generic product generally have the same labeling as the reference listed drug (RLD);

    d. Considering the EpiPen auto-injector as a whole and its individual constituent parts, differences between the Teva product and the EpiPen auto-injector do not introduce new risks, taking into account both risks intrinsic to the Teva product and risks associated with switching from one epinephrine auto-injector to another without training or physician intervention; and

e. The Teva product is shown to be bioequivalent to the EpiPen auto-injector through appropriately designed bioequivalence testing to examine potential performance differences resulting from design differences and to assure equivalent clinical outcomes in the context of generic substitution.

2. Require Teva to provide the information necessary to make the above determinations, including specific information regarding product design and operating principles, as well as the results of comparative performance tests between the Teva product and the EpiPen auto-injector, as detailed in the Petition.

3. Require withdrawal of the ANDA and submission of an NDA under section 505(b)(2) of the FD&C Act because human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use.

4. Not assign a therapeutic equivalence code to the Teva product indicating its therapeutic equivalence to the EpiPen auto-injector if the Teva product is approved under a 505(b)(2) NDA, unless the Agency finds that the two products are bioequivalent and can be expected to have the same clinical effect and safety profile when administered for the approved use and substituted without retraining.

5. Convene a joint meeting of the appropriate advisory committees to provide expert advice and clarity to the Agency on the complex scientific, technical, regulatory, and policy issues implicated by the data-driven evaluation of the "sameness" of the Teva proposed generic epinephrine auto-injector and the EpiPen auto-injector.

(Petition at 4-5.)

As grounds for your requests, your Petition cites previously issued Agency citizen petition responses[1] and guidances[2] that generally articulate Agency's thinking with regard to evaluating the approvability of an ANDA for a proposed generic auto-injector (Petition at 1-3, 10-13, 23-25), and states that this Petition is specific to the Teva product. You assert that application of the standards enumerated in the cited petition responses and guidances should lead FDA to not approve the Teva application, or to preclude a therapeutic equivalence rating if the product is approved under section 505(b)(2) of the FD&C Act.

[1] These include Docket No. FDA-2009-P-0578 (submitted by Dey Pharma, L.P.) and Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040 (submitted by King Pharmaceuticals, Inc.).

[2] These include the guidance for industry and staff on *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*, and the guidance for industry and FDA premarket and design control reviewers on *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the Search for FDA Guidance Web Page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

You state that there are significant differences between the Teva product and the EpiPen that preclude the Teva product's approval under section 505(j) of the FD&C Act. You state that these include differences in design and operating principles, such as the manner in which the safety cap is released, preparation of the needle, and the method of injection (Petition at 9, 14-21). You assert that these differences would prevent a patient or caregiver trained on the EpiPen auto-injector from being able to use the Teva product safely and effectively in an emergency or in accordance with the EpiPen instructions for use (Petition at 14). For similar reasons, you assert that even under a 505(b)(2) approval, the product differences enumerated throughout the Petition preclude a designation of therapeutic equivalence.

As described in section I.B of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific 505(j) application.

FDA has made no final determination on whether to approve or not approve any ANDA relying on EpiPen as the RLD. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an application before taking final action on the approvability of the application as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of 505(j) applications in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the 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 (§ 314.105) or may not be approved (section 505(c) and (j) of the FD&C Act; §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). 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 (section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing (id.). 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.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA or NDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the

process established under the FD&C Act and FDA regulations.[3] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an application when a final decision on the approvability of any such application has not yet been made.[4] Accordingly, we are denying without comment your requests on the specific requirements for approval of an application relying on EpiPen as the RLD.

III. CONCLUSION

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

Sincerely,

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

[3] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond that described in this response) would not be appropriate in this case because the Petition's requests focus on narrow issues of whether a specific drug product proposed in a 505(j) application should contain certain data that is dependent on the specific drug product before we have reached a final decision on whether to approve or not approve any such 505(j) application. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[4] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending 505(j) application before we have reached a final decision on whether to approve or not approve the application.