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EVP, Global Regulatory Affairs
United Therapeutics Corporation
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700 Thirteenth Street, N.W.
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August 16, 2024

Re: Docket No. FDA-2024-P-2326

Dear Dean Bunce:

This letter responds to your citizen petition received on July 10, 2024 (Petition), which amended your citizen petition received on May 10, 2024, requesting that the Food and Drug Administration (FDA, the Agency, or we) rescind its tentative approval of the new drug application (NDA) for Yutrepia (treprostinil) submitted by Liquidia Technologies, Inc. (Liquidia), due to "FDA's findings concerning…pervasive and systemic [Current Good Manufacturing Practice (CGMP)] violations" by Liquidia's active pharmaceutical ingredient (API) supplier LGM Pharma LLC (LGM) (Petition at 2). You state that LGM is currently under a Consent Decree,[1] and that the Complaint giving rise to the Consent Decree alleges that LGM's CGMP violations "repeatedly caused the introduction of adulterated drugs into interstate commerce" (Petition at 2-3). You state that the Complaint also alleges that the CGMP violations were "ongoing before, during, and after the Agency's award of tentative approval to Yutrepia." (Petition at 1-2). You assert that only after LGM has satisfied the terms of its Consent Decree should FDA permit Liquidia to resubmit its Yutrepia NDA (Petition at 3).

The Petition requests that FDA take the following actions:

1) Rescind its award of tentative approval to Liquidia's Yutrepia NDA;

2) Issue Liquidia a complete response letter for the Yutrepia NDA; and

3) Withhold any approval of the Yutrepia NDA – whether a tentative approval or ultimately a full approval – until LGM has fully and successfully discharged its obligations under the Consent Decree and Liquidia supplies the Agency with sufficient data and information to establish that the identity, strength, quality and purity of its proposed Yutrepia drug product in fact meets all the statutory and regulatory requirements for approval.

(Petition at 3).

[1] Consent Decree, *United States v. LGM Pharma LLC* (S.D. Fl., January 12, 2023).

We have carefully considered your Petition and other information available to the Agency. For the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Yutrepia

On January 24, 2020, Liquidia submitted an NDA for Yutrepia pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355 (b)(2)).[2] The 505(b)(2) NDA for Yutrepia relied on the Agency's previous findings of safety and effectiveness for Tyvaso (NDA 022387) for which United Therapeutics Corporation (UTC or you) holds the NDA.

Tyvaso is a prostacyclin mimetic indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. Tyvaso is a drug-device combination product that consists of a sterile formulation of treprostinil solution for oral inhalation using the Tyvaso Inhalation System.[3]

FDA tentatively approved the Yutrepia NDA on November 4, 2021.[4] In a press release dated July 27, 2023, Liquidia stated that it had amended its application to add an indication for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD), and that if approved by FDA, Yutrepia would be indicated for the treatment of both PH-ILD and pulmonary arterial hypertension.[5]

B. 505(b)(2) NDAs

Section 505(b)(2) of the FD&C Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments). Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness as a stand-alone NDA. For a 505(b)(2) NDA, however, some of the information required for approval comes from studies not conducted by or for the applicant and

[2] See Yutrepia Tentative Approval Letter to Liquidia Technologies from FDA (November 4, 2021) available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf

[3] See Tyvaso inhalation solution's Prescribing Information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022387s020lbl.pdf

[4] See Yutrepia Tentative Approval Letter to Liquidia Technologies from FDA (November 4, 2021) available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf.

[5] Press Release, Liquidia, Liquidia Submits Amendment to Add PH-ILD Indication to Tentatively Approved NDA for YUTREPIA (treprostinil) Inhalation Powder (July 27, 2023), https://www.liquidia.com/news-releases/news-release-details/liquidia-submits-amendment-add-ph-ild-indication-tentatively

for which the applicant has not obtained a right of reference or use.[6] For instance, a 505(b)(2) NDA may rely on FDA's previous finding that a listed drug is safe and effective as evidence in support of the proposed product's safety and effectiveness.

If an NDA meets the substantive requirements for approval but cannot receive final approval due to patent or exclusivity reasons, FDA will issue a tentative approval.[7] This tentative approval indicates that the drug meets the necessary standards under the FD&C Act but cannot be approved at that time due to an exclusivity period or court order.[8]

C. Current Good Manufacturing Practice

Under section 505 of the FD&C Act, prior to approval of an NDA, FDA will refuse to approve an NDA if the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the applicant's drug are inadequate to preserve the drug's identity, strength, quality, and purity.[9]

Domestic or foreign facilities that manufacture drugs for the U.S. market must meet FDA's CGMP requirements, including section 501(a)(2)(B) of the FD&C Act ((21 U.S.C. 355 (a)(2)(B)), for finished pharmaceuticals and active pharmaceutical ingredients (APIs) and 21 CFR parts 210 and 211 for finished pharmaceuticals.

FDA's guidance for industry, ICH Q7, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016), contains recommendations from FDA on CGMP for APIs. In this guidance, FDA defines "manufacturing" to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and the related controls.[10]

[6] Specifically, section 505(b)(2) of the FD&C Act states as follows:

> An application [may be] submitted under [section 505(b)(1)] for a drug for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

[7] See 21 CFR 314.3(b)(definition of tentative approval).

[8] See id.

[9] See sections 505(d) and 501(a)(2)(B) of the FD&C Act.

[10] Id. at 1.

II. DISCUSSION

A. A Rescission of the Tentative Approval of the Yutrepia NDA is Not Necessary

The Petition asserts that "FDA's regulations unambiguously specify that an applicant's eligibility for [tentative approval] always is subject to change in light of new evidence regarding the sponsor's compliance with the statutory requirements for approval, regardless of when that information comes to light" (Petition at 17). The Petition further asserts that because CGMP compliance is a statutory requirement for approval, neither tentative nor full approval of an NDA may be "awarded or maintained where any aspect of the applicant's supply chain is noncompliant or in doubt," and requests that FDA rescind its previously granted tentative approval of Yutrepia due to the violations of CGMP requirements that FDA had found at LGM's facility (Petition at 17-19).

Based on our review of Liquidia's manufacturers and suppliers and comprehensive evaluation of relevant information[11] available to the Agency regarding the manufacturing, processing, packing, and holding of Yutrepia, we do not agree that recission of the tentative approval of the Yutrepia NDA is warranted.

The Petition identifies LGM as the "sole" supplier of the API, treprostinil sodium, for Liquidia (Petition at 1). However, Liquidia has informed FDA that YS Life Science Company, Limited (Yonsung), formerly Yonsung Fine Chemicals Company, Limited, is Liquidia's sole treprostinil sodium manufacturer. LGM is Liquidia's importer of record for treprostinil sodium and coordinates customs and shipping logistics, including any associated documentation. Liquidia has also informed FDA that between March of 2020 and February of 2024, three shipments of treprostinil sodium were shipped from Yonsung to an LGM facility, where they were stored before being shipped to Liquidia. Further, Liquidia has informed FDA that, beginning on February 14, 2024, shipments of treprostinil sodium have been and will be sent directly from Yonsung to Liquidia. LGM will not be involved in the physical handling of the shipments and will not store or warehouse treprostinil sodium.

To support your request that FDA rescind its tentative approval of Yutrepia, you attempt to draw a comparison to other circumstances, including FDA's decision to rescind a previously granted tentative approval of Ranbaxy's abbreviated new drug applications due to information regarding CGMP noncompliance in two Ranbaxy manufacturing facilities (Petition at 7, 18).[12] However, that FDA can rescind a grant of tentative approval does not mean that it must or should rescind its grant of tentative approval for Yutrepia based on Liquidia's relationship with LGM. LGM will not store or warehouse treprostinil sodium because current and future shipments of treprostinil sodium will be routed directly from Yonsung to Liquidia. The Agency does not find that there is justification for rescinding the award of tentative approval for the Yutrepia NDA.

[11] This citizen petition response includes information of a type that is generally regarded as confidential commercial information. FDA obtained consent from Liquidia to proceed with the limited disclosure of certain information in this citizen petition response.

[12] See *Ranbaxy Labs., Ltd. v. Burwell*, 82 F. Supp. 3d 159, 192 (D.D.C. 2015).

B. A Complete Response Letter is Not Appropriate

The Petition urges the Agency to issue a complete response letter to Liquidia for the Yutrepia NDA (Petition at 3). The Petition describes findings from FDA's CGMP inspections of LGM between 2010 and 2022 (Petition at 11-12). The Petition contends that these findings support the issuance of a complete response letter because due to LGM's responsibilities under its agreements with Liquidia, LGM is not a "disinterested intermediary or facilitator" but rather plays a significant role in Liquidia's supply chain (Petition at 9).

The Petition asserts that when new information comes to FDA's attention that warrants rescission of a previously granted tentative approval, "the appropriate course of action is for FDA to issue a complete response letter requiring the applicant to correct all deficiencies" (Petition at 7).[13] The Petition also asserts that applicants that have received a complete response letter due to CGMP violations may only resubmit their application once FDA has reinspected all noncompliant facilities (Petition at 7). Given Liquidia's present arrangement with LGM, we reject the assertion that a complete response letter is supported on these grounds.

FDA issues complete response letters when we determine that we will not approve an NDA or ANDA in its present form.[14] The complete response letter describes deficiencies FDA has identified in an application.[15] FDA has reviewed relevant information available to the Agency regarding the manufacturing, processing, packing, and holding of Yutrepia, and has found that while LGM is subject to obligations under a Consent Decree, Liquidia has indicated that all future shipments of treprostinil sodium will be shipped directly from Yonsung to Liquidia and will not be stored or warehoused at an LGM facility. Because LGM does not store or warehouse the treprostinil sodium, LGM's obligations under the Consent Decree are not relevant to the Yutrepia NDA.

C. There is No Basis for Withholding Approval Until After LGM's Satisfaction of the Consent Decree Obligations

Pages 13-16 of the Petition outline LGM's obligations under the Consent Decree. Pages 2 and 19 of the Petition further state that FDA should withhold any approval of the Yutrepia NDA "until LGM has fully and successfully discharged its obligations under the Consent Decree and Liquidia supplies the Agency with sufficient data and information to establish that the identity, strength, quality and purity of its proposed [Yutrepia] drug product in fact meets all statutory and regulatory requirements for approval."

[13] Note that while regulations at 21 CFR § 314.110(a)(4) state that, when possible, the complete response letter will recommend actions an applicant may undertake to correct deficiencies that the Agency has identified and place an application in condition for approval, an applicant is not required to correct those deficiencies. For example, an applicant may elect to withdraw their application.

[14] 21 CFR § 314.110(a).

[15] 21 CFR § 314.110(a)(1).

As explained in subsection II.B. of this response, LGM's facilities are no longer utilized in Liquidia's Yutrepia manufacturing supply chain. Therefore, LGM's fulfillment of its Consent Decree obligations is not a basis for withholding tentative or full approval of the Yutrepia NDA.

III. CONCLUSION

In sum, we deny your request to rescind the tentative approval of Liquidia's Yutrepia NDA. We also deny your request to issue a complete response letter for the Yutrepia NDA. We further deny your request that FDA withhold approval of the Yutrepia NDA until LGM has fully discharged its obligation under the Consent Decree.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2024.08.15 23:01:53 -04'00'

Patrizia Cavazzoni
Director
Center for Drug Evaluation and Research