IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

LIQUIDIA TECHNOLOGIES, INC.,

Plaintiff,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, ROBERT M. CALIFF, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, XAVIER BECERRA, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES,

Defendants, and

UNITED THERAPEUTICS CORP.,

Intervenor-Defendant.

Case No. 1:24-cv-2428-TJK

ANSWER

Intervenor-Defendant United Therapeutics Corporation ("UTC") brings this Answer and these Cross-Claims to Liquidia Technologies, Inc.'s ("Liquidia") Complaint* against Defendants U.S. Food and Drug Administration ("FDA"), Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Department of Health and Human Services ("HHS"), and Xavier Becerra, in his official capacity as Secretary of HHS (collectively, "Defendants" or "FDA").

* For ease of reference, UTC includes the headings contained in Liquidia's Complaint. Although no response is necessary to each of the headings, to the extent that a response is required and that the headings could be construed to contain factual allegations, UTC denies the allegations.

INTRODUCTION

1. Liquidia challenges FDA's unlawful decision to extend market exclusivity to United Therapeutics Corporation ("UTC"), the incumbent manufacturer of a drug for treating pulmonary hypertension called treprostinil, and prohibit competition from Liquidia's Yutrepia, a safe and effective alternative treatment for patients with pulmonary hypertension. FDA's action is contrary to law and arbitrary and capricious. It improperly allows UTC to maintain its decades-long monopoly in violation of clear congressional intent permitting exclusivity only in strictly limited circumstances involving innovation. FDA exceeded its statutory mandate by improperly crediting a single study that fails to justify any exclusivity at all, and by granting UTC broad exclusivity for far more than the "innovation" the study purportedly covered, encompassing unstudied indications, patient populations, drug-device combination products, and formulations. FDA's decision should be vacated, and Liquidia must be allowed to bring Yutrepia to market for the benefit of patients.

Answer to ¶ 1. Paragraph 1 states legal conclusions to which no response is required. To the extent a response is required, denied.

2. The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (Sept. 24, 1984) (the "Hatch-Waxman Amendments") amended the Federal Food, Drug, and Cosmetic Act of 1938 ("FDCA") to provide sponsors of new drug applications ("NDA"), under certain conditions, with limited periods of protection from competition for the innovation represented by the sponsor's approved drug. These are known as exclusivity periods.

Answer to ¶ 2. Paragraph 2 states legal conclusions to which no response is required. To the extent a response is required, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (Sept. 24, 1984), speaks for itself and is the best source for its content.

Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 2.

3. This case involves one specific type of exclusivity in the FDCA, three-year new clinical investigation exclusivity ("NCI exclusivity"), which is afforded only where FDA finds a new clinical investigation essential to the approval of a new drug and that a competitor drug shares the same "conditions of approval." 21 U.S.C. § 355(c)(3)(E)(iii).

Answer to ¶ 3. Paragraph 3 states legal conclusions to which no response is required. To the extent a response is required, admitted that this case involves NCI exclusivity. In addition, 21 U.S.C. § 355(c)(3)(E)(iii) speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 3.

4. Notably, the FDCA limits the scope of NCI exclusivity for the new drug solely to the innovative change supported by the "new clinical investigation[]" that was "essential" to the FDA's decision to approve the NDA in the first instance. *Id.* This statutory limitation on the scope of NCI exclusivity serves the congressional purpose of the Hatch Waxman Amendments aimed at encouraging innovation in drug development while also accelerating patient access to affordable alternatives to such drugs through competition. *See AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 85 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (limiting "[NCI] exclusivity for significant innovations" furthers the FDCA's "careful balance between providing exclusivity rights to promote innovation and making generic alternatives available to patients").

Answer to ¶ 4. Paragraph 4 states legal conclusions to which no response is required. To the extent a response is required, 21 U.S.C. § 355(c)(3)(E)(iii) and *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60 (D.D.C. 2012), speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 4.

5. FDA's decision to award NCI exclusivity to UTC's new drug, Tyvaso Dry Powder Inhalation ("Tyvaso DPI") (the "Exclusivity Decision"), is not supported by any new clinical investigation, as defined and required by the FDCA and FDA regulations. Moreover, FDA's Exclusivity Decision improperly ascribed a broad scope to the "conditions of approval" supported by the one and only study—the BREEZE Study—it cites as "new" in its Exclusivity Decision.

Answer to ¶ 5. Paragraph 5 states legal conclusions to which no response is required. To the extent a response is required, UTC admits that FDA has recognized NCI exclusivity for UTC's Tyvaso Dry Powder Inhalation ("Tyvaso DPI"). Except as explicitly admitted in this paragraph, UTC denies the allegations of paragraph 5.

6. The result of FDA's Exclusivity Decision is that, contrary to congressional direction and FDA's own mission of allowing safe and effective products to reach the market, patients suffering from pulmonary hypertension ("PH") will be denied access to an additional safe and effective treprostinil treatment for pulmonary arterial hypertension ("PAH") and pulmonary hypertension associated with interstitial lung disease ("PH-ILD").

Answer to ¶ 6. Paragraph 6 states legal conclusions to which no response is required. To the extent a response is required, denied.

7. Liquidia filed an NDA seeking FDA approval for Yutrepia, its dry powder inhalation form of treprostinil to treat patients with PAH, on January 24, 2020, more than a year *before* UTC submitted its NDA for Tyvaso DPI, the drug blocking full approval of Yutrepia, on April 16, 2021. On July 24, 2023, Liquidia amended its Yutrepia NDA to treat patients with PH-ILD as well.

Answer to ¶ 7. UTC admits that Liquidia filed an NDA seeking FDA approval on or around January 24, 2020. UTC admits that UTC submitted its NDA for Tyvaso DPI on April 16, 2021.

UTC admits that Liquidia submitted to FDA a putative amendment to the Yutrepia NDA to treat patients with PH-ILD on or around July 24, 2023. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 7.

8. FDA's Exclusivity Decision, and its asserted scope of that NCI exclusivity, block FDA's full approval for Yutrepia's distribution to patients suffering from PAH and PH-ILD, contravene the plain text of the FDCA and FDA regulations, and constitute a final agency action that violates the Administrative Procedure Act ("APA").

Answer to ¶ 8. Paragraph 8 states legal conclusions to which no response is required. To the extent a response is required, admitted that the exclusivity described in FDA's Exclusivity Decision precludes FDA from granting final approval to Yutrepia. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 8.

9. Liquidia is entitled to declaratory and injunctive relief in the form of (i) a ruling declaring FDA's Exclusivity Decision unlawful because it exceeds FDA's statutory authority; (ii) a vacatur setting aside FDA's Exclusivity Decision; and (iii) preliminary and permanent injunctive relief requiring FDA to grant full approval to Yutrepia's NDA, or at minimum, limiting FDA's Exclusivity Decision to apply only to PAH patients thereby requiring FDA to grant full approval to Yutrepia's NDA for PH-ILD patients.

Answer to ¶ 9. Paragraph 9 states legal conclusions to which no response is required. To the extent a response is required, denied.

PARTIES

10. Plaintiff Liquidia is a clinical biopharmaceutical startup that develops life-saving therapies for patients, including those with rare diseases. Liquidia is organized under the laws of the State of Delaware. Its registered office is 251 Little Falls Drive, Wilmington Delaware 19808,

and its principal place of business is 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560. The first product developed by Liquidia is Yutrepia, an inhaled dry powder treprostinil formulation that safely and effectively treats patients with two kinds of PH—PAH and PH-ILD. Liquidia is the sponsor for the Yutrepia NDA.

Answer to ¶ 10. UTC admits the allegations in the second and fifth sentences of paragraph 10. UTC otherwise lacks sufficient knowledge to form a belief as to Liquidia's remaining allegations in paragraph 10 and therefore denies them.

11. Defendant FDA is an administrative agency of the United States government and a component of HHS charged with implementing the FDCA and responsible for the Exclusivity Decision described in this Complaint. FDA's headquarters and principal place of business are located at 10903 New Hampshire Ave., Silver Spring, MD 20903. Its governmental activities occur nationwide.

Answer to ¶ 11. The allegations in paragraph 11 are directed to another defendant.

12. Defendant Robert M. Califf, M.D., is the Commissioner of Food and Drugs and head of FDA, and is sued in his official capacity only. Commissioner Califf is responsible for administering the FDCA, and for overseeing FDA's actions described in this Complaint. He oversees governmental activities that occur nationwide.

Answer to ¶ 12. The allegations in paragraph 12 are directed to another defendant.

13. Defendant HHS is a cabinet-level department of the United States government that oversees FDA and the actions described in this Complaint. Its headquarters and principal place of business are located at 200 Independence Avenue, S.W., Washington, DC 20201. Its governmental activities occur nationwide.

Answer to ¶ 13. The allegations in paragraph 13 are directed to another defendant.

14. Defendant Xavier Becerra is Secretary of Health and Human Services and head of HHS, and is sued in his official capacity only. Secretary Becerra is ultimately responsible for activities at HHS and FDA, including administering the FDCA, and for overseeing the actions described in this Complaint. He maintains an office and carries out official duties in this district, and he oversees governmental activities that occur nationwide.

Answer to ¶ 14. The allegations in paragraph 14 are directed to another defendant.

JURISDICTION AND VENUE

15. This action arises under and asserts violations of the FDCA, 21 U.S.C. § 301 *et seq.*, and the APA, 5 U.S.C. § 551 *et seq.* The Court has subject-matter jurisdiction of this action pursuant to 28 U.S.C. §§ 1331, 1346, and 1361.

Answer to ¶ 15. Paragraph 15 states legal conclusions to which no response is required.

16. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e). HHS is located in this district, and Secretary Becerra maintains his office and performs his official duties in this district.

Answer to ¶ 16. Paragraph 16 states legal conclusions to which no response is required. To the extent that paragraph 16 contains allegations directed to other defendants, UTC lacks knowledge or information to form a belief as to their truth.

17. Sovereign immunity has been waived for the declaratory and injunctive relief sought in this Complaint. 5 U.S.C. § 702. This Court is authorized to grant Liquidia's request for declaratory relief pursuant to the Declaratory Judgment Act. 28 U.S.C. §§ 2201–2202.

Answer to ¶ 17. Paragraph 17 states legal conclusions to which no response is required.

18. FDA's Exclusivity Decision is a final agency action reviewable under the APA. *See* 5 U.S.C. § 704.

Answer to ¶ 18. Paragraph 18 states legal conclusions to which no response is required.

19. This dispute is ripe for judicial review because the issues presented are fit for judicial decision and Liquidia would incur substantial hardship were judicial review withheld.

Answer to ¶ 19. Paragraph 19 states legal conclusions to which no response is required.

20. Liquidia has standing to challenge this action because FDA's Exclusivity Decision, and its corresponding decision to deny full approval to Yutrepia, have deprived Liquidia of its right to lawfully distribute Yutrepia to patients nationwide. Had Liquidia received FDA's full approval for Yutrepia on August 16, 2024, as anticipated and required by law, Liquidia would have launched distribution of Yutrepia to patients nationwide within days of FDA's decision. In light of FDA's Exclusivity Decision, Liquidia's inability to distribute Yutrepia, which would have been Liquidia's sole commercial product, is causing irreparable injury to Liquidia and to patients with PAH and PH-ILD. *See* Liquidia, SEC Form 10-Q (Aug. 7, 2024).[1]

Answer to ¶ 20. Paragraph 20 states legal conclusions to which no response is required. To the extent a response is required, the document cited in this paragraph speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 20.

GENERAL ALLEGATIONS

I. STATUTORY AND REGULATORY BACKGROUND

21. Under the FDCA, FDA must conclude a new drug is safe and effective before it

[1] *See* https://www.sec.gov/ix?doc=/Archives/edgar/data/1819576/000155837024011206/lqda-20240630x10q.htm

can be introduced lawfully into interstate commerce. 21 U.S.C. § 355(a). The FDCA contemplates three types of drug applications to FDA for small molecule (*i.e.*, non-biological) drugs: (1) a full NDA under section 505(b)(1) of the FDCA, (2) an abbreviated NDA under section 505(j) of the FDCA, and (3) an intermediate form of NDA under section 505(b)(2) of the FDCA.

Answer to ¶ 21. Paragraph 21 states legal conclusions to which no response is required. To the extent a response is required, 21 U.S.C. § 355 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 21.

22. An NDA must include, among other things, adequate studies to show that the drug will be safe, and "substantial evidence" that the drug will be effective under the conditions of use prescribed, recommended, or suggested in its labeling. "Substantial evidence" is a term of art meaning one or more (usually at least two) adequate and well-controlled clinical trials conducted by qualified experts. 21 U.S.C. § 355(d); *see* 21 C.F.R. § 314.126.

Answer to ¶ 22. Paragraph 22 states legal conclusions to which no response is required. To the extent a response is required, 21 U.S.C. § 355(d) and 21 C.F.R. § 314.126 speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 22.

23. Under section 505(b)(1) of the FDCA, a sponsor may seek approval for a drug by providing FDA with full reports of investigations of safety and effectiveness. 21 U.S.C. § 355(b)(1). This type of application requires the applicant to conduct clinical and non-clinical studies to demonstrate the safety and effectiveness of the proposed new drug for its intended use.

Answer to ¶ 23. Paragraph 23 states legal conclusions to which no answer is required. To the extent a response is required, section 505(b)(1) speaks for itself and is the best source for its

content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 23.

24. Under section 505(b)(2)'s intermediate pathway (applicable to the Yutrepia NDA), the sponsor may submit an application to change or modify a "listed drug" for which the FDA already has made a finding of safety and effectiveness. 21 U.S.C. § 355(b)(2).

Answer to ¶ 24. Paragraph 24 states legal conclusions to which no answer is required. To the extent a response is required, section 505(b)(2), as codified in 21 U.S.C. § 355(b)(2), speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 24.

25. While a section 505(b)(2) NDA "must directly demonstrate that the proposed drug product is safe and effective," *Veloxis Pharmaceuticals, Inc. v. FDA*, 109 F. Supp. 3d 104, 108 (D.D.C. 2015), the section 505(b)(2) NDA sponsor need not conduct all the clinical studies itself and can rely, wholly or in part, "on clinical studies that were previously submitted to FDA in support of another drug" by a different sponsor. *Id.* at 109 (modified); 21 U.S.C. § 355(b)(2).[2] This is because, as Congress and FDA have recognized, it is duplicative and wasteful to carry out studies to reiterate what is already known about a drug. Consequently, a section 505(b)(2) NDA contains full reports of clinical studies demonstrating the safety and effectiveness of the proposed drug, but differs from a section 505(b)(1) NDA because it may draw on safety and/or efficacy data from previously approved drugs, or from published studies. Section 505(b)(2) NDAs must identify

[2] *See also Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, FDA (Feb. 11, 2016), https://www.fda.gov/drugs/cder-small-business-industry- assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity (Section 505(b)(2) "expressly permits FDA to rely for approval of an NDA, on data not developed by the applicant such as published literature or the agency's finding of safety and effectiveness of a previously approved drug.").

the "listed drug" on which their sponsor relies in seeking approval. 21 C.F.R. § 314.54(a)(1)(iii).

Answer to ¶ 25. Paragraph 25 states legal conclusions to which no answer is required. To the extent a response is required, Sections 505(b)(1) and 505(b)(2), as codified in 21 U.S.C. § 355(b)(1), (2), respectively, 21 C.F.R. § 314.54(a)(1)(iii), and *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104 (D.D.C. 2015), speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 25.

26. After it has reviewed an NDA, FDA typically (1) grants final approval, allowing immediate distribution subject to proper notice and labeling for the drug's approved indication(s); (2) grants tentative approval, indicating that the drug is safe and effective for use but that FDA must delay final approval for some reason, such as due to another drug's ongoing exclusivity period; or (3) provides a complete response letter, in which FDA notifies the NDA sponsor of deficiencies that preclude FDA from approving the NDA in its present form.

Answer to ¶ 26. Paragraph 26 states legal conclusions to which no response is required. To the extent a response is required, UTC admits that, after completing review of an NDA, FDA may grant final approval of the application, grant tentative approval of the application, or provide a complete response letter notifying the applicant of the deficiencies that prevent FDA from approving the applicant's NDA. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 26.

27. Under the Hatch-Waxman Amendments, following approval of an NDA, the FDCA allows for a three-year NCI exclusivity period only if specific statutory requirements are satisfied.

Answer to ¶ 27. Paragraph 27 states legal conclusions to which no response is required. To the extent a response is required, UTC admits that the FDCA requires a three-year NCI exclusivity period when certain statutory requirements are satisfied. Except as explicitly admitted in this

paragraph, UTC denies the allegations in paragraph 27.

28. ***First***, the FDCA requires that the drug's NDA "contain[] reports of new clinical investigations (other than bioavailability studies) . . . conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii).

Answer to ¶ 28. Paragraph 28 states legal conclusions to which no response is required. To the extent a response is required, 21 U.S.C. § 355(c)(3)(E)(iii) speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 28.

29. FDA has promulgated regulations implementing this statutory provision. Like the FDCA, FDA regulations exclude bioavailability studies from the clinical investigations eligible for NCI exclusivity. 21 C.F.R. § 314.108(a) (Clinical investigation means "any experiment other than a bioavailability study."). FDA regulations define "bioavailability" as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action." 21 C.F.R. § 314.3.

Answer to ¶ 29. Paragraph 29 states legal conclusions to which no response is required. To the extent a response is required, 21 C.F.R. § 314.108(a) and 21 C.F.R. § 314.3 speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 29.

30. Critically, for purposes of this case, FDA regulations expressly limit what may constitute a "new clinical investigation" to:

> ***[A]n investigation in humans the results of which*** have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and ***do not***

> ***duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product***. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

21 C.F.R. § 314.108 (emphases added).

Answer to ¶ 30. Paragraph 30 states legal conclusions to which no response is required. To the extent a response is required, 21 C.F.R. § 314.108 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 30.

31. ***Second***, FDA must find that those "new clinical investigations" were "essential to the approval of the application." 21 U.S.C. § 355(c)(3)(E)(iii).

Answer to ¶ 31. Paragraph 31 states legal conclusions to which no response is required. To the extent a response is required, 21 U.S.C. § 355(c)(3)(E)(iii) speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 31.

32. ***Third***, FDA must "identif[y] the relevant conditions of approval shared between [the drug receiving NCI exclusivity and the competitor drug's NDA]." *Veloxis*, 109 F. Supp. 3d at 120; *see* 21 U.S.C. § 355(c)(3)(E)(iii).

Answer to ¶ 32. Paragraph 32 states legal conclusions to which no response is required. To the extent a response is required, *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104 (D.D.C. 2015), and 21 U.S.C. § 355(c)(3)(E)(iii) speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 32.

33. As explained in *Veloxis*, FDA's identification of the "conditions of approval" "can be no broader than the innovations presented to the FDA in the new clinical investigations that led to the FDA's approval of the first-in-time 505(b) NDA." *Id.* at 121 n.16.

Answer to ¶ 33. Paragraph 33 states legal conclusions to which no response is required. To the extent a response is required, *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104 (D.D.C. 2015), speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 33.

34. The FDCA also requires a "logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting three-year [NCI] exclusivity." *See AstraZeneca*, 872 F. Supp. 2d at 80.

Answer to ¶ 34. Paragraph 34 states legal conclusions to which no response is required. To the extent a response is required, *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60 (D.D.C. 2012), speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 34.

35. This aligns with FDA's historical interpretation of the limited scope of the term "conditions of approval." *See* FDA, Center for Drug Evaluation and Research ("CDER"), NDA No. 206406 (Envarsus XR) General Advice Letter 21 (Jan. 15, 2015) ("Veloxis Letter"), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206406Orig1s000AdminCorres.pdf ("[C]onditions of approval" means only the "***innovative change*** that is supported by the new clinical investigations" that entitled the first-approved drug to NCI exclusivity) (emphasis added); 1989 Preamble to the Proposed Rule Implementing Title 1 of the Drug Price Competition and Patient Term Restoration Act, Abbreviated New Drug Application, Proposed Rule, 54 Fed. Reg.

28872, 28899 (July 10, 1989) ("1989 Preamble").[3] And as FDA regulations make clear, "[i]f the innovation is a new use, then exclusivity protects only that labeling claim and ***not the active ingredients, dosage form, or route of administration***." 1989 Preamble (emphasis added).

Answer to ¶ 35. Paragraph 35 states legal conclusions to which no response is required. To the extent a response is required, the documents and regulatory materials cited in this paragraph speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 35.

36. Once FDA has identified the narrow scope of NCI exclusivity derived from the innovative change studied in a new clinical investigation, FDA may only block a competitor's NDA for those specific "conditions of approval" (*e.g.*, indications or patient populations) for which NCI exclusivity was granted.

Answer to ¶ 36. Paragraph 36 states legal conclusions to which no response is required. To the extent a response is required, denied.

37. Otherwise, a drug sponsor could simply publish successive "new" studies every three years—with no innovation—showing that a new drug containing the same ingredients functions similarly to its older drugs (whose exclusivity periods have already expired) and demand that FDA tack on another exclusivity period—preserving its monopoly and precluding the very competition the FDCA intended by limiting NCI exclusivity to three years. This is precisely what FDA has unlawfully countenanced in its Exclusivity Decision here.

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[3] *See also Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, FDA (Feb. 11, 2016), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity ("Exclusivity provides the holder of an approved [NDA] limited protection from new competition in the marketplace for the innovation represented by its approved drug product.").

Answer to ¶ 37. Paragraph 37 states legal conclusions to which no response is required. To the extent a response is required, denied.

I. FACTUAL AND PROCEDURAL BACKGROUND

A. Treprostinil Is a Proven Treatment for PH Patients.

38. PH is a condition that causes elevated blood pressure in the pulmonary arteries. The increased strain that this elevated blood pressure places on the right ventricle of the heart can lead to right ventricular failure and death.[4] There are many potential causes of PH, and it is a comorbid condition for many other diseases.

Answer to ¶ 38. UTC admits that PH involves elevated blood pressure in the pulmonary vasculature. UTC further admits that there are many potential causes of PH, and the document cited in paragraph 38 speaks for itself. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 38.

39. The identification of various PH subtypes has led to the development of improved and differentiated treatment strategies.

Answer to ¶ 39. UTC admits that there are different treatment strategies for different causes of PH. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 39.

40. PH subtypes are classified into five different groups ("WHO Groups") based on shared histology, pathophysiology, clinical presentation, and treatment strategy, pursuant to a World Health Organization ("WHO") symposium in 2013.

[4] *See, e.g.*, J.R. Sysol & Roberto F. Machado, *Classification and Pathophysiology of Pulmonary Hypertension*, CONTINUING CARDIOLOGY EDUCATION (July 27, 2018), https://onlinelibrary.wiley.com/doi/epdf/10.1002/cce2.71.

Answer to ¶ 40. UTC admits that the World Health Organization ("WHO") has classified PH into five groups. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 40.

41. FDA considers each of these five WHO Groups distinct diseases or conditions.[5] Thus, a drug approved for one PH indication is not necessarily approved for other PH indications.

Answer to ¶ 41. UTC admits that the document cited in paragraph 41 speaks for itself and that a drug approved for one indication is not necessarily approved for other indications. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 41.

42. PAH, also known as WHO Group 1, is characterized by increased mean pulmonary arterial pressure and pulmonary vascular resistance due to changes in pulmonary vasculature. PAH may be idiopathic, heritable, toxin-induced, or caused by other diseases or disorders such as connective tissue disorders and HIV, among other causes.[6] A hallmark of PAH patients is limited exercise capacity.[7]

Answer to ¶ 42. UTC admits that WHO Group 1 PH is also known as Pulmonary Arterial Hypertension ("PAH"). UTC admits that PAH may be idiopathic, heritable, toxin-induced, or caused by other diseases. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 42.

43. Pulmonary Hypertension Due to Lung Disease and/or Hypoxia, also known as

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[5] *Orphan Drug Designation: Disease Considerations*, FDA (last updated Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-designation-disease-considerations.

[6] Sysol & Machado, *supra* note 4.

[7] *See, e.g.*, Robin M. Fowler, Kevin R. Gain & Eli Gabbay, *Exercise Intolerance in Pulmonary Arterial Hypertension*, PULMONARY MEDICINE (June 10, 2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377355/pdf/PM2012-359204.pdf.

WHO Group 3, is associated with chronic obstructive pulmonary disease ("COPD"), interstitial lung disease ("ILD"), and other pulmonary diseases with similar presentation.[8]

Answer to ¶ 43. UTC admits that WHO Group 3 PH is associated with pulmonary diseases including chronic obstructive pulmonary disease ("COPD") and interstitial lung disease ("ILD"). The document cited in paragraph 43 speaks for itself. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 43.

44. PH-ILD is a subset of WHO Group 3. Interstitial lung disease describes a group of diseases that cause scarring and inflammation of the lungs, which can result in difficulty breathing and poor exchange of oxygen between the lungs and blood vessels. Arteries in the lungs tighten to allow blood to travel to the areas of the lungs receiving the most oxygen, leading to high blood pressure and ultimately pulmonary hypertension as a result of the interstitial lung disease.

Answer to ¶ 44. UTC admits that PH-ILD is a subset of WHO Group 3 PH. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 44.

45. Pulmonary hypertension can worsen over time and may lead to heart failure. Both WHO and the New York Heart Association ("NYHA") have a classification system to describe the stages of heart failure based upon patient symptoms when performing physical activities.[9] While the WHO/NYHA classification is separate from the WHO Groups of PH, it is used to further characterize the severity of symptoms experienced by patients with PH, and has been referenced in the approved indications for several UTC treprostinil products.[10]

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[8] Sarah Beshay, Sandeep Sahay & Marc Humbert, *Evaluation and Management of Pulmonary Arterial Hypertension*, PUBMED (Aug. 19, 2020), https://pubmed.ncbi.nlm.nih.gov/32829182/.

[9] *See, e.g.*, *Classes and Stages of Heart Failure*, AMERICAN HEART ASSOCIATION (last reviewed Jun. 7, 2023), https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

[10] *See, e.g.*, Orenitram Label at 1 (revised Nov. 2020), https://www.accessdata.fda.gov/

Answer to ¶ 45. UTC admits that PH can worsen over time and may lead to heart failure. The documents cited in paragraph 45 speak for themselves. UTC further admits that WHO and NYHA have classification systems for functional classes. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 45.

46. Class I patients have no limitations on physical activity. Patients in Classes II–III are considered to have intermediate heart failure and have limitations in their physical activities. As patients progress from Class II to Class III, they are likely to experience fatigue, shortness of breath, and other symptoms that limit physical activity. Patients in Class IV suffer from symptoms of heart failure even when at rest and physical discomfort with any amount physical activity.

Answer to ¶ 46. UTC admits that the document Liquidia cited in footnote 9 describes the "Patient Symptoms" for Classes I-IV. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 46.

47. Treprostinil is a prostacyclin analog that causes direct vasodilation of pulmonary and systemic vascular beds to reduce pulmonary arterial pressure.[11]

Answer to ¶ 47. UTC admits that treprostinil is a prostacyclin analog. UTC admits that treprostinil is the active ingredient in FDA-approved pharmaceutical products used to reduce pulmonary arterial pressure and the document cited in paragraph 47 speaks for itself. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 47.

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drugsatfda_docs/label/2020/203496Orig1s013lbl.pdf ("The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms…"); Tyvaso Label at 1 (revised July 2009), https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022387LBL.pdf ("Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.").

[11] *See, e.g.*, Pegah Zare & Daniel Heller, *Treprostinil*, NATIONAL LIBRARY OF MEDICINE (last updated May 8, 2023), https://www.ncbi.nlm.nih.gov/books/NBK545152/.

48. FDA has consistently found that treprostinil effectively treats PAH and PH-ILD.

Answer to ¶ 48. UTC admits that FDA has approved pharmaceutical products in which treprostinil is the active ingredient provided to patients who have PAH or PH-ILD. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 48.

B. UTC Has Enjoyed Over Twenty Years of Market Exclusivity for Its Treprostinil Products to Date.

49. UTC has maintained monopoly power over treprostinil drugs for treatment of PAH and PH-ILD by reformulating treprostinil and splicing the patient populations for the drugs to claim eligibility for successive seven-year orphan drug exclusivity ("ODE") and three-year NCI exclusivity periods spanning more than twenty years.[12]

Answer to ¶ 49. Paragraph 49 states legal conclusions to which no answer is required. To the extent a response is required, denied.

50. For example, on May 21, 2002, FDA approved UTC's Remodulin (treprostinil) injection for treatment of PAH (WHO Group 1). The ODE period for Remodulin began on May 21, 2002 and expired on May 21, 2009.[13]

Answer to ¶ 50. UTC admits that FDA approved UTC's Remodulin injection for treatment of PAH on May 21, 2002. UTC further admits that the exclusivity period for Remodulin triggered by the May 21, 2002 approval began on May 21, 2002 and expired on May 21, 2009. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 50.

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[12] Under the Orphan Drug Act and FDA regulations, the FDA may confer a seven-year ODE period for certain drugs that treat rare conditions. A drug that has already been approved for the given disease or condition may not receive ODE again after that ODE period has elapsed. 21 U.S.C. § 360cc; 21 C.F.R. Part 316. ODE is not at issue in this case, except to the extent that it offers context for previous exclusivity periods enjoyed by UTC for treprostinil.

[13] *Search Orphan Drug Designations and Approvals*, FDA ("Orphan Drug Database"), https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=105197 (last accessed Aug. 20, 2024).

51. While it was enjoying ODE for Remodulin, UTC submitted an NDA for Tyvaso Inhalation Solution on June 27, 2008, and received approval on July 30, 2009, for the treatment of PAH (WHO Group 1) in patients with NYHA Class III symptoms, to increase walk distance.[14]

Answer to ¶ 51. UTC admits that it submitted an NDA for Tyvaso for PAH on June 27, 2008. UTC admits that it received approval for its Tyvaso NDA for the treatment of PAH on July 30, 2009. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 51.

52. FDA granted an ODE period to UTC's Tyvaso Inhalation Solution (treprostinil) on June 17, 2010, and limited that exclusivity to patients with NYHA Class III symptoms to increase walk distance, a subset of PAH (WHO Group 1). The ODE period for Tyvaso Inhalation Solution began on July 30, 2009 and expired on July 30, 2016.[15]

Answer to ¶ 52. The document cited in paragraph 52 speaks for itself, but UTC denies that the document supports the allegation for which it is provided. UTC admits that FDA granted an ODE period for Tyvaso and that that exclusivity was designated on June 17, 2010, and ended on July 30, 2016. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 52.

53. The efficacy of inhaled treprostinil was demonstrated by one clinical study, the TRIUMPH 001 study (the "TRIUMPH Study"),[16] submitted in support of the Tyvaso Inhalation

[14] FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Approval Letter (July 30, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022387s000ltr.pdf.
[15] *Id*.
[16] Vallerie V. McLaughlin *et al.*, *Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension*, J. AM. COLL. CARDIOL. (May 4, 2010), https://pubmed.ncbi.nlm.nih.gov/20430262/; *see also Clinical Investigation Into Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension (PAH) (TRIUMPH)*, CLINICALTRIALS (last updated Jan. 2, 2024), https://www.clinicaltrials.gov/study/NCT00147199.

Solution NDA.[17] On June 1, 2020, UTC submitted a supplemental NDA for Tyvaso Inhalation Solution to add a new indication for treatment of PH-ILD (WHO Group 3) to improve exercise ability, which FDA approved on March 31, 2021.[18] UTC and FDA subsequently relied on the same TRIUMPH Study to establish the safety and efficacy of Tyvaso DPI for PH-ILD.[19]

Answer to ¶ 53. UTC admits that the TRIUMPH Study was submitted in support of the Tyvaso Inhalation Solution NDA. UTC further admits that it submitted supplement 17 to NDA 022387 for Tyvaso PH-ILD on June 1, 2020, and that FDA approved that supplement on March 31, 2021. UTC further admits that the TRIUMPH Study was referenced in filings submitted in support of NDA 022387. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 53.

54. On December 20, 2013, FDA approved UTC's Orenitram (treprostinil) for treatment of PAH (WHO Group 1), and UTC received ODE for PAH to improve exercise capacity. The ODE period for Orenitram began on December 20, 2013 and expired on December 20, 2020.[20]

Answer to ¶ 54. Admitted.

55. On October 18, 2019, FDA approved a second ODE period for Orenitram for a subset of WHO Group 1 patients, those treated to delay disease progression only. Notably, while the label for Orenitram states that the drug is indicated to treat PAH (WHO Group 1) to improve exercise capacity based on a study that established effectiveness predominately for patients with

[17] *See*, FDA, CDER, NDA No.22-387 (Tyvaso Inhalation Solution) Clinical Review at 20 (Apr. 3, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022387s000MedR.pdf.
[18] FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Supplemental Approval Letter (Mar. 31, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022387Orig1s017ltr.pdf.
[19] *See, e.g.*, FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Multi-Discipline Review at 7, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/022387Orig1s017.pdf.
[20] Orphan Drug Database, *supra* note 13.

WHO functional Classes II–III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue, only this latter patient population, namely those who have disease and are treated to delay disease progression, are covered by Orenitram's second ODE period, which began on October 18, 2019 and ends on October 18, 2026.[21]

Answer to ¶ 55. UTC admits that FDA approved an ODE for Orenitram "[i]ndicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression." UTC admits that an ODE period for Orenitram began on October 18, 2019 and ends on October 18, 2026. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 55.

56. In addition to these ODE periods, Tyvaso Inhalation Solution and Tyvaso DPI received a three-year NCI exclusivity period limited to treatment of PH-ILD, which expired earlier this year, on March 31, 2024. As UTC represented to investors in an SEC filing, the "three-year [NCI] exclusivity for the treatment of PH-ILD" that "covered both Tyvaso DPI and nebulized Tyvaso [Inhalation Solution] for the treatment of PH-ILD, and precluded the FDA from approving a PH-ILD indication for Yutrepia prior to the expiration of clinical trial exclusivity," had "expired in March 2024." UTC, SEC Form 10-Q (May 1, 2024).[22]

Answer to ¶ 56. UTC admits that Tyvaso Inhalation Solution and Tyvaso DPI received a three-year NCI exclusivity period that expired in March 2024. UTC further admits that it filed a Form 10-Q with the U.S. Securities and Exchange Commission in May 2024, the content of which speaks for itself. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 56.

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[21] *Id.*

[22] *See* https://www.sec.gov/ix?doc=/Archives/edgar/data/1082554/000108255424000025/uthr-20240331.htm.

57. Leading up to FDA's Exclusivity Decision granting yet another period of NCI exclusivity to Tyvaso DPI, the UTC's treprostinil drugs (including Tyvaso DPI itself) had finally exhausted all their exclusivity periods that could otherwise bar FDA's full approval of Yutrepia to treat patients with PAH and PH-ILD. FDA nevertheless decided to grant another round of broad NCI exclusivity to Tyvaso DPI covering treatment of both PAH and PH-ILD—duplicating Tyvaso DPI's already-expired NCI exclusivity for PH-ILD.

Answer to ¶ 57. Paragraph 57 states legal conclusions to which no answer is required. To the extent a response is required, UTC admits that FDA concluded that Tyvaso DPI is entitled to NCI exclusivity, with that exclusivity covering treatment of both PAH and PH-ILD. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 57.

C. Tyvaso DPI Relied on the Same Data Package as Tyvaso Inhalation Solution to Demonstrate Safety and Effectiveness.

58. Both Tyvaso Inhalation Solution and Tyvaso DPI are administered through oral inhalation. While Tyvaso Inhalation Solution must be used in conjunction with an inhalation system nebulizer that aerosolizes a liquid medication solution into respirable particles, Tyvaso DPI utilizes a different drug delivery mechanism to aerosolize a dry powder formulation of treprostinil into respirable particles. The inhalation system nebulizer for Tyvaso Inhalation Solution is battery powered, so patients periodically charge the battery.[23] To nebulize treprostinil, the system also requires patients to fill a reservoir with water, and relies on ampules with the drug product.[24] Tyvaso DPI on the other hand uses cartridges that deliver treprostinil to a more-compact Tyvaso DPI inhaler compared to the Tyvaso inhalation system and does not require batteries to operate

[23] *See* Tyvaso Inhalation System Instructions for Use Manual (revised Aug. 2022), https://www.tyvaso.com/pdf/TD300_instructions_for_use.pdf.
[24] *Id.* at 31.

because it is not electronically powered.[25]

Answer to ¶ 58. UTC admits that the documents cited in paragraph 58 speak for themselves and are the best source for their content. Except as explicitly in this paragraph, UTC denies the allegations in paragraph 58.

59. UTC submitted an NDA for Tyvaso DPI under section 505(b)(1) of the FDCA on April 16, 2021, and received approval by FDA on May 23, 2022 for the treatment of PAH (WHO Group 1) and PH-ILD (WHO Group 3), to improve exercise ability.[26] FDA considered the Tyvaso DPI NDA under section 505(b)(1) because, although it relied on previously-submitted safety and efficacy data submitted to FDA for the Tyvaso Inhalation Solution NDA, UTC owns the rights to all such data such that Tyvaso DPI did not need to apply under the 505(b)(2) pathway.

Answer to ¶ 59. Paragraph 59 states legal conclusions to which no response is required. To the extent a response is required, UTC admits that it submitted an NDA for Tyvaso DPI under section 505(b)(1) on April 16, 2021 and received FDA approval on May 23, 2022 for the treatment of PAH and PH-ILD. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 59.

60. The NDA for Tyvaso DPI consisted of: (1) safety and efficacy data resubmitted from UTC's earlier TRIUMPH Study and the INCREASE Study, which were submitted to FDA with the Tyvaso Inhalation Solution NDA; (2) bioavailability data to justify extrapolation of the previously submitted data for Tyvaso Inhalation Solution to Tyvaso DPI; and (3) the BREEZE

[25] *See* Tyvaso DPI Instructions for Use (revised Nov. 2023), https://www.tyvaso.com/pdf/TYVASO-DPI-instructions-for-use.pdf.
[26] FDA, CDER, NDA No. 214324 (Tyvaso DPI) Approval Letter (May 23, 2022), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/214324Orig1s000ltr.pdf.

Study.[27]

Answer to ¶ 60. UTC admits that the NDA for Tyvaso DPI included the TRIUMPH and INCREASE Studies, bioavailability data, and the BREEZE Study. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 60.

61. The Tyvaso DPI NDA relied upon the TRIUMPH Study and INCREASE Study as evidence of the safety and effectiveness of treprostinil when administered by inhalation.[28]

Answer to ¶ 61. UTC admits that the TRIUMPH and INCREASE Studies were referenced in the Tyvaso DPI NDA. UTC further admits that the TRIUMPH and INCREASE Studies provide evidence that treprostinil solution administered by inhalation is safe and effective for certain indications and under certain circumstances. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 61.

62. The TRIUMPH Study was a 12-week randomized, double-blind, placebo-controlled study to investigate the efficacy and tolerability of Tyvaso Inhalation Solution in 235 patients with PAH already receiving other PAH treatments. The primary endpoint was the change in 6-minute walk distance ("6MWD") at week 12 compared to baseline.[29] The INCREASE Study was a 16-week randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of Tyvaso Inhalation Solution in 326 patients with PH-ILD. The primary efficacy

[27] Leslie A. Spikes et al., *BREEZE: Open-label clinical study to evaluate the safety and tolerability of treprostinil inhalation powder as Tyvaso DPI™ in patients with pulmonary arterial hypertension*, PULMONARY CIRCULATION 2 (Apr. 12, 2022) (the "BREEZE Study"), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9063953/pdf/PUL2-12-e12063.pdf; *see also Open-label, Clinical Study to Evaluate the Safety and Tolerability of TreT in Subjects With PAH Currently Using Tyvaso (BREEZE)*, CLINICALTRIALS (last updated Jan. 24, 2024), https://clinicaltrials.gov/study/NCT03950739?term=BREEZE&cond=PAH&rank=1.

[28] FDA, CDER, NDA No. 214324 (Tyvaso DPI) Clinical Review 10 ("Tyvaso DPI Clinical Review"), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214324Orig1s000MedR.pdf.

[29] Vallerie V. McLaughlin *et al.*, *supra* note 16.

endpoint was the change in 6MWD at peak exposure of the drug from baseline to week 16.[30]

Answer to ¶ 62. The TRIUMPH Study and INCREASE Study speak for themselves and are the best source for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 62.

63. For the Tyvaso DPI NDA, UTC also submitted relative bioavailability data based on (1) the TIP-PH-102 study, a 6-treatment crossover bioavailability study of Tyvaso Inhalation Solution and Tyvaso DPI in 36 healthy subjects, and (2) the BREEZE Study.[31]

Answer to ¶ 63. The TIP-PH-102 study and BREEZE Study speak for themselves and are the best source for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 63.

64. The BREEZE Study was a three-week open-label study with a primary objective of "evaluat[ing] the safety and tolerability of treprostinil inhalation powder (TreT) in patients currently treated with treprostinil inhalation solution."[32] Secondary endpoints were assessment of pharmacokinetics following administration, efficacy based upon 6MWD and patient evaluation of PAH symptoms, and a preference questionnaire.[33] Of the 51 patients enrolled, 49 completed the three-week treatment phase. Notably, the study excluded patients diagnosed with PH for reasons other than PAH (WHO Group 1), such as PH-ILD patients.[34]

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[30] Aaron Waxman *et. al.*, *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, NEW ENGLAND J. OF MED., Vol 384(4) (Jan 13, 2021), https://www.nejm.org/doi/full/10.1056/NEJMoa2008470; *see also Safety and Efficacy of Inhaled Treprostinil in Adult PH with ILD Including CPFE*, CLINICALTRIALS (last updated July 27, 2022), https://www.clinicaltrials.gov/study/NCT02630316.
[31] *Id.* at 18.
[32] The BREEZE Study, *supra* note 27.
[33] *Id.*
[34] *Id.*; BREEZE Clinical Trials, *supra* note 27.

Answer to ¶ 64. The BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted, UTC denies the allegations in paragraph 64.

65. The BREEZE Study failed to produce clinically-valid findings because it was an open-label study with a number of patients too small to render statistically-significant results. To the extent the BREEZE Study offered any observations, they were duplicative of the prior studies. For example, the BREEZE Study observed that adverse events ("AEs") were "consistent with studies of [Tyvaso Inhalation Solution] in patients with PAH, and there were no study drug-related serious AEs." FDA's clinical review of Tyvaso DPI also observed the prevalence of AEs in the BREEZE Study was similar to those reported in the TRIUMPH Study.[35] Crucially, FDA's review expressly noted that UTC and FDA did not rely at all on the BREEZE Study to establish Tyvaso DPI's efficacy, which was already assumed given the prior studies.[36] As FDA's Tyvaso DPI clinical review made clear: Other than the TRIUMPH and INCREASE Studies submitted with the Tyvaso Inhalation Solution NDA, "[n]o additional evidence for effectiveness was submitted as part of the [Tyvaso DPI NDA]."[37]

Answer to ¶ 65. The BREEZE Study and FDA's clinical study review for Tyvaso DPI speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 65.

66. The most charitable reading of the BREEZE Study is that PAH patients already using stable dosing of Tyvaso Inhalation Solution faced no worse outcomes for the first three weeks when switching to equivalent doses of Tyvaso DPI. This is not an "innovative change"

[35] *Id.*
[36] Tyvaso DPI Clinical Review, *supra* note 28, at 12.
[37] *Id.*

warranting exclusivity under the statute and FDA regulations.

Answer to ¶ 66. Denied.

67. It is undisputed that the Tyvaso DPI NDA included no new clinical investigations involving patients with PAH who did not switch from Tyvaso Inhalation Solution, and no new clinical investigations involving patients with PH-ILD.

Answer to ¶ 67. UTC admits that the BREEZE Study required a diagnosis of PAH for inclusion. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 67.

68. Tyvaso Inhalation Solution and Tyvaso DPI previously received three-year NCI exclusivity limited to treatment of PH-ILD, which began on March 31, 2021, and expired three years later, on March 31, 2024. According to UTC's SEC filing from earlier this year, the "three-year [NCI] exclusivity for the treatment of PH-ILD . . . covered both Tyvaso DPI and nebulized Tyvaso [Inhalation Solution] for the treatment of PH-ILD, and precluded the FDA from approving a PH-ILD indication for Yutrepia prior to the expiration of clinical trial exclusivity." That NCI exclusivity period, according to UTC, "expired in March 2024." UTC, SEC Form 10-Q (May 1, 2024).[38]

Answer to ¶ 68. UTC admits that Tyvaso Inhalation Solution and Tyvaso DPI received three-year NCI exclusivity for the treatment of PH-ILD beginning on March 31, 2021. SEC Form 10-Q cited by Plaintiff in paragraph 68 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 68.

D. Liquidia's NDA for Yutrepia and Related Litigation.

[38] *See supra* note 22.

69. On January 24, 2020, long before UTC filed its Tyvaso DPI NDA, Liquidia submitted to FDA NDA 213005 for Yutrepia (treprostinil inhalation powder) for treatment of PAH. Per section 505(b)(2) of the FDCA, the Yutrepia NDA referenced the previously-submitted safety data from Tyvaso Inhalation Solution in support of its NDA. The Yutrepia NDA relied on no other listed drug in its NDA.

Answer to ¶ 69. UTC admits that Liquidia submitted to FDA NDA 213005 for Yutrepia (treprostinil inhalation powder) for the treatment of PAH. On information and belief, UTC further admits that the Yutrepia NDA referenced data from Tyvaso Inhalation Solution. UTC lacks sufficient knowledge or information to form a belief as to the truth of the remaining allegations in Paragraph 69 and therefore denies them.

70. Liquidia also conducted its own clinical investigations, including two Phase 1 studies in healthy volunteers, as well as a Phase 3, open-label, multicenter trial (the "INSPIRE Study"), which assessed the safety and tolerability of Yutrepia both in patients (1) new to prostacyclin therapy, and (2) those transitioning from Tyvaso Inhalation Solution.[39]

Answer to ¶ 70. UTC lacks sufficient knowledge or information to form a belief as to the truth of the allegations in paragraph 70 and therefore denies them.

71. Liquidia submitted these clinical investigations with Yutrepia's NDA in 2020 more than a year before UTC filed Tyvaso DPI's NDA in 2021.

Answer to ¶ 71. UTC lacks sufficient knowledge or information to form a belief as to the truth of the allegations in paragraph 71 and therefore denies them.

[39] Nicholas S. Hill *et al.*, *INSPIRE: Safety and Tolerability of Inhaled Yutrepia (treprostinil) in Pulmonary Arterial Hypertension (PAH)*, PubMed (July 1, 2022), https://pubmed.ncbi.nlm.nih.gov/36034402/.

72. In November 2021, FDA initially issued a tentative approval ("TA") for Yutrepia for the treatment of PAH to improve exercise ability in patients with NYHA functional Classes II–III symptoms based upon the primary endpoints of the INSPIRE Study and comparable bioavailability to Tyvaso Inhalation Solution. At the time, FDA did not grant full approval solely due to a 30-month stay and injunction resulting from Hatch-Waxman litigation between UTC and Liquidia, which ultimately proved to be meritless.[40]

Answer to ¶ 72. UTC admits that FDA issued a tentative approval for Yutrepia for the treatment of PAH in or around November 2021. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 72.

73. UTC submitted to FDA the Tyvaso DPI NDA for treatment of PAH and PH-ILD to improve exercise ability on April 16, 2021.

Answer to ¶ 73. Admitted.

74. On July 24, 2023, Liquidia submitted an amendment to the still-pending Yutrepia NDA to add treatment of patients with PH-ILD to improve exercise ability consistent with guidance received from FDA. FDA accepted Yutrepia's NDA amendment for review in September 2023 and the FDA targeted January 2024 as the timeframe by which Liquidia could expect FDA's determination regarding the Yutrepia NDA, as amended.

Answer to ¶ 74. UTC admits that Liquidia submitted a purported amendment regarding a PH-ILD indication to the Yutrepia NDA on or around July 24, 2023. UTC further admits that FDA accepted the Yutrepia NDA amendment for review in or around September 2023. Except as

[40] FDA, CDER, NDA No. 213005, Tentative Approval Letter (Mar. 28, 2024) ("NDA 213005 Tentative Approval"), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf.

explicitly admitted in this paragraph, UTC denies the allegations in paragraph 74.

75. On March 28, 2024, the District Court in Delaware lifted the injunction that effectively prohibited FDA from issuing full approval of the Yutrepria NDA until expiration of the underlying patent. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 2024 WL 2805082 (D. Del. May 31, 2024). This ruling eliminates the FDA's stated justification for denying full approval to Yutrepia, as the NCI exclusivity for PH-ILD for Tyvaso Inhalation Solution and Tyvaso DPI expired on March 31, 2024.

Answer to ¶ 75. UTC admits that the District Court in Delaware issued the cited ruling on May 31, 2024, and that ruling speaks for itself. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 75.

76. On February 20, 2024, UTC sued FDA, challenging FDA's decision to allow Liquidia to amend its NDA to add the PH-ILD indication. Complaint, *UTC v. FDA*, No. 24-484 (D.D.C. Feb. 20, 2024), ECF No. 1. On March 29, 2024, UTC's motion for a temporary restraining order and/or preliminary injunction was denied by the United States District Court for the District of Columbia. Minute Entry, *UTC v. FDA*, No. 24-484 (D.D.C. Mar. 29, 2024).

Answer to ¶ 76. Paragraph 76 states legal conclusions to which no answer is required. To the extent a response is required, admitted.

77. Had Liquidia received FDA's full approval for Yutrepia on August 16, 2024, rather than a tentative approval, it had planned to lawfully distribute Yutrepia to patients within days of receiving that approval.

Answer to ¶ 77. UTC lacks sufficient knowledge or information to form a belief as to the truth of the allegations in paragraph 77 and therefore denies them.

78. FDA's decision to improperly grant sweeping NCI exclusivity for Tyvaso DPI bars access to patients nationwide who stand to benefit from Yutrepia's safe and effective treatment of PAH and PH-ILD.

Answer to ¶ 78. Denied.

79. In addition, FDA's erroneous decision further delays competition in the treprostinil market, reinforcing UTC's twenty-year monopoly and denying vulnerable patients choice and access to affordable drug alternatives to treat PAH and PH-ILD.

Answer to ¶ 79. Denied.

E. FDA's August 16, 2024 Tyvaso DPI Exclusivity Decision and the Yutrepia Tentative Approval Letter.

80. On August 16, 2024, FDA concluded that the Yutrepia NDA demonstrated safety and effectiveness in treating patients with PAH and PH-ILD, and provided complete labeling for Yutrepia covering both indications. FDA, however, decided only to grant tentative approval for Yutrepia in a letter to Liquidia dated August 16, 2024 ("Yutrepia Tentative Approval Letter"). The Yutrepia Tentative Approval Letter denied Yutrepia full approval because FDA had found pursuant to its Exclusivity Decision that Tyvaso DPI qualifies for three-year NCI exclusivity and that such exclusivity delays the approval of Yutrepia for both PAH and PH-ILD indications.[41]

Answer to ¶ 80. UTC admits that FDA granted tentative approval for Yutrepia on August 16, 2024. FDA's tentative approval letter speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 80.

[41] *See* Press Release, Liquidia, *U.S. FDA Grants Tentative Approval of YUTREPIA™ (treprostinil) Inhalation Powder for Patients with Pulmonary Arterial Hypertension (PAH) and Pulmonary Hypertension Associated with Interstitial Lung Disease (PH-ILD)* (Aug. 19, 2024), https://www.liquidia.com/node/11366/pdf.

81. According to FDA, the TRIUMPH Study and the INCREASE Study provided sufficient evidence of safety and effectiveness of treprostinil when administered by oral inhalation. Therefore, to the extent the BREEZE Study provided any safety data regarding inhaled treprostinil, this data was duplicative of prior studies.

Answer to ¶ 81. FDA's Yutrepia Tentative Approval Letter speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 81.

82. Further, FDA acknowledged that the BREEZE Study provided bioavailability data supporting the Tyvaso DPI NDA, since the bioavailability and safety profiles of Tyvaso Inhalation Solution and Tyvaso DPI are similar even though they differ in dosage form and certain features of use. Thus, the data from the BREEZE Study is either duplicative of those prior studies or is a bioavailability study categorically excluded from the definition of a new clinical investigation under the FDCA and FDA regulations. 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108.

Answer to ¶ 82. Paragraph 82 states legal conclusions to which no response is required. To the extent a response is required, the BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 82.

83. Notably, while both Circuit precedent and FDA's longstanding interpretation of "conditions of approval" limit three-year NCI exclusivity to the innovative change that the new clinical investigations are essential for NDA approval, FDA never articulated the innovative change investigated in the BREEZE Study for Tyvaso DPI.[42]

[42] *See* FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=21

Answer to ¶ 83. Paragraph 83 states legal conclusions to which no response is required. To the extent a response is required, denied.

84. Since any grant of NCI exclusivity is tied to, and limited by, the innovative change for that drug known only through the new clinical investigation, FDA disregarded the FDCA and FDA regulations when its Exclusivity Decision granted sweeping NCI exclusivity to Tyvaso DPI in the absence of any such innovative findings in the BREEZE Study.

Answer to ¶ 84. Paragraph 84 states legal conclusions to which no response is required. To the extent a response is required, denied.

II. FDA'S GRANT OF NCI EXCLUSIVITY TO TYVASO DPI MUST BE VACATED

A. FDA Exceeded Its Statutory Authority Under the FDCA, Violated Its Own Regulations, and Took Action that Was Arbitrary and Capricious, and Contrary to Law When Granting NCI Exclusivity to Tyvaso DPI and Overstating the Scope of that Exclusivity.

85. FDA's Exclusivity Decision and corresponding determination that such exclusivity blocks final approval of Yutrepia violates the FDCA and the APA. For NCI exclusivity to lawfully attach, the Tyvaso DPI NDA must: (1) contain one or more "new clinical investigations (other than bioavailability studies)" whose innovative findings are (2) "essential" to the approval of the NDA. FDA had no authority to recognize NCI exclusivity for Tyvaso DPI based on the BREEZE Study because it is not a new clinical investigation essential to the approval of Tyvaso DPI.

Answer to ¶ 85. Paragraph 85 states legal conclusions to which no response is required. To the extent a response is required, denied.

4324&Appl_type=N (last visited Aug. 20, 2024) (characterizing Tyvaso DPI's NCI exclusivity period as "NP" or "new product"—even though Tyvaso DPI is not a new product).

1. The Tyvaso DPI NDA Contained No New Clinical Investigations Other than Bioavailability Studies.

86. FDA improperly concluded that the Tyvaso DPI NDA contained new clinical investigations other than bioavailability studies. According to FDA regulations, a new clinical investigation is "an investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or safety for a new population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108.

Answer to ¶ 86. Paragraph 86 states legal conclusions to which no response is required. To the extent a response is required, 21 C.F.R. § 314.108 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 86.

87. FDA has previously stated that most qualifying studies will be efficacy studies, but that safety studies demonstrating a product is safer than originally thought and that permit broader use of the drug may qualify for exclusivity. *See* 1989 Preamble.

Answer to ¶ 87. The document cited in paragraph 87 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 87.

88. Under the FDCA and FDA regulations, the TRIUMPH Study and the INCREASE Study fail to qualify as "new clinical investigations" because they were previously submitted by UTC to support the Tyvaso Inhalation Solution NDA in 2008, and supplemental NDA in 2020, respectively, which UTC merely cross-referenced in its Tyvaso DPI NDA filed in 2021.

Answer to ¶ 88. Paragraph 88 states legal conclusions to which no response is required. To the extent a response is required, denied.

89. FDA admits that another study in the Tyvaso DPI NDA, the TIP-PH-102 Study, is a "bioavailability study" that cannot form the basis for NCI exclusivity under the FDCA.

Answer to ¶ 89. The TIP-PH-102 Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 89.

90. But neither can the BREEZE Study. The BREEZE Study is not a "new clinical investigation[]"; it was a three-week ***confirmatory*** study conducted in 51 [PAH] patients on stable doses of Tyvaso Inhalation Solution who switched to a corresponding dose of Tyvaso DPI. The BREEZE Study compared patients already taking Tyvaso Inhalation Solution to those taking Tyvaso DPI for three weeks and ultimately found "comparable systemic exposure [of treprostinil] between the two formulations."[43]

Answer to ¶ 90. Paragraph 90 states legal conclusions to which no response is required. To the extent a response is required, the BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 90.

91. As FDA concedes, to support approval of Tyvaso DPI, UTC relied on safety and efficacy data submitted in the Tyvaso Inhalation Solution NDA from the TRIUMPH Study and the INCREASE Study and provided ***relative bioavailability data*** from the TIP-PH-102 and BREEZE Studies to justify extrapolation of the previously submitted data to Tyvaso DPI. FDA thus erred by treating the BREEZE Study as a "new clinical investigation" for the purposes of NCI

[43] The BREEZE Study, *supra* note 27, at 2.

exclusivity, when FDA's own analysis characterizes it as a bioavailability study, which is expressly excluded under the FDCA and its implementing regulations as the type of study to which NCI exclusivity can attach. 21 C.F.R. § 314.108.

Answer to ¶ 91. Paragraph 91 states legal conclusions to which no response is required. To the extent a response is required, the TRIUMPH Study, the INCREASE Study, and the BREEZE Study speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 91.

92. FDA's clinical review of Tyvaso DPI confirms that UTC's application relied upon the TRIUMPH Study and INCREASE Study to demonstrate the safety and efficacy of treprostinil and found that, aside from these previously-submitted studies, UTC submitted no new evidence for efficacy.[44] Thus, under FDA's own findings, the BREEZE Study was not an efficacy study.

Answer to ¶ 92. Paragraph 92 states legal conclusions to which no response is required. To the extent a response is required, FDA's clinical review of the Tyvaso DPI application speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 92.

93. The BREEZE Study further fails to meet the regulatory definition of a new clinical investigation because the results of that study "duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108. Specifically, the INCREASE Study had already established safety and effectiveness in PH-ILD patients (WHO Group 3), and FDA relied upon that study to approve Tyvaso for that patient population. Thus, to the extent that FDA

[44] Tyvaso DPI Clinical Review, *supra* note 28, at 12.

implicitly and erroneously relied on the BREEZE Study to establish safety and effectiveness of the inhalation powder dosage form for use in PH-ILD patients, even though the study did not specifically investigate use in that patient population, the BREEZE Study clearly duplicates the prior findings of the INCREASE Study. FDA's contrary conclusion without explanation in its Exclusivity Decision fails to satisfy the "new clinical investigation" requirement in the FDCA and FDA regulations, and is arbitrary and capricious, and contrary to law.

Answer to ¶ 93. Paragraph 93 states legal conclusions to which no response is required. To the extent a response is required, the BREEZE Study and INCREASE Study speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 93.

94. Significantly, FDA's clinical review for Tyvaso DPI concluded that the BREEZE Study merely identified "no new risks associated with treprostinil formulated as an inhaled powder."[45] So, at most, the BREEZE Study merely duplicated the same findings of the earlier studies and confirmed that PAH patients already taking Tyvaso Inhalation Solution would not face new adverse consequences when taking the equivalent dose of treprostinil in dry powder format.

Answer to ¶ 94. UTC admits that the BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 94.

95. In addition, because the BREEZE Study only studied Tyvaso DPI in PAH patients who were already being treated with stable doses of Tyvaso Inhalation Solution, the BREEZE Study cannot have demonstrated broader use of Tyvaso DPI.

[45] Tyvaso DPI Clinical Review, *supra* note 28, at 13.

Answer to ¶ 95. Paragraph 95 states legal conclusions to which no answer is required. To the extent a response is required, the BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 95.

96. Thus, the BREEZE Study fails to meet the definition of a "new clinical investigation" for safety data. *See* 1989 Preamble ("There may, however, be occasional clinical investigations qualifying for exclusivity that establish that a product is safer than originally thought and that permit broader use of the drug. Studies that establish new risks will not be eligible for exclusivity because protection of the public health demands that all products' labeling contain all relevant warnings.").[46]

Answer to ¶ 96. Paragraph 96 states legal conclusions to which no response is required. To the extent a response is required, the BREEZE Study and the document cited in paragraph 96 speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 96.

97. Additionally, FDA policy in the 1989 Preamble indicates that "broader use of the drug" is associated with new safety findings. Therefore, any argument that the BREEZE Study demonstrated broader use of the drug treprostinil as it allowed patients to more easily carry the drug and device and dispose of the cartridge after—without any finding of broader use, such as for new indications or patient populations—is insufficient to satisfy the definition of "new clinical investigations" under the FDCA, FDA regulations, and Circuit precedent. Moreover, the BREEZE Study did not even study whether patients found the cartridge easier to carry or dispose of.

[46] 1989 Preamble at 28899.

Answer to ¶ 97. Paragraph 97 states legal conclusions to which no response is required. To the extent a response is required, the document cited in paragraph 97 and the BREEZE Study speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 97.

98. The BREEZE Study was not a new clinical investigation and no other study submitted by UTC qualifies either, and so Tyvaso DPI was statutorily ineligible for NCI exclusivity on this basis alone.

Answer to ¶ 98. Paragraph 98 states legal conclusions to which no response is required. To the extent a response required, the BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 98.

1. The BREEZE Study Produced No Findings Essential to the Approval of Tyvaso DPI's NDA.

99. FDA's grant of NCI further violates the FDCA because the BREEZE Study was not "essential to the approval" of Tyvaso DPI.

Answer to ¶ 99. Paragraph 99 states legal conclusions to which no response is required. To the extent a response is required, denied.

100. By its own admission, the BREEZE Study simply switched "patients with PAH currently treated with [Tyvaso] [I]nhalation [S]olution" to Tyvaso DPI and confirmed comparable outcomes at the three-week mark. The BREEZE Study merely "confirm[ed]" that identical doses of treprostinil (via Tyvaso DPI) would not harm PAH patients who switched from equivalent doses of treprostinil (via Tyvaso Inhalation Solution).[47]

[47] The BREEZE Study, *supra* note 27, at 4.

Answer to ¶ 100. The BREEZE Study speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 100.

101. Indeed, the BREEZE Study's exceedingly narrow scope and the fact that it was not powered to achieve any statistically-significant results meant that it offered ***zero*** clinically-valid findings. By design, it provided ***zero*** efficacy and safety data for patients diagnosed with PH-ILD, ***zero*** findings for PAH patients not already using equivalent doses of Tyvaso Inhalation Solution, ***zero*** clinically-valid findings for treatment of PAH patients beyond the third week of using Tyvaso DPI, and ***zero*** clinically-valid findings for any treprostinil dry powder drug-device combination product, or formulation other than Tyvaso DPI.

Answer to ¶ 101. Denied.

102. In short, attaching NCI exclusivity to Tyvaso DPI based on the BREEZE Study runs counter to the Hatch Waxman Amendments and FDA's own stated policy to award exclusivity only for the "innovative change" investigated in the study. There was *no* innovative change that the BREEZE Study investigated, and FDA's Exclusivity Decision granting broad NCI exclusivity to Tyvaso DPI without any restrictions on its specific formulation, delivery mechanism, indications or the patient populations is contrary to law.

Answer to ¶ 102. Paragraph 102 states legal conclusions to which no response is required. To the extent a response is required, denied.

103. ***First***, the BREEZE Study cannot be considered essential to the approval for the PH-ILD indication because the BREEZE Study did not study any PH-ILD patients. As discussed above, PH-ILD is a specific subset of PH, distinct from PAH, with a different etiology—namely increases in pulmonary blood pressure due to poor oxygenation from underlying interstitial lung

disease. In other exclusivity contexts involving treprostinil,[48] FDA has indicated that it considers different WHO Groups different diseases or conditions. FDA has not articulated any reason why this would be any different for purposes of NCI exclusivity of treprostinil, where the operative study rendered zero findings for patients with PH-ILD. Not only did the BREEZE Study fail to confirm safety for PH-ILD patients, those patients were excluded from study participation altogether.

Answer to ¶ 103. Paragraph 103 states legal conclusions to which no response is required. To the extent a response is required, denied.

104. ***Second***, to the extent FDA asserts that the BREEZE Study was essential to the approval of Tyvaso DPI to assess tolerability of the new dosage form, FDA did not rely on the BREEZE Study to determine safety and tolerability for the patient population with an underlying respiratory condition, which UTC recognizes "could worsen V/Q matching," which occurs when lungs receive oxygen without blood flow or blood flow without oxygen in patients using pulmonary vasodilators. "PFTs [pulmonary functional tests] (including FVC [forced vital capacity]) and exacerbations of lung disease were included as safety endpoints in the INCREASE study due to the potential risk of V/Q mismatch."[49] But the BREEZE Study did not assess these safety endpoints, or for that matter, any clinically-valid endpoints.

Answer to ¶ 104. The document cited in paragraph 104 and the BREEZE Study speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 104.

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[48] *See supra* ¶¶ 49–57.

[49] *Study Overview: Increase Was Designed to Access the Efficacy and Safety of TYVASO in Patients with PH-ILD*, UTC (May 2022), https://www.tyvasohcp.com/ph-ild/efficacy-safety/increase-study/.

105. As UTC has stated, this potential risk was not addressed in the BREEZE Study, but rather in the INCREASE Study previously submitted for Tyvaso Inhalation Solution. Because the BREEZE Study failed to assess ***any*** safety and tolerability for patients with PH-ILD, and because FDA relied wholly upon the previously-submitted INCREASE Study for safety data for treatment of PH-ILD, the FDCA prohibits FDA's Exclusivity Decision awarding NCI exclusivity to Tyvaso DPI for the BREEZE Study because it was not "essential to approval" of Tyvaso DPI for PH-ILD.

Answer to ¶ 105. Paragraph 105 states legal conclusions to which no response is required. To the extent a response is required, denied.

106. ***Third***, FDA's finding of NCI exclusivity for the PH-ILD indication cannot stand for another key reason: FDA previously awarded NCI exclusivity for this indication back in 2021 based on another study, thus, rendering the BREEZE Study duplicative and, once again, categorically ineligible for "new clinical investigation" treatment under the FDCA and FDA regulations. As UTC's recent SEC filing noted, Tyvaso Inhalation Solution and Tyvaso DPI's NCI exclusivity period for PH-ILD already expired in March 2024. UTC, SEC Form 10-Q (May 1, 2024).[50] It is contrary to law, therefore, for FDA to allow UTC to further extend its twenty-year monopoly by granting a second NCI exclusivity period covering the exact same indication for the exact same drug for a study that duplicated the findings of previously-submitted studies.

Answer to ¶ 106. Paragraph 106 states legal conclusions to which no response is required. To the extent a response is required, denied.

107. Because the BREEZE Study had no innovative findings "essential" to approval of Tyvaso DPI's NDA, Tyvaso DPI was statutorily ineligible for NCI exclusivity.

[50] *See supra* note 22.

Answer to ¶ 107. Paragraph 107 states legal conclusions to which no answer is required. To the extent a response is required, denied.

2. To the Extent the BREEZE Study Could Support NCI Exclusivity for Tyvaso DPI, FDA Unlawfully Blocked Yutrepia from Coming to Market by Overreading the Scope of Any Such Exclusivity.

108. Even if the Tyvaso DPI were somehow eligible for NCI exclusivity (it is not), the FDCA mandates that the scope of any such exclusivity must be limited to the narrow "conditions of approval" actually investigated in the BREEZE Study that are shared by a competitor NDA. Because those conditions do not foreclose both of Yutrepia's indications (for treatment of PAH and PH-ILD), nor Yutrepia's unique drug delivery mechanism or formulation, the scope of the NCI exclusivity recognized by FDA for Tyvaso DPI is impermissibly overbroad under the FDCA and FDA regulations, and cannot lawfully block Yutrepia's full approval.

Answer to ¶ 108. Paragraph 108 states legal conclusions to which no response is required. To the extent a response is required, denied.

109. Given the exceedingly narrow scope of the BREEZE Study, the FDCA prohibits FDA from identifying unstudied "conditions of approval" to grant NCI exclusivity in excess of its incremental findings. Under the FDCA, FDA may not rely on unstudied "conditions of approval" to grant broad NCI exclusivity. Thus, FDA could not grant Tyvaso DPI any NCI exclusivity for treatment of PAH patients aside from those already using Tyvaso Inhalation Solution (the narrow patient population in the BREEZE Study), nor for PH-ILD patients (because patients with PH-ILD were categorically excluded from the BREEZE Study).

Answer to ¶ 109. Paragraph 109 states legal conclusions to which no response is required. To the extent a response is required, denied.

110. FDA interprets "conditions of approval" to be the innovation represented by the

approved drug product for which the new clinical investigation was essential. *See* Veloxis Letter, at 21 ("[C]onditions of approval" means only the "innovative change that is supported by the new clinical investigations" that entitled the first-approved drug to NCI exclusivity); *AstraZeneca*, 872 F. Supp. 2d at 121 n.16. ("conditions of approval" "can be no broader than the innovations presented to the FDA in the new clinical investigations that led to the FDA's approval of the first-in-time 505(b) NDA").

Answer to ¶ 110. Paragraph 110 states legal conclusions to which no response is required. To the extent a response is required, the documents and cases cited in this paragraph speak for themselves and are the best sources for their content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 110.

111. For example, oral inhalation of treprostinil to improve exercise ability in patients with PAH and PH-ILD had already been established in the TRIUMPH Study and the INCREASE Study, and therefore no new clinical investigation was needed to answer questions about the safety or efficacy of treprostinil for this route of administration or these indications. Moreover, it is difficult to understand how the three-week BREEZE Study furnished any innovative, non-duplicative data on "chronic use" of treprostinil, particularly when FDA already had data from previously-submitted studies and three prior UTC NDAs for this same active moiety.

Answer to ¶ 111. Paragraph 111 contains statements of opinion to which no response is required. To the extent a response is required, UTC admits that the TRIUMPH Study, INCREASE Study, and BREEZE Study speak for themselves, and UTC denies Plaintiff's interpretation of those documents. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 111.

112. To the extent that FDA focuses on the new dosage form of the inhalation powder

as the innovative change, the BREEZE Study fares no better as the source for NCI exclusivity supporting this innovation as it did not study the effectiveness of this route of administration. Rather, the BREEZE Study only examined whether the relative safety of Tyvaso DPI matched that expected for treprostinil based on the AEs reported from patients already taking Tyvaso Inhalation Solution. This argument is also contrary to FDA's tentative approval of Yutrepia's NDA for oral dry powder inhalation, finding it safe and effective based on its cross-reference to the Tyvaso Inhalation Solution NDA—not the BREEZE Study or the Tyvaso DPI NDA.

Answer to ¶ 112. Paragraph 112 states legal conclusions to which no response is required. To the extent a response is required, the BREEZE Study speaks for itself and is the best source of its content. UTC denies Plaintiff's interpretation of that document. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 112.

113. Given that the safety and efficacy of administering aerosolized particles of medication containing treprostinil had already been well-established by previously-submitted studies, at most, the innovative change represented by Tyvaso DPI is found in its drug-delivery device or the excipients used in the unique formulation of the powder. If the "innovative change" represented by Tyvaso DPI is attributable only to the device, then that innovative change has not been supported by any clinical studies specifically on that device. Any NCI exclusivity based on Tyvaso DPI's proprietary drug-delivery device, therefore, cannot lawfully block full approval of Yutrepia, which is a different alternative drug-device combination product altogether.

Answer to ¶ 113. Paragraph 113 states legal conclusions to which no response is required. To the extent a response is required, denied.

114. Likewise, if the supposedly innovative change from the BREEZE Study is the excipients enabling the powder dosage form, then there must be a logical relationship with the

BREEZE Study to support NCI exclusivity. Based on the study design and its lack of relevant affirmative endpoints, however, the BREEZE Study articulates no such relationship between the excipients and its findings. Thus, any NCI exclusivity arising from Tyvaso DPI's unique excipients cannot lawfully block full approval of Yutrepia because the BREEZE Study failed to meaningfully analyze those excipients; and in any event, those excipients differ from Yutrepia's.

Answer to ¶ 114. Paragraph 114 states legal conclusions to which no response is required. To the extent a response is required, denied.

115. To the extent that FDA asserted concerns about specific risks presented by the powder dosage form generally, this is merely a post-hoc rationalization. None of the clinical trial endpoints suggest that the study was designed to specifically evaluate potential safety risks specific or unique to a powder inhalation formulation, or indeed any safety or tolerability risk outside of the already known risks of treprostinil for oral inhalation. In fact, the BREEZE Study did not include a placebo population, and so it failed to capture any clinically-valid data upon which to compare the effect of administering respirable, micron-sized drug particles that are aerosolized from a dry powder (Tyvaso DPI) against the effect of administering respirable, micron-sized drug particles that are aerosolized from a solution (Tyvaso Inhalation Solution). Nor does FDA identify any risks associated specifically with a powder inhalation form within the risk-benefit analysis of its clinical review of Tyvaso DPI.

Answer to ¶ 115. Denied.

116. To the extent FDA did seek confirmation regarding the risks of using a dry powder formulation of treprostinil, those questions were already answered by Liquidia's INSPIRE Study for Yutrepia when FDA granted tentative approval for Yutrepia in November 2021, further casting doubt on any supposed innovation from the BREEZE Study.

Answer to ¶ 116. Paragraph 116 contains statements of opinion to which no response is required. To the extent a response is required, denied.

117. Moreover, "if the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients." 60 Fed. Reg. at 28896–97. Based on the clear limitations of the BREEZE Study, FDA could not find NCI exclusivity for treatment of PAH patients that were not already using Tyvaso Inhalation Solution, nor NCI exclusivity for PH-ILD patients generally.

Answer to ¶ 117. Paragraph 117 states legal conclusions to which no response is required. To the extent a response is required, the document cited in paragraph 117 speaks for itself and is the best source for its content. Except as explicitly admitted in this paragraph, UTC denies the allegations in paragraph 117.

118. In sum, Yutrepia does not share "conditions of approval"—*i.e.*, the innovative findings of the BREEZE Study "essential" to approval—that form the basis for FDA's asserted NCI exclusivity for Tyvaso DPI.

Answer to ¶ 118. Paragraph 118 states legal conclusions to which no response is required. To the extent a response is required, denied.

119. Yutrepia meets all FDA requirements for demonstrating safety and efficacy for its intended use, as acknowledged by FDA, and there are no valid exclusivities or patents that may prevent its full approval.

Answer to ¶ 119. Paragraph 119 states legal conclusions to which no response is required. To the extent a response is required, denied.

120. In denying full approval of Yutrepia based upon the NCI exclusivity improperly

granted to Tyvaso DPI, FDA has exceeded its statutory authority under the FDCA, and interpreted FDCA Section 505(c)(3)(E)(iii)in a manner that is arbitrary and capricious and contrary to law.

Answer to ¶ 120. Paragraph 120 states legal conclusions to which no response is required. To the extent a response is required, denied.

121. Immediate, unconditional approval of Yutrepia is legally and factually mandated by the FDCA, its implementing regulations, FDA policy, and longstanding precedent.

Answer to ¶ 121. Paragraph 121 states legal conclusions to which no response is required. To the extent a response is required, denied.

[Liquidia's] CAUSES OF ACTION

COUNT I
APA—5 U.S.C. § 706(2)(C) & (A)

FDA's Decision to Grant NCI Exclusivity to Tyvaso DPI [Allegedly] Exceeds FDA's Statutory Authority and Was Arbitrary, Capricious, An Abuse of Discretion, and Otherwise Not in Accordance with Law

122. Liquidia repeats and realleges the allegations contained in the preceding paragraphs as if fully set forth herein.

Answer to ¶ 122. UTC reaffirms and incorporates its responses to paragraphs 1 through 121 of the Complaint as if fully set forth herein.

123. The APA prohibits FDA from issuing a final decision that is in excess of statutory jurisdiction, authority, or limitations. 5 U.S.C. § 706(2)(C).

Answer to ¶ 123. Paragraph 123 states legal conclusions to which no answer is required. To the extent a response is required, denied.

124. The APA prohibits FDA from issuing a final decision that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

Answer to ¶ 124. Paragraph 124 states legal conclusions to which no answer is required. To the extent a response is required, denied.

125. FDA's Exclusivity Decision to grant Tyvaso DPI NCI exclusivity exceeds FDA's statutory authority to award such exclusivity.

Answer to ¶ 125. Paragraph 125 states legal conclusions to which no answer is required. To the extent a response is required, denied.

126. Under the FDCA, FDA cannot recognize NCI exclusivity for an NDA submitted under section 355(b) unless "such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." FDCA, 21 U.S.C. § 355(c)(3)(E)(iii).

Answer to ¶ 126. Paragraph 126 states legal conclusions to which no answer is required. To the extent a response is required, denied.

127. FDA's determination that Tyvaso DPI is entitled to NCI exclusivity exceeds FDA's statutory authority because:

(a) The BREEZE Study was not a new clinical investigation within the meaning of the statute and no other study submitted with the Tyvaso DPI NDA qualifies;

(b) The BREEZE Study was not "essential to the approval" of Tyvaso DPI as defined by the FDCA and its implementing regulations; and

(c) Even assuming the BREEZE Study could qualify as a new clinical investigation, the BREEZE Study did not support any of the "condition[s] of approval" shared by Yutrepia and thus should not

block FDA's approval of Yutrepia.

Answer to ¶ 127. Paragraph 127 and its sub-parts state legal conclusions to which no answer is required. To the extent a response is required, denied as to paragraph 127; denied as to sub-part (a); denied as to sub-part (b); and denied as to sub-part (c).

128. Liquidia has no other adequate remedy at law.

Answer to ¶ 128. Paragraph 128 states legal conclusions to which no answer is required. To the extent a response is required, denied.

129. For the foregoing reasons, FDA's grant of exclusivity to Tyvaso DPI exceeds FDA's statutory authority, and is arbitrary and capricious, an abuse of discretion, and contrary to law. Thus, FDA's Exclusivity Decision must be set aside.

Answer to ¶ 129. Paragraph 129 states legal conclusions to which no answer is required. To the extent a response is required, denied.

COUNT II
APA—5 U.S.C. § 706(2)(C) & (A)

FDA's Interpretation of the Scope of the NCI Exclusivity for Tyvaso DPI [Allegedly] Exceeds FDA's Statutory Authority and Was Arbitrary, Capricious, An Abuse of Discretion, and Otherwise Not in Accordance with Law

130. Liquidia repeats and realleges the allegations contained in the preceding paragraphs as if fully set forth herein.

Answer to ¶ 130. UTC reaffirms and incorporates its responses to paragraphs 1 through 129 of the Complaint as if fully set forth herein.

131. The APA prohibits FDA from issuing a final decision that is in excess of statutory jurisdiction, authority, or limitations. 5 U.S.C. § 706(2)(C).

Answer to ¶ 131. Paragraph 131 states legal conclusions to which no answer is required. To

the extent a response is required, denied.

132. The APA prohibits FDA from issuing a final decision that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

Answer to ¶ 132. Paragraph 132 states legal conclusions to which no answer is required. To the extent a response is required, denied.

133. FDA's Exclusivity Decision granting Tyvaso DPI NCI exclusivity covering all PAH and PH-ILD patients contravenes the FDCA's limitation that the scope of NCI exclusivity can be no broader than the innovations presented in the new clinical investigations essential to the NDA's approval. *Veloxis*, 109 F. Supp. 3d at 121 n.16.

Answer to ¶ 133. Paragraph 133 states legal conclusions to which no answer is required. To the extent a response is required, denied.

134. FDA's Exclusivity Decision awarding a broad scope of NCI to Tyvaso DPI is also arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the "conditions of approval" for Tyvaso DPI for which it could be awarded exclusivity must be narrowly limited to only those changes studied in the BREEZE Study, such as the BREEZE Study's specific patient population of PH patients who switched from Tyvaso Inhalation Solution.

Answer to ¶ 134. Paragraph 134 states legal conclusions to which no answer is required. To the extent a response is required, denied.

135. For the foregoing reasons, FDA's determination regarding the scope of Tyvaso DPI's NCI exclusivity exceed FDA's statutory authority, and is arbitrary and capricious, an abuse of discretion, and contrary to law. Thus, the FDA's Exclusivity Decision must be set aside.

Answer to ¶ 135. Paragraph 135 states legal conclusions to which no answer is required. To

the extent a response is required, denied.

[Liquidia's] PRAYER FOR RELIEF

WHEREFORE, Liquidia respectfully requests that this Court provide the following relief:

A. An order pursuant to 28 U.S.C. § 2201 declaring that:

B. FDA's Exclusivity Decision for Tyvaso DPI exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law;

C. FDA's Exclusivity Decision applying Tyvaso DPI's NCI exclusivity to PH-ILD patients exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law;

D. FDA's failure to immediately issue full approval to the Yutrepia NDA exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law; and

E. Yutrepia is entitled to immediate and full approval for one or more indications.

F. Preliminary and permanent mandatory injunctions ordering FDA to grant immediate, full approval of the Yutrepia NDA for one or more indications.

G. An award of costs and reasonable attorney fees to the extent permitted by law, including 28 U.S.C. § 2412; and

H. Such other relief as this Court may deem just and proper.

Answer to Prayer For Relief. The requests in the Request for Relief do not set forth factual allegations. To the extent that any factual allegations are implicit in the Request for Relief, they are denied.

WHEREFORE, UTC denies that plaintiff is entitled to any of the relief requested.

UNITED THERAPEUTICS CORPORATION'S CROSS-CLAIMS AGAINST FOOD AND DRUG ADMINISTRATION, ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of FDA; the UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES ("HHS"); and XAVIER BECERRA, in his official capacity as Secretary of HHS

Defendant-Intervenor and Cross-Claimant United Therapeutics Corporation ("UTC") brings these Cross-Claims against Defendants the Food and Drug Administration ("FDA"); Robert M. Califf, M.D., in his official capacity as Commissioner of FDA; the United States Department of Health and Human Services ("HHS"); and Xavier Becerra, in his official capacity as Secretary of HHS, and alleges as follows:

I. NATURE OF THE ACTION

1. For at least three decades, FDA's rules, precedents, and procedures have barred applicants from amending a pending drug application to seek approval for a newly proposed drug use (called an "indication") that was not requested in the applicant's original application, instead requiring a new application. In that new application, the applicant must demonstrate that the drug is safe and effective for the newly proposed indication and must pay a separate FDA "user fee" to fund the additional review that a new indication requires. Of particular relevance here, the new application must also go through the procedures that Congress specifically designed to ensure that any potential patent disputes could be adjudicated *before* FDA approves a potentially infringing drug product or use.

2. In this case, FDA disregarded its own rules, precedents, and procedures by accepting an amendment from Liquidia Technologies, Inc. ("Liquidia") that does precisely what FDA has always prohibited: add a new indication to its pending application. That arbitrary and capricious departure from FDA's established rules, precedents, and policies was improper on its own. However, FDA's decision also subverts the intricate statutory framework Congress designed

to ensure that—for the protection of *both* innovators like UTC *and* imitators like Liquidia—the federal courts have enough time to resolve drug-related patent disputes before FDA can approve a new drug. FDA's decision to accept Liquidia's amendment upset the carefully crafted legislative bargain at the heart of the Hatch-Waxman Act. The decision to accept Liquidia's amendment is unlawful, arbitrary and capricious, and must be vacated.

3. UTC is a biotechnology company focused on the development and commercialization of products that address the needs of patients with chronic and life-threatening conditions, including cardiovascular and pulmonary diseases and pediatric cancers.

4. UTC developed TYVASO (treprostinil), an inhaled form of the drug treprostinil that FDA has approved for two clinically distinct indications: (1) the treatment of pulmonary arterial hypertension ("PAH"), and (2) pulmonary hypertension associated with interstitial lung disease ("PH-ILD").

5. In January 2020, Liquidia submitted a New Drug Application ("NDA") seeking FDA marketing approval for an inhaled treprostinil product that, as originally submitted to FDA, would be indicated exclusively for the treatment of PAH (but not PH-ILD). Liquidia sought approval for this product and indication under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2), which allows an applicant to shortcut the normal FDA review process by relying on FDA's prior approval of an existing drug and its associated clinical data—in Liquidia's case, by piggybacking on FDA's prior approval of UTC's TYVASO as safe and effective in the treatment of PAH.

6. In exchange for taking that shortcut, 505(b)(2) applicants like Liquidia must follow the requirements Congress established to protect the patent rights of the innovator on whose prior approval and data the 505(b)(2) applicant relies. As relevant here, the 505(b)(2) applicant must

provide a "certification" to patents listed by the innovator in FDA's *Approved Drug Products with Therapeutic Equivalents* publication ("Orange Book"). If the innovator has timely listed a patent for the previously approved product, and the applicant notifies the innovator that it has certified that it intends to begin marketing its own product before that patent expires (a so-called "paragraph IV" certification), then the innovator may bring suit for patent infringement without waiting for the 505(b)(2) applicant to commit a traditional act of patent infringement (such as selling its infringing product). 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990).

7. To ensure adjudication of patent disputes *before* the approval and resulting launch of a product that would irrevocably change the market, Congress created the "30-month stay" that is central to this case. If the innovator files suit promptly after receiving notice of an applicant's paragraph IV certification, FDA's ability to approve the pending application is stayed for 30 months—typically enough time for the district court to decide the patent litigation. *See* 21 U.S.C. § 355(c)(3)(C). If the patent litigation ends sooner, so does the stay. *See id.* § 355(c)(3)(C)(i)-(ii). This process facilitates the efficient resolution of patent disputes before approval and launch.

8. There is an exception to the 30-month stay for legally permissible amendments to 505(b)(2) applications that are already pending. To prevent minor changes (such as a change in color) from triggering a new stay, the statute provides that a 30-month stay applies to listed patents for which information was submitted "before the date on which the application (*excluding an amendment or supplement to the application*) was submitted." 21 U.S.C. § 355(c)(3)(C) (emphasis added). Thus, when an applicant submits a lawful amendment to a pending 505(b)(2) application, its submission of a paragraph IV certification on patents listed after the original application was filed will not trigger a stay of final approval.

9. To avoid disrupting the statutory process for pre-approval patent adjudication and to properly allocate its own resources, FDA regulations and guidance have always limited the types of changes allowed by amendment. Indeed, since at least 1993, FDA's "Bundling Rule" has provided that an applicant may not add a new *indication* to a pending application—which includes a "tentatively approved" application—via an amendment; rather, the applicant must submit a new application. This longstanding rule, which FDA has reiterated repeatedly and as recently as January 2024, ensures that when a 505(b)(2) applicant seeks approval for a new indication that provokes a patent dispute, a 30-month stay will apply to allow orderly resolution of the suit before approval. *See* SOPP 8401 Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA), at 12 (Jan. 8, 2024), https://www.fda.gov/media/85659/download. Since new indications are often protected by different patents than those addressed by the applicant's initial certification, this established procedure is essential for the patent-litigation process to work as Congress intended.

10. In July 2023, Liquidia submitted an amendment to its pending 505(b)(2) NDA to add PH-ILD as a proposed new indication. Under the FDA's Bundling Rule and as the Agency's precedents repeatedly have made clear, this amendment was improper. FDA should have rejected the application and required Liquidia to submit a new NDA for this indication. Nevertheless, FDA accepted Liquidia's amendment for substantive review. PR92523 (Press Release, FDA Accepts Submission to Add PH-ILD to YUTREPIA Label (Sept. 25, 2023), https://www.liquidia.com/node/10646/pdf).

11. On December 29, 2023, UTC submitted a letter to FDA identifying FDA's unlawful action in accepting Liquidia's Amended 505(b)(2) NDA for substantive review and urging FDA to rescind that unlawful action. Liquidia submitted a response and UTC submitted a reply. FDA

took the position that until it responded to UTC's letter, its position on the propriety of Liquidia's amendment was not yet final.

12. On August 16, 2024, FDA issued a decision in response to UTC's letter. In its letter, FDA affirmed its decision to "depart from the policy stated in its guidance documents" by allowing Liquidia to pursue a new indication on a pending application by way of an amendment and thus bypass the automatic 30-month stay that would have arisen had FDA required Liquidia to file a new NDA when demanded by UTC. Ex. A at 1 (Aug. 16, 2024 General Advice Letter to United Therapeutics Corporation) (the "Bundling Decision"). On the same day, FDA granted tentative approval to Liquidia's Amended 505(b)(2) NDA. In the approval letter, FDA stated that final approval authorizing Liquidia to market YUTREPIA (Liquidia's Proposed 505(b)(2) Product) for the original PAH indication and the new PH-ILD indication sought in the amendment could not occur until the expiration of the three-year new clinical investigation exclusivity period under 21 U.S.C. § 355(c)(3)(E)(iii), which will expire on May 23, 2025. Based on the Bundling Decision, FDA may approve Liquidia's NDA for both the PAH and PH-ILD indications immediately once the new clinical investigation exclusivity expires, notwithstanding the 30-month stay to facilitate patent litigation to which UTC is entitled by statute.

13. FDA's decision to disregard binding rules, precedents, and procedures has deprived UTC of an important statutory protection. Liquidia's amended NDA implicates multiple UTC patents listed in the Orange Book, including those specific to the PH-ILD indication. Liquidia has submitted paragraph IV certifications as to those patents, and UTC has timely sued Liquidia for patent infringement. If Liquidia made these paragraph IV certifications as part of the new 505(b)(2) NDA required by the Agency's rules, precedents, and procedures, FDA would be barred from approving that NDA for up to 30 months (extending beyond May 23, 2025) to allow time for

UTC's infringement claims to be adjudicated. That is what should have happened. Instead, by accepting Liquidia's request to pursue its new indication as an amendment, rather than a new application, FDA allowed Liquidia to sidestep the 30-month stay, deprived UTC of a valuable statutory right, and undermined the statutory process for resolving patent disputes.

14. UTC brings these cross-claims under the Administrative Procedure Act, 5 U.S.C. §§ 551 *et seq.* These cross-claims arises out of the same transaction or occurrence that is the subject matter of Liquidia's original action—namely, Liquidia's 505(b)(2) NDA seeking FDA approval for Liquidia's Proposed 505(b)(2) Product, YUTREPIA, and FDA's decisions with respect to that application. *See* Fed. R. Civ. P. 13(g). UTC seeks an order declaring that FDA's decision to accept Liquidia's amendment for substantive review in express disregard of its longstanding Bundling Rule was arbitrary and capricious, in excess of its statutory authority, without observation of procedure, or otherwise unlawful. UTC seeks an order vacating FDA's acceptance of Liquidia's amendment. Liquidia of course remains free to seek marketing approval for its follow-on product in PH-ILD in addition to the original PAH application if it wants—but it needs to follow FDA rules and submit a new application.

II. PARTIES

15. UTC is a corporation organized and existing under the laws of the State of Delaware and having a place of business at 1000 Spring Street, Silver Spring, Maryland 20910.

16. Defendant FDA is an agency of the United States government within HHS. The Secretary of Health and Human Services has delegated to FDA the authority to administer relevant provisions of the FDCA. FDA is headquartered in Silver Spring, Maryland.

17. Defendant Robert M. Califf, M.D., is the Commissioner of Food and Drugs. The Commissioner of Food and Drugs has the delegated authority to administer the FDCA. He is sued in his official capacity only.

18. Defendant HHS is a cabinet-level executive department charged with enhancing the health and well-being of all Americans. HHS is headquartered in Washington, D.C.

19. Defendant Xavier Becerra is Secretary of Health and Human Services. The Secretary of Health and Human Services is the official charged by law with administering the FDCA. He is sued in his official capacity only.

III. JURISDICTION AND VENUE

20. This Court has subject matter jurisdiction pursuant to 28 U.S.C. § 1331, because this case arises under the laws of the United States.

21. UTC brings these cross-claims under the Administrative Procedure Act, 5 U.S.C. §§ 551 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. § 2201.

22. Venue is proper in this district under 28 U.S.C. § 1391(e)(1) because at least one defendant resides in this district.

IV. LEGAL BACKGROUND

A. FDA Approval of New Drug Products

23. The FDCA mandates that before FDA approves a new drug product, the sponsor must prove that the drug product is effective and safe for use in each of its proposed indications. *See* 21 U.S.C. § 355(d)(2); *see generally* § 355(a). To do so, the FDCA and its implementing regulations require those seeking to market a new drug to obtain approval of an application submitted pursuant to section 505(b) or (j) of the FDCA.

24. To market a new brand-name drug, an applicant typically submits an NDA under section 505(b)(1) of the FDCA, 21 U.S.C. § 355(b)(1). Obtaining approval of an NDA under section 505(b)(1) requires that the drug's sponsor provide FDA with "full reports of investigations" that the applicant has "made to show whether or not such drug is safe for use and whether such drug is effective in use." *Id.* § 355(b)(1)(A). To that end, the NDA must include a clinical data

section providing "[a] description and analysis of each controlled clinical study pertinent to a proposed use of the drug" and a "summary of the data demonstrating substantial evidence of effectiveness for the claimed indications." 21 C.F.R. § 314.50(d)(5)(ii), (v).

B. The Hatch-Waxman Act

25. 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, amended the FDCA to remove barriers to entry, increase availability of drugs, and reduce prescription costs. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998). In so doing, the Hatch-Waxman Act established two abbreviated pathways allowing drug products to come to market more quickly than if full studies for safety and effectiveness were required: the abbreviated new drug application ("ANDA") pathway for generic drugs (duplicates), and the 505(b)(2) pathway for follow-on products. This case involves the latter.

26. An applicant can secure approval for a generic drug by submitting an ANDA that establishes that the generic drug is bioequivalent and pharmaceutically equivalent to a previously approved reference listed drug ("RLD") that FDA has already found to be safe and effective. 21 U.S.C. § 355(j)(2)(A). In other words, the ANDA relies on the safety and effectiveness data for the RLD. The 505(b)(2) pathway is used when the new drug is not just a bioequivalent copy of the RLD but shares some relevant characteristics with a previously approved drug. "Like the full NDA, a 505(b)(2) NDA must directly demonstrate that the proposed drug product is safe and effective" for each of the indications for which it seeks FDA approval. *Veloxis Pharm., Inc. v. FDA*, 109 F. Supp. 3d 104, 108 (D.D.C. 2015); *see also* 21 C.F.R. § 314.54(a)(ii); 21 C.F.R. § 314.50(d)(5)(ii), (v). But to the extent that the drug shares characteristics with the proposed new product, the 505(b)(2) NDA can rely, at least in part, "on clinical studies that were previously submitted to the FDA in support of another drug and that were not conducted or licensed by the

505(b)(2) sponsor." *Veloxis*, 109 F. Supp. 3d at 109 (brackets omitted); FDA, Determining Whether to Submit an ANDA or a 505(b)(2) Application (May 2019), at 4, https://www.fda.gov/media/124848/download.

27. In creating these abbreviated processes, Congress addressed two challenges. *First*, Congress recognized that many listed drugs are protected by valuable patents (e.g., for active ingredients, methods of delivery, and/or methods of use), and it needed to preserve and reinforce the Patent Act's crucial incentives and protections for pharmaceutical innovation. *Second*, Congress recognized that uncertainty over the validity, enforceability, and applicability of those patents might discourage a follow-on product's sponsor from marketing its drug *even after FDA approval*. That is so because the Patent Act had always prevented parties from resolving patent-related disputes until after an alleged infringer actually "makes, uses, offers to sell, or sells any patented invention, within the United States or imports [it] into the United States." 35 U.S.C. § 271(a). The utility of Hatch-Waxman's abbreviated pathways would have been substantially diminished if follow-on applicants could not obtain patent certainty without risking the entry of an infringement judgment and potential damages or injunctive relief.

28. To "strike[] a balance between the sometimes-competing policy interests of inducing pioneering research and development of new drugs and enabling production of low-cost, generic copies of those drugs," *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 557 F.3d 1346, 1347 (Fed. Cir. 2009), the Hatch-Waxman Act established a multi-part process designed with one objective in mind: to ensure that potential patent disputes between innovators and imitators can be resolved *before* the approval and launch of a potentially infringing follow-on product.

29. First, to help prospective follow-on product sponsors identify potential patent barriers to entry, the Hatch-Waxman Act requires the sponsor of an FDA-approved NDA to file

with FDA "the patent number and the expiration date of any patent which claims the drug . . . and with respect to which a claim of patent infringement could reasonably be asserted [against a competitor]." 21 U.S.C. § 355(b)(1); *see also* 21 C.F.R. § 314.50(h). FDA is then required to "make available to the public" a list of the patents NDA holders have submitted to the agency, which it publishes in the Orange Book. 21 U.S.C. § 355(j)(7)(A)(i); *see also* § 355(c)(2).

30. Next, the Hatch-Waxman Act requires each 505(b)(2) NDA or ANDA to include "a certification … with respect to each [Orange Book-listed] patent which claims the listed drug … or … a use for such listed drug." § 355(c)(2)(A) (505(b)(2) applications), (j)(2)(A)(vii) (ANDAs); *see also* 21 C.F.R. § 314.53(f). If a 505(b)(2) or ANDA applicant wants to market a follow-on drug before the expiration of any patent listed in the Orange Book for a given brand-name drug, it must certify that the patent is invalid or unenforceable or will not be infringed by the generic drug (which, as noted above, is referred to as a "paragraph IV" certification). 21 U.S.C. § 355(c)(2)(A)(iv), (j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A). Whenever a follow-on applicant makes such a certification, it must then timely notify both the brand-name drug's sponsor and the relevant patentees and explain the basis for its paragraph IV certification. *Id.* § 355(b)(3)(B). To ensure that both innovators and follow-on sponsors can obtain patent certainty at the earliest possible opportunity, the statute deems an applicant's submission of a paragraph IV certification to FDA as an artificial act of patent infringement that can immediately be litigated before the product is marketed. 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990) ("Quite obviously, the purpose of [35 U.S.C. §§ 271](e)(2) and (e)(4) is to enable the judicial adjudication upon which the ANDA and paper NDA schemes depend."); *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1305 (D.C. Cir. 2010).

31. The statute is further designed to ensure that orderly patent litigation promptly follows from the submission of a paragraph IV certification. Where the brand manufacturer files suit within 45 days of receiving the legally required notice of a paragraph IV certification, it earns the right to an automatic stay that bars FDA from approving the 505(b)(2) NDA or ANDA until the earlier of the expiration of the patent, resolution of the suit, or thirty months after the patentee's receipt of notice. 21 U.S.C. § 355(c)(3)(C); 21 C.F.R. § 314.107(b)(3)(viii). Taken as a whole, the purpose of the Hatch-Waxman Act is to ensure that patent disputes are resolved in an orderly fashion before an FDA approval irretrievably alters the composition of the marketplace.

C. The Bundling Rule and Incentivizing Major Modifications

32. Before Congress amended the Hatch-Waxman Act in 2003, brands were able to secure additional 30-month stays for insignificant patents listed after the submission of a 505(b)(2) application or ANDA. For example, a brand manufacturer might secure a patent covering minor secondary changes to a drug product (*e.g.*, related to color or packaging) and trigger a new stay, even though the change "really did not indicate a different or improved use for the product[.]" As one key sponsor of the relevant legislation explained:

> We heard in committee examples of the brand name manufacturer making extremely minor changes, such as in the color or the design of the packaging or the scoring of the pill that really did not indicate a different or improved use for the product but, rather, were devices intended to keep the generic off the market for a while longer.

148 Cong. Rec. S6844 (2002) (statement of Sen. Collins). Congress sought to curb this practice in the Medicare Modernization Act of 2003 ("MMA"), Pub. L. No. 108-173, 117 Stat. 2066 (2003), by amending the statute to specify that patents first listed after the application was filed do not result in a stay. 21 U.S.C. § 355(c)(3)(C) (patents must have been submitted before "the date on which the application (excluding an amendment or supplement to the application) was submitted"). But Congress did not intend for the MMA's limitation on the 30-month stay to address follow-on

patents for significant changes reflecting "different or improved use[s] for [a] product," which are the kinds of "innovations that Congress sought in the [Hatch-Waxman] Bill." 48 Cong. Rec. at S6844 (statement of Sen. Collins); Examining Issues Related to Competition in the Pharmaceutical Marketplace: A Review of the FTC Report, Generic Drug Entry Prior to Patent Expiration: Hearing Before the SubComm. on Health of the Comm. on Energy and Com., 107 Cong. 21 (2002). To the contrary, Congress understood that a major modification to a pending 505(b)(2) application could not be made in an amendment but, rather, required a separate application. Such a major modification could thus give rise to a new 30-month stay, if covered by a patent listed before the new application.

33. The MMA was enacted against the backdrop of FDA's Bundling Rule from 1993, which governed the kinds of modifications that could be added to a pending NDA in an amendment. The Bundling Rule as issued in 1993 provided that "a pending original or supplemental application should not be amended to add a new indication" and explained that, "[i]f the original application is not yet approved, a request for approval of other indications or claims" should "be submitted in a separate, original, application." FDA, Interim Guidance: Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992 at 6 (1993) ("1993 Bundling Rule"). When Congress adopted the MMA 10 years later, it acknowledged the import and continuing force of the Bundling Rule, stating that it "d[id] *not* intend [the MMA] to alter current [FDA] practice regarding acceptance of … amendments and supplements to pending and approved [applications].... Instead, Congress intends [the MMA] to reflect the FDA's current practice regarding those changes and variations to both innovator and generic drugs that may be approved under amendments and supplements to previously filed NDAs and ANDAs." H.R. Rep. No. 108-391, at 835 (2003). The

text of the MMA further confirms that Congress acted to avoid disturbing the Bundling Rule and understood the distinction between substantial alterations that should be the subject of a new application (and should trigger a new 30-month stay) and largely immaterial modifications where an additional 30-month stay might not be appropriate. *Compare* 21 U.S.C. § 355(b)(4)(A) (applicants may not seek approval of a different drug in an amendment), *and* 149 Cong. Rec. S8197 (2003) (statement of Sen. Frist) (discussing prudence of clarifying FDA's "policy that an amendment or supplement...cannot cover a drug other than the original drug" because it is an "obvious loophole."), *with* 21 U.S.C. § 355(b)(4)(B) (permitting amendments to seek approval for a different strength), *and* 1993 Bundling Rule at 4-5 (permitting different strengths in a single application).

34. Following adoption of the 2003 MMA, FDA has reaffirmed its Bundling Rule in relevant and substantial part, including as applied to new indications. The current version of the Bundling Rule, set forth in 2004, states:

> If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration . . . can be regarded, for the purposes of assessing user fees, as one application. . . . *After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim. . . . If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application*. If the initial application is approved, the application can be subsequently supplemented to add a new indication.

2004 Bundling Rule, at 4-5 (emphasis added).

35. In regulations implementing the MMA, FDA characterized the Bundling Rule as imposing requirements on NDA applicants. *See, e.g.*, FDA, Proposed Rule, Abbreviated New Drug Applications and 505(b)(2) Applications, 80 Fed. Reg. 6802, 6851 (Feb. 6, 2015) ("[A]n applicant *may not* seek approval for these types of changes to a drug through an amendment or supplement

... the applicant *is required* to submit a new 505(b)(2) application") (emphasis added); FDA, Final Rule, Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69,580, 69,616, 69,635 (Oct. 6, 2016) ("These changes must be requested in a new 505(b)(2) application. This final requirement conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application."). FDA has also historically interpreted its regulations in accordance with the Bundling Rule, such that "[m]ost requests for approval of a different indication or condition of use by a 505(b)(2) applicant should not be made as an amendment to the 505(b)(2) application," because new indications represent the type of significant innovation that the Hatch-Waxman Act sought to incentivize and protect. 81 Fed. Reg. at 69,616. Similarly, FDA has promulgated regulations recognizing that a pending drug application cannot be amended to incorporate major changes, which would undermine the statutory design. For example, FDA regulations preclude amendments that would require the review of data to support an indication or claim that was not submitted with the original drug application, while amendments for minor modifications are permissible. *See* 21 C.F.R. § 314.60(b)(6).

36. Nevertheless, FDA now asserts that, in 2018, FDA undertook a heretofore undisclosed process to determine "how and whether to bundle certain amendments from the applicants of a pending 505(b)(2) applications [sic] that proposed to add a new indication that previously had been approved for the relied-upon listed drug." Ex. A at 16. "[C]onsidering the propriety of such amendments in the context of the Bundling guidance, FD&C Act, and FDA's regulations to implement portions of the MMA, FDA determined that it would be a preferable practice to allow an applicant to amend its pending 505(b)(2) application to add a new indication in the limited circumstance where new clinical data are not necessary to support the new indication." *Id.* at 16–17.

37. FDA never disclosed to the public that it had undertaken this "consider[ation]," and never explained, prior to the Bundling Decision, to any applicant the reasoning for its change in policy, notwithstanding FDA's prior practice of requiring compliance with the Bundling Rule. *Id.* Indeed, FDA still has not publicly announced its purported change in this consequential policy.

V. FACTUAL BACKGROUND

A. UTC Obtains NDA for TYVASO for the Treatment of PAH and PH-ILD

38. PAH is a rare disease affecting the pulmonary vasculature. PAH is characterized by high pressure in the pulmonary arteries, which increases strain on the right ventricle of the heart, often leading to heart failure and death.

39. On or around June 27, 2008, UTC sought approval of NDA No. 022387 for TYVASO (treprostinil) Inhalation Solution for the treatment of PAH. NDA 022387 Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022387s000ltr.pdf.

40. UTC relied on the TRIUMPH I phase 3 clinical study in support of NDA No. 022387, which evaluated the efficacy of TYVASO in 235 clinically stable subjects with PAH during a 12-week, randomized, double-blind, placebo-controlled, multicenter investigation. *See* Prescribing Information for TYVASO at 4, 9, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022387s020lbl.pdf.

41. On or around July 30, 2009, FDA approved UTC's NDA for TYVASO for the treatment of PAH.

42. Unlike PAH, PH-ILD encompasses a group of parenchymal lung diseases that are characterized by significant scarring and increased fibrotic tissue within the bronchioles and alveolar sacs of the lungs, which prevents oxygenation and free gas exchange between the alveolar sacs and pulmonary capillaries.

43. On or around June 1, 2020, UTC sought approval for supplemental NDA No. 22387/S-017 for TYVASO for the treatment of a new indication, PH-ILD. UTC's Supplement Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022387Orig1s017ltr.pdf. FDA approved UTC's supplemental NDA for PH-ILD in 2021.

44. TYVASO is currently listed in the Orange Book with the following patent information:

Patent Data

Patent No.	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
9339507	03/10/2028		DP			05/17/2016
9358240	05/05/2028			U-1849		06/08/2016
9593066	12/15/2028	DS				03/14/2017
9604901	12/15/2028	DS				03/28/2017
10376525	05/14/2027			U-1849		04/29/2020
10716793	05/14/2027			U-1849		07/21/2020
11723887	12/15/2028	DS				08/15/2023
11826327	02/03/2042			U-3749		11/28/2023

B. Liquidia Relied on TYVASO as the Listed Drug to Submit an Original 505(b)(2) NDA to Market a Version of Treprostinil for the Treatment of PAH

45. On or around January 24, 2020, Liquidia sought approval for NDA No. 213005 for treprostinil inhalation powder ("Liquidia's Proposed 505(b)(2) Product") under section 505(b)(2) of the FDCA ("Original 505(b)(2) NDA"). Liquidia's November 2021 Tentative Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf. Liquidia's Original 505(b)(2) NDA sought approval to market Liquidia's Proposed 505(b)(2) Product for the treatment of PAH. PR112520, Press Release, Liquidia Receives Complete Response Letter from FDA for LIQ861 (treprostinil) Inhalation Powder for the

Treatment of Pulmonary Arterial Hypertension (Nov. 25, 2020), https://www.liquidia.com/node/8351/pdf.

46. Liquidia's Original 505(b)(2) NDA contained paragraph IV certifications to the then-listed Orange Book patents for TYVASO—specifically, U.S. Patent Nos. 9,339,507 ("the '507 patent"), 9,358,240 ("the '240 patent"), 8,497,393 ("the '393 patent"), 9,593,066 ("the '066 patent"), and 9,604,901 ("the '901 patent").

47. Thereafter, Liquidia submitted an additional paragraph IV certification to FDA regarding U.S. Patent No. 10,716,793 ("the '793 patent"). The '793 patent was timely submitted for listing in the Orange Book for TYVASO on or around July 21, 2020, which was after Liquidia's Original 505(b)(2) NDA was initially submitted to FDA.

48. Liquidia submitted paragraph IV certifications to FDA on each of these patents, thus representing that, in Liquidia's view, the '507, '240, '393, '066, '901, and '793 patents are invalid, unenforceable, and/or would not be infringed by Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Original 505(b)(2) NDA. Liquidia's certifications represent its intention to engage in the commercial manufacture, use, and/or sale of Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Original 505(b)(2) NDA prior to the expiration of the '507, '240, '393, '066, '901, and '793 patents.

49. On or around November 4, 2021, FDA tentatively approved Liquidia's Original 505(b)(2) NDA. Liquidia's November 2021 Tentative Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf. Tentative approval means that the application cannot yet be finally approved until after a period of exclusivity has run.

50. Meanwhile, UTC filed an infringement action against Liquidia based on its paragraph IV certifications. The case went to trial, and UTC prevailed on the '793 patent. Under an order from the U.S. District Court for the District of Delaware, the effective date of final approval for Liquidia's NDA may not be before expiration of the '793 patent in 2027, by virtue of that court's judgment of infringement. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-cv-755, ECF No. 436 (D. Del. Sept. 9, 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023), *cert. denied*, No. 23-804 (U.S. Feb. 20, 2024); 35 U.S.C. § 271(e)(4). On December 26, 2023, Liquidia filed a motion under Rule 60(b) seeking to modify that judgment and allow immediate approval based on a decision of the U.S. Patent Trial and Appeal Board finding the '793 patent unpatentable. On March 28, 2024, the U.S. District Court for the District of Delaware granted Liquidia's Rule 60(b) motion, vacating the portion of its final judgment that had blocked the final approval of Liquidia's Original 505(b)(2) NDA. UTC appealed that decision; its appeal remains pending. *See* Fed. Cir. No. 2024-1658.

C. Liquidia Submitted an Amendment to Its Pending Original 505(b)(2) NDA to Add a New Indication for PH-ILD

51. On or around July 24, 2023, Liquidia submitted an amendment to its tentatively approved 505(b)(2) NDA, seeking to add a new indication: treatment of PH-ILD ("Amended 505(b)(2) NDA"). Press Release, Liquidia Submits Amendment to Add PH-ILD Indication to Tentatively Approved NDA for YUTREPIA™ (treprostinil) Inhalation Powder (July 27, 2023), https://www.liquidia.com/node/10556/pdf.

52. Liquidia's Amended 505(b)(2) NDA contained paragraph IV certifications to the then-listed Orange Book patent information for TYVASO—specifically, to the '507 patent, the '240 patent, the '066 patent, the '901 patent, the '793 patent, and U.S. Patent No. 10,376,525 ("the '525 patent"). *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 20-cv-00755 (D.

Del. Nov. 15, 2023), D.I. 458-5 (E-mail from Brian Cooney, U.S. Food & Drug Admin., to Jennifer Weidman, Liquidia Techs., Inc. (Sept. 14, 2023)) ("Sept. 2023 FDA Correspondence").

53. In or around July 2023, Liquidia certified to FDA that the '507, '240,'066, '901, '793, and '525 patents are invalid, unenforceable, and/or would not be infringed by Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Amended 505(b)(2) NDA. Liquidia's certifications represent its intention to engage in the commercial manufacture, use, and/or sale of Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Amended 505(b)(2) NDA prior to the expiration of the '507, '240, '066, '901, '793, and '525 patents.

54. Within 45 days of receipt of notice of Liquidia's paragraph IV certifications, on or around September 5, 2023, UTC asserted the '793 patent in a suit for patent infringement under, *inter alia*, 35 U.S.C. § 271(e) due to Liquidia's intention to engage in the commercial manufacture, use, and/or sale of Liquidia's Proposed 505(b)(2) Product for the treatment of PH-ILD prior to the expiration of the '793 patent (the "PH-ILD Delaware Litigation"). *See* Complaint, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 23-cv-975 (D. Del. Sept. 5, 2023), D.I. 1.

55. On or around September 25, 2023, FDA accepted for review Liquidia's amendment to add the new PH-ILD indication to Liquidia's Original 505(b)(2) NDA. *See* Press Release, FDA Accepts Submission to Add PH-ILD to YUTREPIA Label (Sept. 25, 2023) at 1, https://www.liquidia.com/node/10646/pdf.

56. On or around November 28, 2023, U.S. Patent No. 11,826,327 ("the '327 patent") was issued by the U.S. Patent and Trademark Office. The '327 patent, duly and legally owned by UTC, was timely submitted for listing in the Orange Book for TYVASO on or around November 28, 2023. The Orange Book lists the use code for the '327 patent as "Method of treating [PH-ILD]

by administering treprostinil or a salt thereof by inhalation using a device." The claims of the '327 patent all relate to administering treprostinil to a patient with PH-ILD.

57. On December 29, 2023, UTC submitted a letter to FDA identifying FDA's unlawful action in accepting Liquidia's Amended 505(b)(2) NDA for substantive review and urging FDA to rescind that unlawful action. At FDA's invitation, Liquidia submitted a responsive letter to FDA on February 2, 2024. UTC submitted a reply letter to FDA on February 12, 2024.

58. In prior litigation in this District challenging FDA's acceptance of the Amended 505(b)(2) NDA, FDA represented to the Court that it had not yet finished considering whether "Liquidia's amendment is proper," and was "actively considering" that question in light of the UTC and Liquidia's submissions. *E.g.,* Fed. Defs.' Opp. to Pl.'s TRO/PI Motion at 11-12, No. 1:24-cv-484-JDB (D.D.C. Mar. 18, 2024). FDA also contended that any action filed against it before it completed its consideration of those suggestions was "incurably premature." Fed. Defs.' Mot. to Dismiss at 13-15, No. 1:24-cv-484-JDB (D.D.C. May 7, 2024).

59. As a result of its acceptance of Liquidia's amendment, FDA determined that a new 30-month stay period would not be triggered by litigation arising from the paragraph IV certifications to patents listed after the submission date for Liquidia's Original 505(b)(2) NDA, including patent certifications resulting from the amendment Liquidia submitted two and a half years after that submission date. *See* Sept. 2023 FDA Correspondence. FDA's Sept. 14, 2023 e-mail to Liquidia states, *inter alia*, "[w]e note that the 45-day period provided for in section 505(c)(3)(C) of the FD&C Act does not apply with respect to a paragraph IV certification for the '887 patent." *Id.*[51]

[51] UTC duly and legally owns U.S. Patent No. 11,723,887 ("the '887 patent"), which was issued by the U.S. Patent and Trademark Office on August 15, 2023. The '887 patent was timely submitted for listing in the Orange Book for TYVASO on August 15, 2023.

60. FDA thus determined that patents submitted for listing in the Orange Book for TYVASO after the Original 505(b)(2) NDA filing date cannot give rise to a 30-month stay of final approval. As noted *supra*, on or around November 28, 2023, the '327 patent was timely submitted for listing in the Orange Book for TYVASO on or around November 28, 2023, with the use code "Method of treating [PH-ILD] by administering treprostinil or a salt thereof by inhalation using a device." On or around November 30, 2023, UTC amended its Complaint in the PH-ILD Delaware Litigation and asserted the '327 patent against Liquidia for patent infringement under, *inter alia*, 35 U.S.C. § 271(e). *See* First Amended Complaint, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 23-cv-975 (D. Del. Nov. 30, 2023), D.I. 8.

61. Thereafter, in or around December 2023, Liquidia further amended its Amended 505(b)(2) Application to include a paragraph IV certification for the '327 patent. Liquidia certified to FDA that the '327 patent is invalid, unenforceable, and/or would not be infringed by Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Amended 505(b)(2) NDA. Liquidia's certification represents its intention to engage in the commercial manufacture, use, and/or sale of Liquidia's Proposed 505(b)(2) Product that is the subject of Liquidia's Amended 505(b)(2) NDA prior to the expiration of the '327 patent.

62. As mentioned above, FDA has determined that patents listed in the Orange Book after the date on which Liquidia submitted its Original 505(b)(2) NDA cannot give rise to a 30-month stay of final approval. *See supra* ¶¶ 32-35. Thus, FDA has also determined that the '327 patent, which was also timely listed in the Orange Book after the date on which Liquidia submitted its 505(b)(2) NDA, cannot give rise to a 30-month stay of final approval. Had FDA required Liquidia to submit a new NDA upon receipt of UTC's December 29, 2023 letter, that patent would have triggered an additional 30-month stay.

D. FDA Issues a Decision Affirming its Acceptance of Liquidia's Amendment and Departing from the Bundling Rule

63. On August 16, 2024, FDA issued a decision in response to UTC's December 29, 2023 letter challenging FDA's decision to accept Liquidia's amendment. In the letter decision, FDA affirmed its decision to accept Liquidia's amendment to add an indication for PH-ILD to its pending application for Liquidia's Proposed 505(b)(2) Product , YUTREPIA. The letter explained that FDA was choosing "to depart from the policy stated in its guidance documents," which it deemed non-binding, on the theory that the amendment fell within a previously undisclosed exception to the Bundling Rule for amendments that do not include any clinical study data to support the new indication. Ex. A at 1. In cursory fashion, FDA stated that considerations supporting its departure from the established review framework "outweigh any potential reliance interests of innovators" like UTC, which it disparaged as "doubtful and at most limited." *Id.* at 23.

64. On the same day, FDA informed Liquidia that it was granting tentative approval to its Proposed 505(b)(2) Product for both the PAH and the PH-ILD indications. ECF No. 13-5 (Aug. 16, 2024 Tentative Approval Letter). FDA further determined that UTC was entitled to an unexpired regulatory exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii) for a new clinical investigation it had conducted that was essential to the approval of a new dry powder formulation of TYVASO (TYVASO DPI), and that Liquidia's Proposed 505(b)(2) Product fell within the scope of this exclusivity, meaning that FDA could not grant final approval to Liquidia's Proposed 505(b)(2) Product in either indication until May 23, 2025. *Id.*

VI. FDA's Decision to Allow Liquidia to Add the New PH-ILD Indication to Its Original 505(b)(2) NDA by Amendment, and FDA's Tentative Approval of the NDA as Amended, Were Unlawful

65. FDA's final decision to accept Liquidia's Amended 505(b)(2) NDA, rather than requiring Liquidia to file a new NDA to seek approval of the PH-ILD indication, violates the

FDA's longstanding Bundling Rule requiring an applicant to submit a new 505(b) NDA if it wants to seek approval for a new indication rather than amending a pending NDA. FDA's decision is inconsistent with the Hatch-Waxman Act's text, structure, and purposes, and it fails to adequately justify its dramatic about-face from the Bundling Rules terms, including by failing to adequately consider the substantial reliance interests of innovators like UTC.

A. Liquidia's Amendment Violated the Bundling Rule and FDA Violated the Bundling Rule by Accepting the Amendment for Review

66. FDA's final decision to accept Liquidia's Amended 505(b)(2) NDA for substantive review and to approve the new PH-ILD indication without requiring Liquidia to submit a new NDA violates the agency's longstanding Bundling Rule. The Bundling Rule establishes FDA's requirements for "what will be considered a separate marketing application" and faithfully implements the text, structure, and purposes of the Hatch-Waxman Act. Bundling Rule at 1.

67. The Bundling Rule states that, "[a]fter initial submission, a pending original or supplemental application should not be amended to add a new indication." *Id.* at 5. Instead, "a request for approval of other new indications...should be submitted in a separate, original application." *Id.* Such a "separate, original application" for a new indication is identified by the Agency as a "Type 9 NDA." *See* FDA, MAPP 5028.3: NDA Classification Codes, at 6 (Dec. 8, 2022), https://www.fda.gov/media/94381/download ("A Type 9 NDA is for a new indication or claim for a drug product that is currently being reviewed under a different NDA (the 'parent NDA'), and the applicant does not intend to market this drug product under the Type 9 NDA after approval. Generally, a Type 9 NDA is submitted as a separate NDA so as to be in compliance with the guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.").

68. FDA has also bound itself by the Bundling Rule. Before the Agency accepts an application (including an amendment) for substantive review, FDA staff have long been required to complete the Agency's "RPM Filing Review" checklist to ensure that the submission is lawful and consistent with the statute. As relevant here, that checklist permits the Agency to accept only those applications that comply with the Bundling Rule: "Has the user fee bundling policy been appropriately applied? *If no, or you are not sure, consult the User Fee Staff*." *See* FDA, Approval Package, Other Review(s), NDA 108603 at PDF page 4 (May 21, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208603Orig1s000OtherR.pdf.

69. Indeed, the Bundling Decision acknowledged that "CDER MAPP 5018.2 states that a sponsor may submit a separate, original NDA 'to be in compliance with the [Bundling Guidance]'," which could be construed to express "the view that the guidance is binding." Ex. A at 25 n.113 (brackets in original).

70. FDA failed to follow the Bundling Rule when it allowed Liquidia to amend its pending Original 505(b)(2) NDA to add a new indication, instead of requiring the company to submit a new original 505(b)(2) application. Bundling Rule at 5. FDA affirmed this decision in its letter of August 16, 2024, and by tentatively approving Liquidia's Amended 505(b)(2) NDA on the same date without requiring Liquidia to submit a new NDA for the PH-ILD indication.

B. FDA Treated Liquidia Differently than Similarly Situated Applicants

71. For decades, FDA consistently and repeatedly enforced the Bundling Rule against companies seeking to add new indications to pending applications. For example, FDA enforced the Bundling Rule in the following applications. *See, e.g.*, FDA, Approval Package, Administrative Document(s) & Correspondence, NDA 021822 (Aptivus), PDF pages 5-6 (May 2006), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021822s000admincorres.pdf (emphasis added); FDA, Approval Package, Administrative Document(s) & Correspondence,

NDA 206682 (Dexmedetomidine Hydrochloride Injection), PDF page 45 (Jan. 2015), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206628Orig1s000Admincorres.pdf; FDA, Approval Package, Proprietary Name Review(s), BLA 761223 (JEMPERLI), at PDF page 3 (May 24, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761223Orig1s000NameR.pdf. FDA's Bundling Decision suggests that, without any explanation to the public, FDA has now adopted a new policy of refraining from enforcing the Bundling Rule when applicants seek to add a new indication but not submit any clinical data alongside it.

72. However, FDA has routinely and extensively enforced the Bundling Rule in various additional contexts, including, but not limited to, attempts to amend pending applications to change the dosage form or route of administration. Such extensive and routine application demonstrates FDA's widespread enforcement of the Bundling Rule for an array of major changes that are likely to implicate patent rights. For example, FDA has enforced the Bundling Rule in the following drug applications. *See, e.g.*, FDA, Approval Package, Administrative and Correspondence Documents, NDA 210709 (TEKTURNA), PDF page 60 (Unacceptable For Filing Review Letter) (May 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/210709Orig1s000AdminCorres.pdf; FDA, Approval Package, Administrative Document(s) & Correspondence, NDA 209400 (Omeprazole Delayed-release Orally Disintegrating Tablets), PDF pages 63-64 (Nov. 2015), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209400Orig1s000AdminCorres.pdf (emphasis added); FDA, Approval Package, Administrative Document(s) & Correspondence, NDA 208780 (Esbriet), PDF page 76 (May 2015), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208780Orig1s000AdminCorres.pdf (emphasis added).

73. FDA's refusal to apply the Bundling Rule to Liquidia's amendment violates a central precept of administrative law—that federal agencies must "treat like cases alike"—and

violates the APA. *Westar Energy, Inc. v. Fed. Energy Regul. Comm'n*, 473 F.3d 1239, 1241 (D.C. Cir. 2007); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997) ("Government is at its most arbitrary when it treats similarly situated people differently."); *Burlington N. & Santa Fe Ry. Co. v. Surface Transp. Bd.*, 403 F.3d 771, 776–77 (D.C. Cir. 2005) ("An agency must provide an adequate explanation to justify treating similarly situated parties differently. Where an agency applies different standards to similarly situated entities and fails to support this disparate treatment with a reasoned explanation and substantial evidence in the record, its action is arbitrary and capricious and cannot be upheld." (citations omitted)).

74. Innovative drug manufacturers like UTC developed strong reliance interests in the application of the Bundling Rule, as it required the submission of new applications with new patent certifications when a generic or 505(b)(2) filer sought approval for a new indication for a proposed product. Based on FDA's longstanding application of the Bundling Rule, innovative drug manufacturers made investment and regulatory-affairs decisions based on the premise that FDA would require generic and 505(b)(2) applicants to comply with the Bundling Rule, as it had for decades, ensuring that such applicants could not use the amendment process to circumvent the statutory right to a 30-month stay that enables innovators to assert their patent rights before the market is irrevocably altered.

75. The reliance interests of innovative drug manufacturers persist, because until at least August 16, 2024, FDA had never revealed to regulated industry that it had altered its policy applying the Bundling Rule as promulgated in 2004, and had never explained why departure from the Bundling Rule was purportedly consistent with governing statute and regulation.

76. Despite innovators' substantial interest in the application of the Bundling Rule because of its implications for patent certifications and the 30-month stay, *supra* ¶¶ 63; 74-75, in

its August 16, 2024 decision, FDA failed to meaningfully consider or account for innovators' reliance interests, dismissing them as "doubtful and at most limited" without reasoning. Ex. A at 23; *cf. Int'l Org. of Masters, Mates & Pilots v. NLRB*, 61 F.4th 169, 179 (D.C. Cir. 2023) (an agency changing its position "must acknowledge that 'longstanding policies may have engendered serious reliance interests that must be taken into account,' as failure to do so renders the new rule arbitrary and capricious.") (quoting *Dep't of Homeland Sec. v. Regents of the Univ. of California*, 591 U.S. 1, 29 (2020)).

CLAIMS FOR RELIEF
Count I
Arbitrary and Capricious Agency Action, 5 U.S.C. § 706(2)
(Violation of the Bundling Rule)

77. UTC incorporates and re-alleges the foregoing paragraphs as though fully set forth herein.

78. FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review, as confirmed in its August 16, 2024 letter decision, was arbitrary and capricious, without observation of procedure required by law, and otherwise not in accordance with law because the agency disregarded the longstanding requirements and procedures set forth in its Bundling Rule. Having set these standards in implementing the FDCA, FDA must adhere to them. *Damus v. Nielsen*, 313 F. Supp. 3d 317, 335–341 (D.D.C. 2018) (recognizing that agency codification of internal policies may give rise to a "binding norm").

79. The Bundling Rule requires FDA to reject proposed 505(b)(2) amendments that seek "to add a new indication or claim." Bundling Rule at 5.

80. FDA violated the Bundling Rule when it accepted Liquidia's Amended 505(b)(2) NDA for substantive review rather than requiring Liquidia to submit a new 505(b)(2) application for the new PH-ILD indication. In doing so, FDA deprived UTC of its statutory right to a 30-

month stay that Congress designed for the manifest purpose of enabling a pre-approval resolution of UTC's patent claims against Liquidia.

81. Because FDA acted contrary to the Bundling Rule, FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review and approval of that application was arbitrary and capricious.

82. Because Liquidia relies upon UTC's previous approval for TYVASO and seeks approval for the PH-ILD indication before UTC's listed patents expire, the Hatch-Waxman Act requires a stay of approval so that UTC's patent claims against Liquidia can be resolved through the statutory pre-launch procedure. FDA's decision to accept Liquidia's Amended 505(b)(2) NDA for substantive review rather than requiring Liquidia to submit a separate 505(b)(2) application and its tentative approval of the bundled application deprived UTC of its statutory right to a 30-month stay.

83. Furthermore, FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review and its tentative approval of that application were arbitrary and capricious for the independent reason that FDA failed to appropriately consider reliance interests. In the Bundling Decision, FDA purportedly changed its policy regarding the application of the Bundling Rule without articulating or meaningfully weighing the reliance interests of innovators in FDA's application of the Bundling Rule. Where an agency has "adopted its new rule with no regard for the parties' reliance interests" the Court is "left with no choice but to vacate the [Agency's] arbitrary and capricious decision for want of reasoned decision making." *Masters, Mates & Pilots*, 61 F.4th at 180. FDA thus acted arbitrarily and capriciously, and its actions must be vacated and set aside.

84. If FDA's decision to accept Liquidia's Amended 505(b)(2) NDA for substantive review and its tentative approval of that application is not vacated and set aside, UTC will suffer substantial and irreparable harm for which there is no adequate remedy at law.

Count II
Arbitrary and Capricious Agency Action, 5 U.S.C. § 706(2)
(Differential Treatment of Similarly Situated Applicants)

85. UTC incorporates and re-alleges the foregoing paragraphs as though fully set forth herein.

86. FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review and its approval of that application were arbitrary and capricious because FDA engaged in different treatment of similarly situated applicants without providing any explanation to reconcile its disparate approach (because there is no such rationale). "If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA." *Bracco*, 963 F. Supp. at 27–28. FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review and its ultimate approval of that application were arbitrary and capricious because FDA permitted Liquidia to amend a pending 505(b)(2) application to add a proposed indication of use even though for decades it consistently and repeatedly has refused to permit other similarly situated applicants to amend pending 505(b)(2) or ANDA applications to add a proposed indication of use.

87. Indeed, FDA's departure from precedent in this case not only arbitrarily and capriciously treated Liquidia more favorably than similarly situated applicants, but has the effect of treating UTC *less* favorably than other similarly situated sponsors. After all, in the precedents described above, *supra*, ¶¶ 71-72 sponsors that were situated similarly to UTC enjoyed the protections afforded by the statute's 30-month stay of approval to litigate the sponsor's patent infringement claims, whereas FDA's departure from settled precedent in this case strips UTC of

that valuable statutory right in derogation of the statute. FDA thus acted arbitrarily and capriciously, and its actions must be vacated and set aside.

88. If FDA's decision to accept Liquidia's Amended 505(b)(2) NDA for substantive review and its tentative approval of that application are not vacated and set aside, UTC will suffer substantial and irreparable harm for which there is no adequate remedy at law.

Count III
Agency Action Not in Accordance with Law, 5 U.S.C. § 706(2)
(Violation of FDCA)

89. UTC incorporates and re-alleges the foregoing paragraphs as though fully set forth herein.

90. FDA's acceptance of Liquidia's Amended 505(b)(2) NDA for substantive review and its approval of that application were agency action in excess of statutory jurisdiction, authority, or limitations, short of statutory right, or otherwise not in accordance with law. FDA's decision to accept Liquidia's Amended 505(b)(2) NDA and to tentatively approve that improperly bundled application undermines the Hatch-Waxman Act's intricate and elaborate system for ensuring that significant patent disputes can be litigated prior to FDA's approval of a new drug for its claimed indications. Congress did not intend to alter FDA's practice of prohibiting the submission of new indications in an amendment to a pending NDA. *See* 1993 Bundling Rule at 6; 2004 Bundling Rule at 4-5. To the contrary, the structure and history of the 2003 MMA demonstrate an intent by Congress to codify FDA practice on this issue.

91. If FDA's decision to accept Liquidia's Amended 505(b)(2) NDA for substantive review and its tentative approval of that application are not vacated and set aside, UTC will suffer substantial and irreparable harm for which there is no adequate remedy at law.

VII. PRAYER FOR RELIEF

WHEREFORE, Cross-Claimant UTC respectfully requests that the Court enter judgment

in its favor and that the Court:

a. declare that FDA's decisions to accept Liquidia's Amended 505(b)(2) NDA for substantive review and to tentatively approve that application were arbitrary and capricious, not in accordance with law, in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; and without observance of procedure required by law;

b. vacate FDA's decisions to accept Liquidia's Amended 505(b)(2) NDA for substantive review and to tentatively approve that application;

c. compel FDA to order Liquidia to submit a new 505(b)(2) NDA and certify to patent information currently listed in FDA's Orange Book if Liquidia continues to pursue approval of its proposed new drug for a PH-ILD indication;

d. compel FDA to stay the approval of any such new 505(b)(2) NDA if Liquidia certifies to Orange Book-listed patent information and is then timely sued for patent infringement;

e. award Cross-Claimant attorneys' fees and costs; and

f. award Cross-Claimant such other and further relief as this Court deems just and proper.

Dated: September 16, 2024

Respectfully submitted,

/s/ Brian T. Burgess

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