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AMENDED CITIZEN PETITION

Pursuant to 21 C.F.R. §§ 10.30 and 10.31 and the Federal Food, Drug, and Cosmetic Act ("FDCA") and on behalf of our client, United Therapeutics Corporation ("UTC"), we submit this Amended Citizen Petition to request that FDA withdraw its unlawful tentative approval ("TA") of Liquidia Technologies, Inc.'s ("Liquidia") section 505(b)(2) New Drug Application ("NDA") for YUTREPIA; issue Liquidia a Complete Response Letter; and refuse to grant final approval ("FA") to Liquidia's YUTREPIA NDA unless and until FDA makes a final determination that Liquidia's sole supplier of active pharmaceutical ingredient ("API") for YUTREPIA—LGM Pharma, LLC ("LGM"), whose involvement in YUTREPIA's commercial supply chain may not be known to the Agency—has been brought into full compliance with all Current Good Manufacturing Practice ("CGMP") requirements.

The basis for this request is straightforward. LGM plays a critical role in Liquidia's YUTREPIA manufacturing process: it is Liquidia's sole API supplier. Yet LGM is the subject of an ongoing Consent Decree following FDA's findings of pervasive violations of FDA's CGMP requirements in connection with its handling and processing of APIs for finished drug product manufacturers like Liquidia.[1] The Complaint giving rise to the Consent Decree documents that those violations

[1] The original version of this Citizen Petition stated that LGM "admitted liability for" violating FDA's CGMP requirements and included a copy of the FDA Complaint (Exh. 1) and resulting Consent Decree (Exh. 4). On June 24, 2024, LGM informed UTC that the Consent Decree was executed by LGM "without admitting or denying" the allegations in the Complaint. Ex. 4 at 1. LGM demanded that UTC retract the Citizen Petition because the Citizen Petition stated that LGM "admitted liability." Given the nature of the GMP violations FDA found and LGM's agreement to "without contest" undertake extraordinary remedial actions, *see* Exh. 4 at 1, UTC believes it fairly characterized the import of the Consent Decree proceeding. But because UTC's statements regarding the implications of LGM's non-denial and corresponding acceptance of responsibility ultimately are immaterial to the proper resolution of this proceeding, UTC is amending this Citizen

were ongoing ***before, during, and after*** the Agency's award of TA to YUTREPIA, and indeed that LGM's CGMP violations were so severe that they ***repeatedly caused the introduction of adulterated drugs into interstate commerce***.[2] Under the Consent Decree, LGM remains subject to a years-long course of corrective-action mandates that FDA designed to protect patients and ensure that LGM's misconduct will not once again cause the introduction of tainted drugs into interstate commerce. Unless and until LGM successfully completes all steps required by the Consent Decree or Liquidia finds a safe alternative to LGM, there can be no assurance that YUTREPIA is not tainted.[3]

Given LGM's crucial role in the commercial manufacturing process for YUTREPIA and FDA's findings of its pervasive and ongoing failures to comply with CGMP, there is no basis for maintaining YUTREPIA's TA—let alone granting FA to YUTREPIA. For decades, the FDCA has required all NDA applicants to disclose the identity and role of every entity and facility involved a proposed new drug's commercial supply chain, 21 U.S.C. § 355(b)(1)(A)(iv), so that FDA can determine whether its methods, facilities, and controls are "adequate to preserve [the proposed new drug's] identity, strength, quality, and purity." *Id*. § 355(d)(3). Without those disclosures, and in the absence of a determination that an applicant's supply chain fully complies with CGMP, it is impossible to know whether a proposed new drug will be safe, effective, and approvable for human use. *See id*. § 355(d).

FDA's findings concerning LGM's pervasive and systemic CGMP violations should have foreclosed the award of TA to YUTREPIA in 2021. By 2018, FDA was aware of LGM's CGMP violations. And the Agency's recognition in 2022 that those violations not only remained ongoing but had worsened should have led FDA to rescind YUTREPIA's TA at that time. After all, FDA's regulations provide—and more than a decade of judicially affirmed FDA policy, procedure, and precedent leave no doubt—that neither TA nor FA can be awarded or maintained where an applicant's supply chain violates CGMP. *See, e.g*., *Ranbaxy Labs., Ltd. v. Burwell*, 82 F. Supp. 3d 159 (D.D.C. 2015). Granting YUTREPIA TA ***after*** FDA had learned of LGM's noncompliance with the CGMP was unlawful, as is maintaining that TA despite the entry of a Consent Decree requiring LGM to rebuild its entire quality system from scratch. And there assuredly can be no basis for granting YUTREPIA FA unless and until the Consent Decree's terms are fully discharged.

Petition solely to more precisely reflect LGM's position. UTC requests that FDA resolve this urgent public-health matter ***without delay*** and on the ***same timeline*** for addressing the original Citizen Petition (*i.e*., no later than 150 days after the Citizen Petition's submission on May 10, 2024).

[2] UTC's knowledge of LGM's compliance, or lack thereof, with the FDCA and related regulations is based solely on publicly available information, notably the FDA Complaint and Consent Decree.

[3] Liquidia has disclosed LGM as its sole API supplier, but to the best of our knowledge, Liquidia has never publicly disclosed LGM's severe, pervasive, and ongoing compliance issues, including in any of its Securities and Exchange Commission ("SEC") filings.

Consistent with the statute, FDA's regulations, the Agency's administrative policies, practices, and precedents, and relevant case law, FDA must immediately withdraw YUTREPIA's TA; issue Liquidia a Complete Response Letter ("CRL") for the YUTREPIA NDA; and require Liquidia to resubmit its YUTREPIA NDA only after LGM has discharged all obligations under the Consent Decree and Liquidia supplies the Agency with data and information that are sufficient to establish that the identity, strength, quality and purity of its proposed YUTREPIA drug product meets all statutory and regulatory requirements for approval despite LGM's crucial role in the YUTREPIA supply chain and FDA's findings concerning its long-term disregard for CGMP. Only then can FDA consider whether to issue FA for YUTREPIA. Patient safety requires nothing less.

I. Actions Requested

UTC respectfully requests that FDA:

(1) Rescind its award of TA to Liquidia's YUTREPIA NDA;

(2) Issue Liquidia a CRL for the YUTREPIA NDA; and

(3) Withhold any approval of the YUTREPIA NDA—whether a TA or ultimately a FA—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.

II. Statement of Grounds

A. Legal Background

1. The Hatch-Waxman Act

As modified by the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act" or "Hatch-Waxman"), Pub. L. No. 98-417, 98 Stat. 1585, the FDCA seeks to balance innovation and patient access to affordable medicines by reducing certain barriers to market entry in appropriate cases. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998) (citing, *inter alia*, H.R. Rep. No. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647).

Before Hatch-Waxman's enactment, applicants seeking FDA approval for generic or modified versions of a previously approved drug—together, "follow-on products"—generally were subject to the same requirements as brand-new NDA products: With limited exceptions, they needed to conduct their own clinical trials and submit full NDAs in order to obtain FDA approval. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612 (2011). That requirement typically made it cost-prohibitive to develop follow-on versions of previously approved drugs, so the Hatch-Waxman Act established two abbreviated drug approval pathways that in certain cases allow follow-on product applicants to rely on FDA's prior finding that a previously approved drug (a "reference

listed drug" or "listed drug" (each, an "RLD")) is safe and effective for its approved use(s): (1) an ANDA under section 505(j) of the FDCA, and (2) a hybrid NDA under section 505(b)(2) of the FDCA. *See, e.g*., *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998).

Under the ANDA pathway, FDA generally has authority to approve a generic version of an RLD if the applicant demonstrates that the proposed ANDA product contains the same active ingredient(s) in the same dosage form, uses the same route of administration, is identical in strength or concentration, and is bioequivalent to an RLD that FDA already has found to be safe and effective for its intended use(s). 21 U.S.C. § 355(j)(2)(A). Where these "sameness" requirements are satisfied, ANDA applicants need not replicate the RLD holder's prior clinical trials, because two materially indistinguishable drug products can be expected to have "the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3.

The 505(b)(2) pathway similarly allows sponsors to seek approval for a follow-on drug product based at least in part on FDA's prior safety and efficacy findings for a previously marketed drug. 21 U.S.C. § 355(b)(2); FDA, Guidance for Industry, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (the "505(b)(2) Guidance"), at 4 (May 2019). But because a 505(b)(2) drug product is not necessarily the same as its RLD in all material respects, a 505(b)(2) sponsor can rely on FDA's prior safety or efficacy findings "for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication or other conditions of use) in common with the relied-upon listed drug(s)." 505(b)(2) Guidance at 4. Given that limitation, 505(b)(2) NDAs must include sufficient data to establish that the proposed follow-on product shares the relevant characteristics of the RLD on which it is relying and then "establish a bridge" between the proposed follow-on product and the RLD in order to justify reliance on FDA's prior findings that the RLD is safe and effective for its intended use(s). *Id*. (italics omitted). Finally, the 505(b)(2) NDA must include sufficient data to support the follow-on product's approval despite any differences from its RLD. *Id.* at 4-5 (citing *inter alia* 21 C.F.R. § 314.54(a)).

2. The FDCA's Quality Requirements

Regardless of whether follow-on product approval is sought *via* ANDA or 505(b)(2) NDA, the FDCA and FDA's implementing regulations have always required that every drug product be manufactured, processed, packed, and held in accordance with CGMP. *See, e.g.*, 21 U.S.C. § 351(a)(2)(B). After all, the approval of any drug application hinges on proof that the drug product will be safe ***and*** effective for use in ***all*** of its intended uses, *id.* §§ 355(b), (j), and no drug product can be considered safe ***or*** effective for ***any*** intended use unless it is manufactured, processed, packed, and held under appropriately controlled conditions.

The statute therefore requires every applicant to include in its application "a full list of the articles used as components of such drug; a full statement of the composition of such drug; [and] a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug." *Id.* § 355(b)(1)(ii)-(iv) (internal numbering omitted). It then provides that FDA "shall" deny any NDA if "the methods used in, and the facilities and

controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity." *Id*. § 355(d)(3); *see also* 21 C.F.R. § 314.125(a)(3)-(b)(1), (b)(13) (requiring FDA to refuse to approve an NDA if "[t]he methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability" or if "[t]he methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211").

These requirements apply with full force and effect not only to establishments involved in the production and disposition of finished drug products, but to those handling drug substances and intermediates prior to the manufacturing, production, and disposition of finished drug products. *See* 21 C.F.R. § 314.50(d). Indeed, precisely so that FDA can ensure that tainted drugs do not enter interstate commerce, the Agency has long made clear that these requirements extend with full force to "[a]ll intermediate … and final drug substance manufacturing and testing sites that are proposed to be involved in the disposition of commercial product" and "[a]ll facilities used for storing or warehousing drug substance, in-process material, and commercial drug product under quarantine prior to a disposition decision." FDA, Guidance for Industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers* (the "Disclosure Guidance"), at 2-3 & n.2 (Oct. 2019); *see also id*. at 6-7.

The statute also makes clear that any such facility's non-compliance with CGMP is not only a basis for ***withholding*** approval in the first instance, but also for ***withdrawing*** a previously granted approval whenever new information "evaluated together with the evidence before [FDA] when the application was approved, [shows that] the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity." 21 U.S.C. § 355(e). Taken together, these provisions leave no doubt that CGMP compliance is a prerequisite to any form of approval and that CGMP noncompliance requires withdrawing any previously granted approval.

3. Tentative Approval

Where a follow-on product application meets all the statute's substantive requirements for approval—including proof of full CGMP compliance throughout its supply chain—FDA typically issues FA. *See* 21 U.S.C. § 355(c)(1); 21 C.F.R. 314.105(a). But in some cases, unexpired patents or exclusivities protecting the RLD nonetheless require FDA to refrain from granting FA even if the follow-on application otherwise meets the scientific and technical requirements for approval. In those cases, FDA's regulations provide for the award of TA.

FDA's regulations repeatedly make—and have always made—clear that eligibility for ***any*** form of approval hinges on proof that a follow-on product sponsor's supply chain fully complies with CGMP:

> FDA will approve an NDA and send the applicant an approval letter ***if none of the reasons in § 314.125[4] for refusing to approve the NDA applies***. FDA will issue a tentative approval letter ***if an NDA otherwise meets the requirements for approval under the [FDCA]***, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the [FDCA] and § 316.31 of this chapter, or ***if a 505(b)(2) application otherwise meets the requirements for approval under the [FDCA]***, but cannot be approved until the conditions in § 314.107(b)(3) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the [FDCA]; or because there is a period of exclusivity for the listed drug under section 505E of the [FDCA]."

21 C.F.R. § 314.105(a) (emphases added); *see also id*. § 314.3(b) (defining TA as "notification that an NDA or ANDA ***otherwise meets the requirements for approval under the [FDCA]***, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the [FDCA] and § 316.31 of this chapter, or that a 505(b)(2) application or ANDA ***otherwise meets the requirements for approval under the [FDCA]***, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the [FDCA]; because there is a period of exclusivity for the listed drug under section 505E of the [FDCA]; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified") (emphasis added).

Although TA is not the same as FA, both approval actions require that an applicant meet ***all*** the statute's substantive requirements for approval, including proof of full CGMP compliance throughout its supply chain. FDA's regulations provide that "[a] drug product that is granted [TA] is ***not*** an approved drug and will ***not*** be approved until FDA issues an approval after any necessary additional review of the NDA." 21 C.F.R. § 314.105(a) (emphasis added); *see also id.* § 314.107(b)(4) ("[TA] of an NDA or ANDA does ***not*** constitute 'approval' of an NDA or ANDA and ***cannot***, absent an approval letter from the Agency, result in an approval under paragraph (b)(3) of this section.") (same).

Approvals—whether tentative or final—are not etched in stone for all time. FDA's TA regulations have always provided that TA merely "is based on information available to FDA at the time of the [TA] letter." *Id*. § 314.105(a). And because new facts can always come to light, FDA's regulations

[4] As we noted *supra* at pg. 4-5, cross-referenced 21 C.F.R. § 314.125 directs FDA to refuse to approve a 505(b)(2) NDA for CGMP non-compliance: if "[t]he methods used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability." *Id*. § 314.125(b)(1). It further requires FDA to refuse approval if "[t]he methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211." *Id*. § 314.125(b)(13).

further provide that TA status remains "subject to change on the basis of new information that may come to FDA's attention," ***including*** new information regarding "***the status of [CGMP]*** of the facilities used in the manufacturing and testing of the drug product." *Id.* (emphasis added). Indeed, the standard language FDA includes in every letter awarding TA—including the very TA letter Liquidia received for YUTREPIA—specifically warns that the Agency's initial TA "determination is subject to change on the basis of any new information that may come to [FDA's] attention." *See e.g.*, YUTREPIA TA Letter, NDA 213005 (Nov. 4, 2021).

As those regulations make explicit, one such circumstance—indeed, the most common circumstance warranting a change in status—is newly discovered evidence that the applicant's supply chain suffers from CGMP problems, whether at the time of the TA or afterwards. *See* 21 C.F.R. § 314.105(a) (expressly referencing new information regarding "the status of [CGMP] of the facilities"). That makes sense: As we emphasized *supra* at pg. 5, the statute articulates circumstances under which the FDA may withdraw any approval—final or otherwise—including cases in which "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity." 21 U.S.C. § 355(e). FDA's regulations parallel its statutory authority. *See, e.g.*, 21 C.F.R. § 314.125(b)(1) (directing FDA to refuse approval where the applicant's own facilities are non-compliant with CGMP); *id*. § 314.125(b)(13) (directing FDA to refuse approval where an applicant's supplier's facilities are non-compliant with CGMP).

Following these regulations, FDA routinely and consistently denies or rescinds approval (including TA) in the face of newly recognized CGMP violations. *See, e.g.*, Final Br. for Appellees [the "FDA Brief"], at 39, *Sun Pharm. Indus., Inc. v. Burwell*, No. 15-5063 (D.C. Cir. filed July 1, 2015) ("FDA has consistently construed the FDCA to condition [TA] on a showing that the substantive requirements for final approval are met—including compliance with [CGMP]…. FDA has consistently taken this position with respect to other applications both before and after the erroneous [TAs] here at issue.") (citing prior administrative precedents). And the courts expressly have affirmed FDA's authority to do so, even when the CGMP violations warranting denial or rescission of an approval are recognized by FDA many years after the fact. *See, e.g.*, *Ranbaxy Labs., Ltd. v. Burwell*, 82 F. Supp. 3d 159, 192 (D.D.C. 2015) ("FDA has the inherent authority to rescind tentative approval" (emphasis omitted)); *see also id*. at 198 ("Even though that error [in awarding TA to a noncompliant applicant] was belatedly corrected, the agency has the inherent authority to correct its mistakes.").

When new information comes to FDA's attention that warrants recission of a previously granted TA, the appropriate course of action is for FDA to issue a CRL requiring the applicant to correct all identified deficiencies (*e.g.*, the CGMP issues that necessitated revocation). *See* 21 C.F.R. § 314.110(a). The applicant must then amend and resubmit its application for further Agency review, but is barred from doing so until after it has fully "address[ed] all deficiencies identified in the [CRL]." *Id*. § 314.110(b)(1). Where a CRL is based on CGMP non-compliance, the applicant's resubmission naturally requires reinspection of all non-compliant facilities and therefore is appropriately categorized as a Class 2 resubmission. *See id*. § 314.110(b)(1)(ii); *see also* FDA, Manual of Policies and Procedures 6020.4 Rev. 2, at 2 (Feb. 26, 2015) ("A resubmission

that requires a reinspection [is] a Class 2 resubmission."). FDA cannot grant FA until it has ensured full CGMP compliance throughout the applicant's supply chain.

B. Factual Background

1. UTC's TYVASO and Liquidia's YUTREPIA

UTC is the sponsor of TYVASO, an inhaled form of the drug treprostinil that FDA has approved for two distinct indications: treatment of pulmonary arterial hypertension ("PAH") and treatment of pulmonary hypertension-interstitial lung disease ("PH-ILD"). UTC sought approval of its TYVASO NDA for treatment of PAH in June 2008, and FDA approved it in July 2009. NDA 022387, Approval Letter (July 30, 2009). UTC then submitted a supplemental NDA for TYVASO for treatment of PH-ILD in June 2020, which FDA approved in 2021. NDA 022387, s-017, Approval Letter (Mar. 31, 2021). UTC's product is the first-and-only approved therapy for PH-ILD.

In January 2020, Liquidia submitted an NDA seeking FDA marketing approval for YUTREPIA for the treatment of PAH. NDA 213005, TA Letter (Nov. 4, 2021). Liquidia submitted its application under section 505(b)(2) and relied in part on FDA's prior approval of UTC's TYVASO as safe and effective in the treatment of PAH. FDA tentatively approved Liquidia's 505(b)(2) NDA for YUTREPIA in November 2021, but FDA has not yet granted FA to the YUTREPIA NDA. *Id*.[5]

2. Liquidia's Exclusive API Supplier LGM Has Agreed to a Consent Decree to Remediate Alleged Systemic CGMP Violations That Repeatedly Caused the Introduction of Adulterated Drugs into Interstate Commerce.

Liquidia's public SEC filings disclose that its YUTREPIA NDA "rel[ies] on ***a sole supplier***, LGM Pharma LLC, for treprostinil," which is the API in YUTREPIA. Liquidia, Form 10-K, at 11 (Apr. 29, 2024) (emphasis added). It further discloses that Liquidia has "entered into a multi-year supply

[5] In July 2023, Liquidia amended its tentatively approved YUTREPIA 505(b)(2) NDA to add a new PH-ILD indication, and FDA accepted the amendment for review in September 2023. Press Release, Liquidia Submits Amendment to Add PH-ILD Indication to Tentatively Approved NDA for YUTREPIA™ (treprostinil) Inhalation Powder, https://www.liquidia.com/node/10556/pdf; Press Release, FDA Accepts Submission to Add PH-ILD to YUTREPIA Label (Sept. 25, 2023) at 1, https://www.liquidia.com/node/10646/pdf. UTC objected to the filing of this amendment pursuant to FDA's Bundling Rule, which precludes the submission of an amendment to a pending 505(b)(2) NDA to add an indication. *See* Complaint, *United Therapeutics Corp. v. Liquidia Techs., Inc*., No. 24-cv-484 (Feb. 20, 2024). FDA maintains that it has not yet determined whether that amendment was proper but nevertheless admits that the amendment was filed pursuant to 21 C.F.R. § 314.101(a)(1). *Id*. To the best of UTC's knowledge, no decision has been made on the approvability of the PH-ILD indication in the YUTREPIA 505(b)(2) NDA.

agreement with [LGM] to produce [APIs] for YUTREPIA," which "expires five years from the first marketing authorization approval" of the product. *Id*.

LGM "is engaged in the importation and distribution of drugs, including [APIs], manufactured primarily by companies operating outside the United States." Compl. For Permanent Injunction (the "FDA Compl."), at 2, *U.S. v. LGM Pharma LLC*, Docket No. 9:23-cv-80040 (S.D. Fl. Jan. 11, 2023) (Exh. 1). The APIs LGM sources from overseas are then used in the manufacture of finished drug products that, like YUTREPIA, are intended for sale in the United States. *See id.* In particular, LGM "receive[s], hold[s], and distribute[s] articles of drug … in interstate commerce, including thousands of API, imported from hundreds of suppliers located primarily outside the United States, and that are further distributed by LGM Pharma to its customers located throughout the United States." *Id.* at 3.

In the case of YUTREPIA, LGM is far more than a disinterested intermediary or facilitator. It instead is party to at least two publicly available agreements between Liquidia, LGM, and the Korean API developer Yonsung Fine Chemicals Co., LTD ("Yonsung") that FDA may not be aware of—one that governs LGM's ***supply*** responsibilities (the "Supply Agreement," Exh. 2) and one that details its ***quality*** responsibilities (the "Quality Agreement," Exh. 3). These agreements vest Yonsung with primary responsibility for producing raw trepostinil API in the first instance, and they charge LGM with an array of critically important compliance and quality responsibilities throughout the ensuing supply, distribution, and commercial chains. These include obligations to: "insure that during storage and shipping the PRODUCT(s) shall be protected from the possibility of deterioration, contamination or comingling with any other material," Quality Agreement at 6-7; "stor[e] and distribut[e the API] in accordance to current industry standards," *id*. at 7; "[q]uarantine PRODUCT(S) with questionable quality" and if necessary "recall PRODUCT(S) from distribution network," *id*.; "respond to complaints by [Liquidia] in a timely manner and according to formally agreed procedures consistent with [CGMP]," *id*. at 5; investigate and "inform [Liquidia] in a timely manner and in writing on the conclusions driven by the investigation performed and on corrective/preventative actions defined and taken," *id*. at 5; "document[] all deviations, investigat[e] Out of Specifications (OOS) and critical deviations," *id*. at 9; "prepar[e] reports on OOS, critical deviations," *id*. at 10; and even "notify[] authorities, external customers, or consumers." *Id*.

The Agreements further compel LGM to "keep complete and accurate records (including without limitation reports, accounts, data, and records of all information and results obtained from performance of services) of all work done by it under this Agreement," "ensure that all Records of the Manufacture of API under this Agreement will be retained and archived in accordance with cGMP," and make those records "available at reasonable times for inspection, examination and copying by FDA," Supply Agreement ¶ 2.4; to "determine the conformity of the API to the Product Specifications" where issues relating to product quality arise, *id*. ¶ 4.7(b); and, ultimately, to bear liability "to the extent that the API was not Manufactured in accordance with the Product

Specifications, cGMPs, Quality Agreement or Applicable Law or the liability otherwise arises from a breach of this Agreement." *Id*. ¶ 4.9.[6]

Finally, it appears that under its arrangement with Liquidia and Yonsung, LGM has also made critical disposition determinations for the treprostinil API. Evidence admitted to the record in UTC and Liquidia's separate patent litigation demonstrates that LGM has made disposition decisions for the treprostinil API, and Liquidia appears to contemplate that LGM will continue to so as part of the manufacturing supply chain during commercial production. In particular, LGM has made independent decisions about the quality and CGMP status of treprostinil API prior to shipping it to Liquidia, based on LGM's own review of GMP data.[7] LGM also has made representations to Liquidia about the quality of lots of API, the conformity of API to specifications as set out in the agreements between Liquidia and LGM, and the suitability of the API for use by Liquidia.[8] Finally, Liquidia has also established that LGM will continue to perform activities in

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[6] The Supply Agreement defines "'Manufacture' or 'Manufacturing' [as] activities directed to and processes used by Supplier [*i.e*., LGM] and/or Manufacturer [*i.e*., Yonsung], as the case may be, in producing, manufacturing, processing, packaging, labeling, quality assurance testing and release, shipping and storage of the API." Supply Agreement ¶ 1.16.

[7] LGM email to Liquidia, Exh. PTX 0104 at LIQ02798181, *United Therapeutics Corp. v. Liquidia Tech., Inc.*, No. 20-755 (D.Del. Mar. 2022) ("A quick note, the Treprostinil shipment from Korea to LGM had a temperature deviation for up to 16C for 9 days. However, our QC released the shipment because Yonsung has long-term stability showing the Treprostinil is stable at room temperature for 6 months. Also, LGM will add a data logger for transit to Liquidia.")

[8] Transcript of Record at 346:11-346:14, *United Therapeutics Corp. v. Liquidia Tech., Inc.*, No. 20-755 (D.Del. Mar. 28, 2022) ("So, the supplier [LGM] is telling and it's providing information to Liquidia that we can move forward with this forward based on stability results; right? A. **That was the decision their quality group made**." (emphasis added)); *id.* at 370:14-25; *id.* at 369:14-370:6:

> Q: **Did LGM provide the lots of Treprostinil sodium to Liquidia after recognizing there had been a temperature excursion** above 8 degrees during shipment for those batches?
>
> A. **We informed Liquidia there had been a temperature excursion during shipment, and then we did provide that material to Liquidia,** yes.
>
> Q. **What determination did LGM make prior to providing those batches** that experienced a temperature excursion to Liquidia prior to shipment to Liquidia?
>
> A. **LGM determined that the material met specifications** for sale to Liquidia and that Liquidia would have the opportunity to analyze and reject or accept the material. Q. H**ow was LGM aware that there had been a temperature excursion** during shipment of these last three batches provided to Liquidia? A. **A data logger had been included within the shipment by Yonsung. And upon looking at that data, it was indicated that there had been a temperature excursion.** (emphasis added)).

support of disposition decisions about the API in the proposed commercial manufacturing supply chain for YUTREPIA.

Despite being vested with such critically important quality and compliance responsibilities, LGM has a long and sordid history of non-compliance with the FDCA and FDA's CGMP regulations. Inspections dating back to at least 2010 show that the company has been plagued by repeated drug quality and misbranding violations. FDA, Inspection Dashboard, FEI 301714077 (last visited Apr. 19, 2024). While many of LGM's earlier-identified violations appear to have been relatively minor and often were rated "Voluntary Action Indicated," FDA's inspections of LGM began to identify far more serious violations by 2018—shortly ***before*** submission of the YUTREPIA NDA and during the time period when that product appears to have been under development using API that was supplied by LGM.

In 2018, FDA inspected LGM's Kentucky facility and listed ***eleven*** inspectional observations, FDA Compl. ¶ 19 ("At the close the 2018 Inspection, FDA investigators issued an FDA Form 483 listing 11 inspectional observations."). That is far above the average of ***four*** observations per Form 483 that year. ProPharma, FDA's Top 4893 Observations for 2018 (May 30, 2019), *available at* https://tinyurl.com/propharm483. Those violations not only were serious, but in several cases overlapped directly with LGM's responsibilities under the Quality and Supply Agreements it executed with Liquidia and Yonsung; among other things, FDA cited LGM for "[f]ailure to have an adequate quality unit," "[f]ailure to adequately investigate and resolve quality complaints," "[f]ailure to adequately qualify API suppliers," "[f]ailure to properly register suppliers with FDA," and "[f]ailure to justify re-labeling of drugs." FDA Compl. ¶ 19.A-E.

FDA initially gave LGM an opportunity to respond to the observations but "subsequently received a series of responses to the FDA Form 483 that did not adequately address the identified violations." *Id*. ¶ 19. FDA therefore reinspected both LGM's Kentucky facility in March 2022 and its corporate headquarters in Florida in April 2022—some five months ***after*** YUTREPIA's November 2021 TA. *Id.* ¶ 12. These inspections revealed even more widespread problems than the 2018 inspection, including an array of instances in which LGM failed to comply with CGMP that are directly applicable to its contractually defined roles in receiving, holding, and distributing API for YUTREPIA.

In particular, FDA's subsequent Form 483s cited multiple observations—some repeated from 2018—detailing quality control issues that the Agency determined continued to pose serious and ongoing risks to the public. These significant deviations included, but were not limited to, the following:

- "Failure to accurately perform quality control measures."
- "Failure to adequately investigate and resolve quality-related complaints."
- "Failure to properly document investigations into deviations and complaints."

- "Failure to qualify API suppliers in accordance with established [Standard Operating Procedures ('SOPs')]."

- "Failure to establish adequate SOPs for distribution of products after manufacturer disqualification and to follow existing SOPs for distribution of such product."

- "Failure to follow established SOPs for registering API manufacturers with FDA."

Id. ¶ 13.A-E.

Accordingly, within a four-year span that began ***before*** Liquidia submitted its YUTREPIA NDA; was ongoing ***at the time*** FDA granted TA to the YUTREPIA NDA; and that continued ***even after*** FDA granted TA to the YUTREPIA NDA, FDA's inspections revealed that LGM was failing to maintain or perform even the most basic quality functions. It was failing to investigate repeated complaints, document its work, or maintain records; violating its own SOPs; knowingly shipping vast quantities of out-of-specification API to its customers; failing to qualify multiple suppliers from whom LGM ordered and received hundreds of APIs; and even was importing APIs from suppliers who were under an Import Alert. *Id.* ¶ 19.C ("LGM Pharma imported API from suppliers placed on FDA Import Alerts, which inform FDA's field staff and the public that the agency has enough evidence to detain imported drugs that appear to be in violation of the FDCA, and imported two shipments of cidofovir API that were manufactured by a Chinese company that had not been evaluated and qualified by Defendants…. LGM Pharma's supplier qualification procedures remain non-compliant.").

Given FDA's findings concerning LGM's severe and pervasive CGMP violations, the United States filed suit in January 2023 alleging that LGM, its CEO, and its senior vice president of quality and regulatory affairs were liable for introducing or causing the introduction of adulterated drugs into interstate commerce. *Id.* ¶ 1. Specifically, the United States sought to "permanently enjoin and restrain" LGM and its senior executives from "(a) violating 21 U.S.C. § 331(a) by introducing or causing to be introduced, or delivering or causing to be delivered for introduction, into interstate commerce, articles of drug that are adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B); and (b) violating 21 U.S.C. § 331(k) by causing articles of drug to become adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B), while such drugs are held for sale after shipment of one or more of their components in interstate commerce." *Id.*

The parties eventually entered into, and the court approved, an extraordinary Consent Decree. *See* Order Requiring Compliance With Consent Decree of Permanent Injunction and Closing Case, No. 9:23-cv-90040 (S.D. Fl., Jan. 30, 2023) (Exh. 4) ("The parties' Consent Decree of Permanent Injunction [ECF No. 4-1, dated January 12, 2023] is approved as an Order of this Court. The parties are ordered to comply with the terms of the Consent Decree of Permanent Injunction."). Given the seriousness of the CGMP violations FDA had documented, the terms of the Consent Decree are onerous and will require an extraordinary commitment of resources over many years. Among other things, they require that:

- LGM "retain . . . an independent person or persons (the 'expert') who is without any personal or financial ties (including, but not limited to, prior employment by the Corporate Defendant), other than a retention agreement to satisfy the requirements of this provision, to Defendants; and who, by reason of background, training, education, or experience, is qualified to conduct inspections of Defendants' facilities to determine whether Defendants' methods and controls for receiving, labeling, holding, and/or distributing drugs, including quality controls, are established and operate in a manner that conforms with [CGMP], and to ensure that Defendants' drugs are not adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B)." Consent Decree ¶ 6.

- The expert must "undertake and complete a comprehensive inspection of Defendants' facilities and the methods and controls used to receive, label, hold, and/or distribute drugs to determine whether Defendants' methods and controls are, at a minimum, in conformity with CGMP and adequate to prevent Defendants' drugs from becoming adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B)." *Id.* ¶ 7.

- The expert must also, "after reviewing all of FDA's inspectional observations from December 2018 to present, and Defendants' responses and implemented and/or proposed remediation procedures and/or corrective actions, develop a comprehensive, written quality assurance and control program ('QA/QC program') that is adequate to ensure continuous compliance with this Decree, the Act, and its implementing regulations." *Id.* ¶ 7.A. That QA/QC program must meet ***sixteen*** criteria—it must:

    - "Include[] written [SOPs] specifying the responsibilities and procedures applicable to QA/QC personnel and establishes procedures to ensure that such written SOPs are followed," *id.* ¶ 7.A.(1);

    - "Require[] that personnel managing, directing and conducting the QA/QC program are adequate in number, location, and qualifications (education, training, and experience, or a combination thereof) to perform the roles and responsibilities assigned to them and ensure that such personnel conduct their duties in conformance with applicable written SOPs and the requirements of this Decree," *id.* ¶ 7.A.(2);

    - "Operate[] in coordination with, and under appropriate oversight of, QA/QC management at Defendants' facilities," *id.* ¶ 7.A.(3);

    - "Include[] written SOPs to ensure that QA/QC management at Defendants' facilities: (i) is promptly notified of deviations and/or violations that could affect the safety, identity, strength, quality, and purity of drugs; (ii) participates in and/or monitors the implementation and verification of corrective actions to prevent future occurrences of such deviations and/or

violations; and (iii) ensures that such written SOPs are continuously followed," *id.* ¶ 7.A.(4);

- "Address[] compliance monitoring and trend analyses necessary to effectively manage compliance with this Decree, the Act, and its implementing regulations, records management systems, and internal audit procedures," *id.* ¶ 7.A.(5);

- "Include[] written SOPs for adequate internal auditing," *id.* ¶ 7.A.(6);

- "Include[] written SOPs to ensure that Defendants thoroughly investigate and document in a timely manner any complaint, return, adverse event, discrepancy, and/or deviation from procedure, and any associated trends in product quality deviations and/or problems, and that Defendants take any needed corrective actions in a timely manner," *id.* ¶ 7.A.(7);

- "Include[] written SOPs to ensure Defendants' employees receive adequate training on CGMP compliance, including prevention and correction of CGMP deviations," *id.* ¶ 7.A.(8);

- "Include[] written SOPs to ensure Defendants maintain accurate and complete traceability of drugs they receive, label, hold, and/or distribute," *id.* ¶ 7.A.(9);

- "Include[] written SOPs for re-labeling and/or supplemental labeling of drugs, that, at a minimum, include provisions prohibiting changes to the identity of a drug on a label without verification, including laboratory analyses," *id.* ¶ 7.A.(10);

- "Include[] written SOPs for qualification and disqualification of manufacturers, suppliers, and vendors of drugs that Defendants receive, label, hold, and/or distribute, including, but not limited to, requiring on-site visits for initial qualification and ongoing monitoring," *id.* ¶ 7.A.(11);

- "Include[] written SOPs that require Defendants to confirm that the identity of the manufacturer of any drug(s) received, labeled, held and/or distributed by Defendants is accurate," *id.* ¶ 7.A.(12);

- "Include[] written SOPs concerning the drug registration and/or listing with FDA by Defendants (including any designation of Defendants as U.S. agents) that, at a minimum, require Defendants to obtain signed, written authorization directly from the manufacturer being registered before Defendants submit such drug registrations and/or listings with FDA (including any designation of Defendants as U.S. agents), and to maintain records of the authorization(s)," *id.* ¶ 7.A.(13);

- "Include[] written SOPs for recall procedures adequate to expeditiously and thoroughly implement and document recalls initiated by Defendants or FDA," *id.* ¶ 7.A.(14);

- "Include[] written SOPs for adequate document control and record-keeping, including validation procedures for any electronic systems used for such purposes," *id.* ¶ 7.A.(15); and

- "Include[] written procedures to ensure that SOPs are periodically re-evaluated so that they remain in continuous compliance with applicable laws and regulations," *id.* ¶ 7.A.(16).

In addition, the expert must:

- "[R]eview all drug registrations and/or listings with FDA which Defendants submitted or caused to be submitted (including any designations of Defendants or their Associated Persons as U.S. agents) to determine whether signed, written authorization for each such drug registration and/or listing exists, and provide a list to Defendants of any drug registrations and/or listings (including any designations of Defendants or their Associated Persons as U.S. agents) for which signed, written authorization was not identified," *id*. ¶ 7.B;

- "[R]eview all entities on Defendants' current list of approved manufacturers, suppliers, and/or vendors, and verify that each has met qualification acceptance criteria consistent with CGMP and adequate to prevent their drugs from becoming adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B)," *id.* ¶ 7.C; and

- "[T]rain Defendants' quality control unit and management on CGMP applicable to the receiving, labeling, holding, and/or distribution of drugs, including the QA/QC program SOPs … and certify that this training has been completed," *id.* ¶ 8.

Only after the above steps are completed can the expert "certify in writing simultaneously to FDA and Defendants," *id.* ¶ 9, whether, among other things:

- "[A]ll deviations from the requirements of this Decree, the Act, and its implementing regulations brought to Defendants' attention by FDA, the expert, and any other source have been corrected, including violations set forth in FDA's Inspectional Observations (Forms FDA 483) from all FDA inspections since 2018," *id.* ¶ 9.B; and

- "Whether Defendants' facilities, methods and controls comply with this Decree, the Act, and its implementing regulations, including whether Defendants' methods and controls are adequate to prevent their drugs from becoming adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B)," *id.* ¶ 9.C.

The Consent Decree then requires LGM and its executives to "report to FDA in writing the actions they have taken to," *id*. ¶ 10:

- "Correct all deviations from the requirements of this Decree, the Act, and its implementing regulations, brought to Defendants' attention by FDA, the expert, or any other source," *id.* ¶ 10.A;

- "Ensure that Defendants' methods, and controls used to receive, label, hold, and/or distribute drugs are established, operated, and administered in conformity with this Decree, CGMP, the Act, and its implementing regulations," *id.* ¶ 10.B;

- "Obtain signed, written authorization from the manufacturer for each drug registration and listing (including any designation as U.S. agent) identified by the expert as missing after the expert's review pursuant to paragraph 7.B; in lieu of obtaining such written authorization, Defendants may withdraw the drug registration and/or listing," *id.* ¶ 10.C;

- "Remove any manufacturers, vendors, and/or suppliers whose qualification was not verified by the expert," *id.* ¶ 10.D; and

- "Notify customers and complete recalls with respect to any violations, discrepancies, problems, or issues affecting the quality or identity of drugs imported and/or distributed by Defendants discovered during the expert's inspection," *id.* ¶ 10.E.

After all these steps are completed, "FDA representatives, without prior notice and when FDA deems necessary, may inspect Defendants' facilities to determine whether Defendants comply with th[e] Decree, CGMP, the Act, and its implementing regulations." *Id*. ¶ 11. And only once any such inspection has been conducted will FDA "notify Defendants in writing whether Defendants appear to be in compliance with this Decree, the Act, and its implementing regulations." *Id.* ¶ 12.

To the best of UTC's knowledge, no such notice has been provided to LGM. Yet in the midst of FDA's investigation into the serious violations at LGM, the Agency tentatively approved the YUTREPIA 505(b)(2) NDA in November 2021. And despite the post-TA filing of a Complaint and resulting Consent Decree documenting the grave risks LGM-supplied APIs pose for the integrity of the U.S. market, YUTREPIA continues to hold that TA to this day.[9]

[9] It is possible that Liquidia never made FDA aware of LGM's crucial role and responsibilities with respect to the YUTREPIA NDA, whether before or after the issuance of TA. Though the complete YUTREPIA NDA has not been publicly released, the limited portions that were introduced into public evidence during the patent litigation between UTC and Liquidia do not appear to contain any disclosure of LGM's involvement with the NDA—let alone its critically important supply and quality responsibilities with respect to the YUTREPIA API, which leave no

C. Argument

There is no lawful basis for maintaining the YUTREPIA NDA's current TA—let alone granting FA to that NDA—until LGM's significant CGMP problems have been fully resolved and FDA has reinspected LGM's "facilities to determine whether Defendants comply with th[e] Decree, CGMP, the [FDC] Act, and its implementing regulations." Consent Decree ¶ 11.[10] FDA's regulations are crystal clear that ***both*** the initial award ***and*** the continued maintenance of a previously awarded TA to a pending 505(b)(2) NDA is permissible ***only*** if the application "otherwise meets the requirements for approval under the [FDC] Act." 21 C.F.R. § 314.105(a); *see also id*. § 314.3(b) (same). This is, of course, also the case to obtain a FA. And FDA's regulations unambiguously specify that an applicant's eligibility for TA 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. *See id*. § 314.105(a) (providing that TA status remains "subject to change on the basis of new information that may come to FDA's attention").

The statutory approval requirements on which both TA and FA depend in turn require proof that a manufacturer's entire supply chain is fully CGMP-compliant. The statute and FDA's implementing regulations are crystal clear about that too. They authorize FDA to approve an NDA ***only*** if the Agency "finds that none of the grounds for denying approval specified in subsection (d) applies." 21 U.S.C. § 355(c)(1). And those grounds expressly and unambiguously require FDA to deny NDA approval both when FDA determines that "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity," 21 U.S.C. § 355(d)(3), and when "upon the basis of the information submitted to [FDA] as part of the application, or upon the basis of any other information before [FDA] with respect to such drug, [FDA] has insufficient information to determine whether such drug is safe for use." *Id*. § 355(d)(4).

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doubt that disclosure of its role was required. *See, e.g*., 21 C.F.R. § 314.50(d); Disclosure Guidance at 2-3 & n.2, 6-7 (detailing the facility disclosure requirements, including the need for a complete disclosure of "the locations of all manufacturing, packaging, and control sites for both drug substance and drug product," including any facility that is: "used for storing or warehousing drug substance, in-process material, and commercial drug product under quarantine prior to a disposition decision;" involved in making "a decision to assign a status within the commercial supply chain [such as] lot release, quarantine awaiting further data, or lot rejection;" or that otherwise is "part of the commercial process control strategy"). In the event FDA determines that Liquidia did not properly disclose LGM's vital role in the YUTREPIA supply chain, the Agency may wish to consider actions beyond those requested in this Petition.

[10] Although not specifically requested in this Petition, the significance, severity, and pervasiveness of LGM's alleged CGMP violations—which FDA found to be ongoing during YUTREPIA's development and persisted even after its submission and TA—call into question whether Liquidia should even be allowed to maintain its NDA.

For decades, FDA has implemented these statutory requirements by demanding that every aspect of an applicant's supply chain be and remain compliant with the Agency's CGMP requirements at all times. The Agency's regulations expressly provide that FDA "will refuse to approve the NDA" whenever "[t]he methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding ***of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability***." 21 C.F.R. § 314.125(a)(3)-(b)(1) (emphasis added). They further provide that FDA "will refuse to approve the NDA" whenever "[t]here is ***insufficient information about the drug to determine whether the product is safe for use***," which plainly includes circumstances where the integrity of the drug product or any its components is questionable. *Id*. § 314.125(a)(3)-(b)(4) (emphasis added). And the Agency's regulations remove any conceivable doubt that CGMP compliance is a mandatory approval requirement by providing that FDA "will refuse to approve the NDA" whenever "[t]he methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product ***do not comply with the current good manufacturing practice regulations in parts 210 and 211***." *Id*. § 314.125(a)(3)-(b)(13).

In short, then, the award and maintenance of TA for a 505(b)(2) NDA indisputably hinges on proof that the application meets all requirements for a final approval; final approval in turn requires proof that the applicant's entire supply chain is fully compliant with CGMP; and so neither TA nor FA can be awarded or maintained where any aspect of the applicant's supply chain is noncompliant or in doubt. Which of course is why the Agency for at least a decade has made clear that its "longstanding interpretation of the FDCA has been, and continues to be, that ***a showing of compliance with current good manufacturing practice is a requirement for [TA]***," FDA Brief at 46 (emphasis added); why "FDA has consistently construed the FDCA ***to condition [TA] on a showing that the substantive requirements for final approval are met—including compliance with current good manufacturing practice***," *id*. at 39, and why FDA—at least until this case—"has ***consistently taken this position with respect to [numerous] applications***." *Id*. (citing precedents; emphasis added).

Indeed, FDA has consistently enforced this position in prior cases (including ones in which it has rescinded previously granted TAs) and it has successfully defended its enforcement of this position in court. In 2014, for instance, FDA rescinded multiple previously awarded TAs after recognizing that the applicant's facilities were CGMP-noncompliant at the time those TAs had been granted. *See* Ltr. from FDA to Ranbaxy Labs. Ltd., Nov. 4, 2014, at 12 (Exh. 5) ("Upon review of our records, the Agency has determined that FDA erred in tentatively approving Ranbaxy's ANDAs for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg, and Valganciclovir Hydrochloride Tablets, 450 mg. Specifically, the compliance status of the facilities referenced in the ANDAs at the time the ANDAs were granted [TA] was inadequate to support approval or [TA]. ***FDA may not tentatively approve an ANDA like Ranbaxy's ANDAs for which there is evidence of non-compliance with CGMP. Accordingly, with this letter, the Agency is correcting its mistake and rescinding the [TA] letters issued regarding these ANDAs***.").

Ranbaxy then sued FDA alleging that quirks in the FDCA's ANDA-specific definition of TA—which is ***not*** applicable to 505(b)(2) NDAs, *see* 21 U.S.C. § 355(j)(5)(B)(iv)(II) (limiting the statute's lone reference to TA to "this paragraph," which addresses 180-day exclusivity for

ANDAs)—precluded FDA from conditioning the award or maintenance of TA on proof of CGMP compliance. The district court rejected that claim, calling Ranbaxy's argument that an application could be awarded TA despite proof of CGMP noncompliance both "untenable" and "patently absurd." *Ranbaxy*, 82 F. Supp. 3d at 188. It likewise rejected Ranbaxy's assertion that FDA lacks authority to rescind a previously granted TA when proof of CGMP noncompliance comes to the Agency's attention only after the award of TA—indeed, many years after the fact. *See, e.g*., *id*. at 193 (holding that FDA has "inherent authority to ensure the FDCA's statutory purpose is followed" by correcting the erroneous award of TA); *id*. at 195 (holding that the exercise of such authority is "particularly [important] in light of the public safety risks presented by disallowing the FDA from correcting its mistakes").

Given the plain text and structure of the FDCA and FDA's implementing regulations; the Agency's longstanding policy precluding the award or maintenance of an approval where CGMP issues exist; FDA's repeated and consistent enforcement of that policy against multiple applicants; and its successful defense of its position in court, there is no basis for maintaining YUTREPIA's TA—and even less justification for awarding it FA—until LGM's compliance issues have been fully remediated. As detailed *supra* at pg. 8-16, FDA found that LGM's non-compliance with CGMP not only was severe and pervasive enough to warrant the imposition of extreme remedies; the company's documented CGMP violations directly overlap with the precise responsibilities LGM's Quality and Supply Agreements required it to perform with respect to Liquidia's YUTREPIA NDA.

Against this backdrop, the YUTREPIA NDA ***never should have been granted TA*** given the extreme and pervasive violations of the Agency's CGMP requirements that FDA had found at the time that TA was awarded. And that TA assuredly cannot be maintained now—forget about progressing to FA—while a critically important facility in the manufacturing of YUTREPIA remains subject to an extraordinary course of judicially enforced corrective actions that will require years of work and extensive monitoring in order to ensure that LGM no longer causes the introduction of adulterated drugs into interstate commerce. Unless and until LGM discharges its obligations under the Consent Decree, and unless and until Liquidia is able to demonstrate to FDA's satisfaction that the CGMP problems at its exclusive API supplier have been fully remediated, Liquidia cannot possibly demonstrate that its YUTREPIA supply chain is CGMP-compliant—and therefore there is no basis for allowing the Company to receive, maintain, or be granted further approval, whether TA or FA.

D. Conclusion

For the foregoing reasons, FDA should rescind its award of TA to Liquidia's YUTREPIA NDA; issue Liquidia a CRL for the YUTREPIA NDA; and withhold any approval of the YUTREPIA NDA—whether a TA or ultimately a FA—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.

III. Environmental Impact

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

IV. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 5, 2024.[11] 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 person or organizations: UTC. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

DocuSigned by:
Dean Bunce
FA6EFB8FC9DC49D...

Dean Bunce

EVP, Global Regulatory Affairs

United Therapeutics Corporation

[11] Liquidia first appears to have disclosed its reliance on LGM as its sole supplier for the eventual YUTREPIA NDA in an SEC Registration Statement that was filed on or about June 28, 2018. *See* Liquidia, SEC Form S-1, at 19 (June 28, 2018). On or about January 30, 2023, FDA disseminated an email bulletin announcing the Consent Decree's entry; though several UTC employees appear to have been subscribed to that listserv, the bulletin contained no reference to Liquidia, trepostinil, or YUTREPIA, *see* https://content.govdelivery.com/accounts/USFDA/bulletins/345e126, and it does not appear that anyone at UTC connected the Agency's blast email to Liquidia, trepostinil, or YUTREPIA at that time. So far as we can tell, no one at UTC made that connection before April 5, 2024, at which point UTC immediately and without delay began investigating the issues giving rise to this Petition—the original version of which was filed just over one month after UTC became conscious of the grounds upon which the actions requested are based.