FDA U.S. FOOD & DRUG ADMINISTRATION

Kurt R. Karst
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JUL 0 6 2018

Re: Docket No. FDA-2018-P-0598

Dear Mr. Karst:

This letter responds to the citizen petition you submitted on behalf of United Therapeutics Corporation (UT), which the Food and Drug Administration (FDA or the Agency) received on February 7, 2018 (Petition). UT is the holder of the new drug application (NDA) for Tyvaso (treprostinil) Inhalation Solution, 0.6 mg/mL, 2.9 mL ampules (NDA 022387).

Your Petition requests that FDA refrain from approving any abbreviated new drug application (ANDA) "for a treprostinil inhalation solution drug-device combination product referencing Tyvaso unless the ANDA:"

(1) Requests approval for a specific delivery device that will be used with, and approved as part of, the proposed generic treprostinil product;

(2) Includes data demonstrating that the proposed device component of the generic product has the same critical design attributes and meets the same performance and quality standards as the innovator device, including human factors and usability standards;

(3) Includes data demonstrating that the proposed generic product, with its proposed commercial delivery device, is bioequivalent to Tyvaso; [and]

(4) Requests approval for a refill kit with the required device components, and includes data demonstrating that those components are compatible with both the generic delivery device and the Tyvaso Inhalation System while maintaining the output specifications of the innovator device.

Petition at 3-4.

This is the fifth citizen petition submitted on behalf of UT regarding the approval of ANDAs for treprostinil inhalation solution products referencing Tyvaso. The first four citizen petitions, dated January 14, 2016, August 10, 2016, April 5, 2017, and September 6, 2017 (Docket Nos.

FDA-2016-P-0187, FDA-2016-P-2478, FDA-2017-P-2162, and FDA-2017-P-5477 respectively) were denied, on June 13, 2016, January 5, 2017, September 1, 2017, and February 2, 2018, without comment on the action requested because we had not yet made a final decision on whether or not to approve any such applications. We note your current Petition makes the same substantive arguments as these earlier citizen petitions.

We have carefully reviewed your Petition, and for the reasons stated below, your Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. Tyvaso NDA

Tyvaso (treprostinil) inhalation solution, 0.6 mg/mL, 2.9 mL ampules, is indicated for the treatment of pulmonary arterial hypertension to improve exercise ability. The Tyvaso NDA includes the Tyvaso Inhalation System Patient Starter Kit, which contains the Tyvaso Inhalation System (i.e., an ultrasonic, pulsed delivery device and its accessories) and a 28-day supply of treprostinil ampules. The Tyvaso NDA also includes the Tyvaso Inhalation System Refill Kit, containing another 28-day supply of treprostinil ampules and device components that require monthly replacements. In addition, the Tyvaso NDA includes two additional package presentations: (1) the Tyvaso Inhalation System Institutional Starter Kit, which contains the Tyvaso Inhalation System and a 4-ampule supply of treprostinil; and (2) a Tyvaso 4 Pack Carton, which contains 4 ampules of treprostinil (Tyvaso labeling, § 16).

The Tyvaso NDA (022387) was approved on July 30, 2009, using the Optineb-ir nebulizer. UT submitted a supplement to its NDA to use the TD-100/A device and the supplement was approved on July 31, 2012. The current Tyvaso Inhalation System uses the TD-300/A device, which was approved on October 19, 2017.

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

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144, 126 Stat. 993), which was signed into law on July 9, 2012. Section 505(q), as originally added by the FDAAA, applies to certain citizen petitions and petitions for stay of Agency action requesting that FDA take any form of action related 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 no 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 your Petition, you request that FDA "refrain from approving any ANDA" referencing Tyvaso unless the ANDA includes certain identified elements (Petition at 3).

First, you contend that "generic versions of Tyvaso must include the delivery system as a component of the ANDA submission" (Petition at 16) (formatting changed). To support this contention, you state the delivery system components for Tyvaso are approved under the NDA and are not separately regulated or marketed as standalone medical devices (Petition at 16). You assert when a device is included as part of the reference listed drug (RLD) and approved under the NDA, an ANDA referencing that RLD is "required to include the device component as part of its application and demonstrate sameness" (i.e., when "[t]he drug and device are one product" and "[t]he delivery system is not separately approved, cleared, or marketed as a medical device") (Petition at 22).

Second, you claim that "ANDA applicants must submit data to show [that] their nebulizers are equivalent to the Tyvaso Inhalation System" (Petition at 23) (formatting changed). Along these lines, you assert that generic products must demonstrate equivalence to the Tyvaso Inhalation System by undertaking specific head-to-head studies related to performance characteristics of the nebulizer (including particle size distribution, nebulization time, and emitted dose) (Petition at 23-27). You also assert that FDA must review the materials, design, and operating principles for the nebulizer in an ANDA to consider whether any differences between the ANDA and the Tyvaso Inhalation System would introduce a new risk (Petition at 27-28).

Third, you claim that "ANDA applicants must demonstrate that their drug/device combination product is bioequivalent to Tyvaso" (Petition at 28) (formatting changed). You assert treprostinil delivered to the airways has both locally acting and systemically acting components. You claim:

> When the generic delivery system components in an integrated drug-device combination product are not identical to those of the RLD, *in vitro* performance studies may be an essential adjunct part of any assessment of bioequivalence. However, *in vitro* studies alone cannot ensure equivalent *in vivo* bioavailability in this case.

Petition at 30.

You also claim that pharmacokinetic studies are essential but insufficient because they are not capable of determining the rate and extent of delivery of treprostinil to the local site of action (Petition at 30). Consequently, you request:

> [I]f the proposed generic product differs from Tyvaso in formulation, or if there are differences in the components of the delivery system that may significantly affect availability of the active moiety at the site of drug action, and that cannot be adequately addressed by *in vitro* measures – a comparative clinical study with pharmacodynamic endpoints will be required in order to assure equivalence in local action between a generic version of treprostinil for inhalation and Tyvaso.

Petition at 30.

Fourth, you assert that "the labeling of a proposed generic product must be the same as Tyvaso's labeling" (Petition at 31) (formatting changed), suggesting an unacceptable difference in labeling would include changes to the labeling that necessitate patient retraining (Petition at 31). You also state the "operating conditions and human factor elements for Tyvaso are complex" and "variations in physical manipulation of the device can affect specific performance factors that ultimately determine the safety and effectiveness of the product" (Petition at 31).

Fifth, you argue that "a combination product referencing Tyvaso that includes a *different* delivery device will require human factors studies and must be submitted and reviewed" as an NDA, pursuant to section 505(b)(2) of the FD&C Act (Petition at 32) (emphasis added and formatting changed). You state that UT conducted human factors studies to support its supplemental NDA to add the TD-100/A nebulizer (Petition at 33). You claim that human factors studies are particularly important for patients who are prescribed pulmonary arterial hypertension drugs administered with a nebulizer (Petition at 35).

In addition, you claim that labeling comprehension studies may be appropriate "to assess whether the RLD and the proposed generic labels impart the same level of understanding to study participants when operating the device" (Petition at 37). You also assert that it is necessary to perform a human factors analysis under conditions of actual use (Petition at 37). If there are significant differences between the labeling or operational aspects of a delivery device of a generic product and its reference product, or where studies are required to ensure safety and effectiveness, you suggest that a 505(b)(2) application is more appropriate than an ANDA (Petition at 37-38).

Finally, you assert that "a combination product referencing Tyvaso must include a refill component that is compatible with the Tyvaso Inhalation System" (Petition at 38) (formatting changed). You claim that the refill kit is not an independent product and that the Tyvaso Inhalation System and the Tyvaso Inhalation System Refill Kit "are both required for the safe and effective use of the drug as documented in the product prescribing information and instructions for use" (Petition at 39). In addition, you argue that the generic refill kit components must "be compatible for use with the Tyvaso Inhalation System (and conversely, that the Tyvaso Inhalation System Refill Kit [must be] compatible with the generic nebulizer device)" (Petition at 39). In particular, you claim that if the ANDA product "includes a delivery device that is

incompatible with the Tyvaso Inhalation System, it must be submitted and reviewed under [section 505(b)(2) of the FD&C Act]" (Petition at 40).

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 ANDA referencing Tyvaso as its RLD.

FDA has made no final determination on whether to approve or not approve any ANDA referencing Tyvaso as its RLD. In the case of ANDAs referencing Tyvaso, our consideration of one or more applications will necessarily inform our decisions on the nature of the data and information necessary to support approval. 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 ANDA before taking final action on the approvability of the ANDA 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 ANDAs 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 in 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 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.[1] Therefore, we do not interpret

[1] 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 this

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 ANDA when a final decision on the approvability of any such ANDA has not yet been made.[2] Accordingly, we are denying without comment your requests on the specific requirements for approval of any ANDA referencing Tyvaso as its RLD.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

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

approach of describing our general policies or standards for approval of a drug application beyond the descriptions provided in this response would not be appropriate in this case because, as stated, our review of a given ANDA would inform our decisions regarding the sufficiency of the specific data and information needed for approval. We will continue to evaluate how to respond to each citizen petition that includes requests regarding any pending application on a case-by-case basis.

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