UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

JAZZ PHARMACEUTICALS, INC.,
3170 Porter Drive,
Palo Alto, CA 94304,

Plaintiff,

v.

XAVIER BECERRA, Secretary of Health and Human Services,
200 Independence Ave. SW
Washington, DC 20201

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Ave. SW
Washington, DC 20201

ROBERT CALIFF, Commissioner of Food and Drugs,
10903 New Hampshire Ave.
Silver Spring, MD 20993

U.S. FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Ave.
Silver Spring, MD 20993

Defendants.

Case No. _____

COMPLAINT

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Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") alleges as follows against Defendants Xavier Becerra, in his capacity as Secretary of Health and Human Services; the Department of Health and Human Services ("HHS"); Robert Califf, in his capacity as Commissioner of Food and Drugs; and the Food and Drug Administration ("FDA"):

PRELIMINARY STATEMENT

1. This dispute is the latest of several that have showcased FDA's stark refusal to implement the Orphan Drug Act in a manner that is consistent with its statutory mandate. *See Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021); *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020) ("*Eagle II*"); *United Therapeutics Corp. v. HHS*, No. 17-01577 (ESH), 2020 WL 6498619 (D.D.C. Sept. 2, 2020); *Eagle Pharms., Inc. v. Azar*, No. 16-790 (TJK), 2018 WL 3838265 (D.D.C. June 8, 2018) ("*Eagle I*"); *Depomed, Inc. v. HHS*, 66 F. Supp. 3d 217 (D.D.C. 2014) (Jackson, J.).

2. Jazz is the sponsor of Xywav® (calcium, magnesium, potassium, and sodium oxybates), an orphan drug intended to treat the symptoms of narcolepsy, a rare sleep disorder characterized by excessive daytime sleepiness and cataplexy. Xywav is protected by orphan-drug exclusivity ("ODE"), granted by operation of the Orphan Drug Act, through July 21, 2027. This case arises from FDA's extraordinary decision to "break" that exclusivity, defying Congress's directive that FDA "may not approve another application" during the exclusivity period except pursuant to express exceptions that FDA concedes are not relevant here. Moreover, to end run the statutory prohibition, FDA purported to declare a ***less safe*** version of oxybate developed by Avadel CNS Pharmaceuticals LLC ("Avadel") to be "clinically superior."

3. FDA's actions here were unlawful. FDA acted in excess of its statutory authority and inconsistently with its own regulations. FDA denied the existence of a controlling policy (despite its publication in the *Federal Register*), and also failed to disclose three prior

determinations that Avadel's product was in fact blocked by Xywav's unexpired exclusivity. FDA also ignored mountains of scientific literature showing that the agency's core factual assertion—that Avadel's product provides new "medical benefits" for narcolepsy patients—is baseless. Indeed, that assertion cannot be squared with FDA's own finding that there is "no evidence" that the efficacy of Avadel's product differs from that of Xywav.

4. FDA's decision will lead to unfortunate confusion among healthcare providers, narcolepsy patients, and their caregivers. Much of that confusion is attributable to Avadel, which has begun to broadly disseminate FDA's claim that Lumryz will provide new "medical benefits" for narcolepsy patients. Avadel also has sent a flurry of correspondence threatening to sue Jazz if Jazz continues to publicly discuss Xywav's clear safety advantage. If allowed to continue, the status quo is likely to mislead healthcare providers, narcolepsy patients, and their caregivers regarding the risks and benefits of narcolepsy treatments.

SUMMARY OF THE CASE

5. The Orphan Drug Act of 1983 was intended to provide "financial incentives" for pharmaceutical companies to develop drugs and biological products to treat rare diseases, which are commonly called "orphan drugs." Pub. L. No. 97-414, § 1(a)(5), 96 Stat. 2049 (1983) (Congressional findings codified as notes to 21 U.S.C. § 360aa). To create such incentives, Congress added a new section 527 to the Federal Food, Drug, and Cosmetic Act ("FDCA"). Subsection (a) of section 527 grants seven years of market exclusivity to drugs that are designated and approved to treat rare diseases. *See* 21 U.S.C. § 360cc(a). According to FDA, the resulting orphan-drug exclusivity is "the primary incentive that Congress created in the Orphan Drug Act." 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992).

6. The current version of section 527(a) dates to the FDA Reauthorization Act of 2017. Pub. L. No. 115-52, Tit. VI, § 607(a)(3), 131 Stat. 1005, 1049 (Aug. 18, 2017). As amended,

section 527(a) provides FDA "may not approve another [new drug application] … for the same drug for the same disease or condition," if submitted by a different company, "until the expiration of seven years from the date of the approval of the approved application." 21 U.S.C. § 360cc(a). Section 527(a) thus operates as a limitation on FDA's authority to approve competing versions of the same drug intended to treat the same disease.

7. That limitation is subject to only two narrowly confined exceptions. By its terms, subsection (a) of section 527 controls and constrains FDA "[e]xcept as provided in subsection (b)." 21 U.S.C. § 360cc(a). Subsection (b) then allows FDA to break an unexpired period of ODE and approve a competing product during the seven-year period of exclusivity only if one of two circumstances prevails: (1) FDA finds, after notice and opportunity to be heard, that the first drug is in shortage; or (2) the sponsor of the first drug consents in writing to the approval. *See* 21 U.S.C. § 360cc(b)(1)-(2).

8. The 2017 amendments also added a new subsection (c) to establish the conditions under which a subsequent drug may earn so-called "serial" exclusivity—*i.e.*, a new period of exclusivity with respect to the same disease. Per section 527(c), an orphan drug that "is otherwise the same … as an already approved or licensed drug" can earn its own "exclusive approval" for "the same rare disease" if its sponsor "demonstrate[s] that such drug is clinically superior to any already approved or licensed drug that is the same drug." 21 U.S.C. § 360cc(c)(1). Importantly—and as FDA itself conceded in its decision here—section 527(c) does not authorize FDA to break unexpired ODE based on clinical superiority. There remain two, and only two, exceptions to orphan drug exclusivity.

9. Pursuant to the 2017 amendments, earning serial exclusivity entails two different showings related to clinical superiority. First, to obtain an orphan-drug designation ("ODD"), the

sponsor seeking a serial exclusivity must offer a ***medically plausible hypothesis*** that its drug will provide "a significant therapeutic advantage over and above" an already approved version of the drug "in terms of greater efficacy, greater safety, or by providing a major contribution to patient care." *See* 21 U.S.C. § 360cc(c)(2) (definition of "clinically superior"); 21 C.F.R. § 316.20(b)(5) (content requirements for an ODD request); 21 C.F.R. § 316.20(a) (approval standard for an ODD request). As FDA has stated, the "medically plausible hypothesis" standard is intended to be forgiving "because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval." 56 Fed. Reg. 3338, 3340 (proposed Jan. 29, 1991).

10. Second, at the approval stage, the sponsor must satisfy a much higher standard. To gain a serial orphan-drug exclusivity ("ODE"), the sponsor must ***actually prove*** clinical superiority. The statute thus decrees that FDA "shall require such sponsor … to demonstrate" clinical superiority "as a condition of such exclusive approval." 21 U.S.C. § 360cc(c)(1).

11. From the enactment of section 527(c) in 2017 through the end of 2022, only nine drugs had successfully obtained orphan-drug exclusivity by way of clinical superiority. *See* FDA, *Clinical Superiority Findings* (May 1, 2023).[1]

12. Jazz's product Xywav® (calcium, magnesium, potassium, and sodium oxybates) is one of those nine drugs. Beginning in 2013, Jazz invested significant time and resources into developing Xywav, including multiple preclinical studies, multiple studies in healthy volunteers, and ultimately a double-blind, placebo controlled trial involving 201 narcolepsy patients. Based

[1] https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings.

on that research, Xywav was approved by FDA in July 2020 to treat cataplexy and excessive daytime sleepiness ("EDS") in narcolepsy patients who are at least seven years old. Jazz separately conducted a double-blind, placebo controlled trial involving 154 patients with idiopathic hypersomnia. Based on that study, Xywav was approved by FDA in August 2021 as a treatment for idiopathic hypersomnia in adults. *See* FDA *News Release: FDA Grants First of its Kind Indication for Chronic Sleep Disorder Treatment* (Aug. 12, 2021).[2]

13. Xywav was developed as a safer version of an older drug called Xyrem® (sodium oxybate). Xyrem was first approved in 2002 and has long been considered an important treatment option for patients with narcolepsy. Because narcolepsy is an incurable and chronic sleep disorder, all oxybate products are intended to be taken every night on an ongoing basis, potentially for the patient's entire life. Taking a ***sodium*** oxybate product requires a patient to consume a clinically significant amount of sodium every night—up to 1,640 mg of sodium at the highest approved dose. *See* FDA, *Xyrem Prescribing Information* § 5.8 (revised Mar. 2022).[3] To provide context, consuming 1,640 mg of sodium amounts to consuming the sodium found in more than nine servings of potato chips. *See* LAY'S® Classic Potato Chips, Nutrition Facts.[4]

14. Elevated sodium intake is linked with hypertension (high blood pressure), which in turn is a leading cause of strokes, heart attacks, and cardiovascular disease. As a result, reducing sodium intake is a well-known public health priority. According to the American Heart Association ("AHA"), the "science behind sodium reduction is clear. Significant evidence links excess sodium intake with high blood pressure, which increases the risk of heart attack, stroke and

[2] https://www.fda.gov/news-events/press-announcements/fda-grants-first-its-kind-indication-chronic-sleep-disorder-treatment.

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021196s040lbl.pdf.

[4] https://www.lays.com/products/lays-classic-potato-chips (last visited June 15, 2023) (170 mg of sodium per serving).

heart failure." AHA, *Get the Scoop on Sodium and Salt* (Dec. 22, 2022).[5] Similarly, the Centers for Disease Control and Prevention ("CDC") advises there is "a strong relationship between the amount of salt consumed and raised levels of blood pressure. When salt intake is reduced, blood pressure begins falling within weeks in most people." CDC, *Sodium* (Dec. 21, 2021).[6] For its part, FDA has made reducing sodium intake one of the agency's highest priorities, because reducing sodium "has the potential to prevent hundreds of thousands of premature deaths and illnesses in the coming years." FDA, *Sodium Reduction* (Oct. 13, 2021).[7]

15. The cardiovascular impacts of elevated sodium intake are particularly relevant for narcolepsy patients. Several studies show that narcolepsy patients are at elevated risk of hypertension and other cardiovascular problems. *See infra* p. 30.

16. Xywav dramatically improved upon Xyrem by reducing the sodium content of oxybate therapy by more than 92%. At the highest approved dose, this represents a reduction in nightly sodium intake of more than 1,500 mg. Authoritative bodies have recognized that eliminating that much sodium is a clinically meaningful benefit for patients because it improves heart health and reduces the risk of developing cardiovascular disease. For instance, the National Academies of Sciences, Engineering, and Medicine ("NASEM") concluded that reducing daily sodium intake by 1,000 mg/day reduces risk of developing hypertension by 20% and the risk of developing cardiovascular disease by 27%. *See* NASEM, *Dietary Reference Intakes for Sodium*

[5] https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/sodium-and-salt.

[6] https://www.cdc.gov/heartdisease/sodium.htm.

[7] https://www.fda.gov/food/food-additives-petitions/sodium-reduction.

and Potassium, 323, 328-29 (2019);[8] *see also* AHA, *Answers by Heart: Why Should I Limit Sodium?*[9] ("Even cutting back by 1,000 mg a day can improve blood pressure and heart health.").

17. FDA's regulations provide that a sponsor can establish that its product is clinically superior by way of greater safety if it eliminates "an ingredient or contaminant that is associated with relatively frequent adverse effects." 21 C.F.R. § 316.3(b)(3)(ii). Pursuant to that regulation, and consistent with the established understanding of the cardiovascular risks associated with elevated sodium intake, FDA determined that Xywav is clinically superior to sodium oxybate by means of greater safety.

18. According to the summary posted to FDA's website:

> The active moiety, oxybate was previously approved as Xyrem (sodium oxybate) for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. Xywav (calcium, magnesium, potassium, and sodium oxybates) is clinically superior to Xyrem by means of greater safety because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem. The differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.

FDA, *Clinical Superiority Findings*, *supra* p. 4.

19. Because Jazz demonstrated clinical superiority, Xywav earned seven years of exclusive approval. Per the express terms of the statute, FDA "may not approve" another company's new drug application ("NDA") for an oxybate product intended to treat EDS or cataplexy in narcolepsy patients until July 21, 2027, unless there is a shortage of Xywav or Jazz consents to the approval. *See* 21 U.S.C. § 360cc(a)-(b).

[8] https://nap.nationalacademies.org/catalog/25353/dietary-reference-intakes-for-sodium-and-potassium.

[9] https://www.heart.org/-/media/files/health-topics/answers-by-heart/why-should-i-limit-sodium.pdf (last visited June 15, 2023).

20. Despite the statutory prohibition, FDA approved an NDA submitted by Avadel for a new sodium oxybate product called Lumryz™ on May 1, 2023. Avadel's product is a reformulation of Xyrem and is intended to treat EDS and cataplexy in adult narcolepsy patients. Lumryz also contains the same high amount of sodium as Xyrem—up to 1,640 mg of sodium at the highest approved dose. Lumryz differs from both Xyrem and Xywav in that it is an extended-release product that is intended to be consumed once a night. In contrast, Xywav and Xyrem are intended to be taken by narcolepsy patients twice a night.

21. FDA's decision to break Xywav's ODE and approve Lumryz was not made through a formal adjudication or similar process. Both Jazz and Avadel submitted letters and other materials to the agency setting forth their respective positions, but neither was able to see the other's submissions or know the other's position. Nor could they know the factual or legal positions that FDA officials were considering. The companies' respective submissions were "simply considered under the FDA's internal review procedures" that "involved no adjudicator, but rather determinations" by the Office of Orphan Product Development ("OOPD"). *Sandoz Inc. v. Beccera*, 57 F.4th 272, 278-79 (D.C. Cir. 2023) (finding that FDA's exclusivity determination process was too informal to justify an issue exhaustion requirement).

22. To date, FDA has still not fully disclosed the documents reflecting its decision in this case. The materials disclosed so far indicate a process marked by an unexplained reversal of opinion within OOPD and a dispute between OOPD and the subject matter experts at FDA who have primary responsibility for drugs intended to treat narcolepsy. That dispute apparently led OOPD to depart from FDA's internal dispute resolution procedures and seek a second opinion from a different FDA center that does not regulate drugs. The back-and-forth apparently took years, and it all occurred in secret.

23. OOPD's final decision was documented in a letter ("Decision Letter") sent to Jazz and Avadel on May 1, 2023. *See generally* Ltr. from FDA to Sidley Austin LLP re: Determination that Xywav's (NDA 212690) unexpired orphan-drug exclusivity ("ODE") does not block approval of Lumryz (NDA 214755) (May 1, 2023) (Exhibit A). In the Decision Letter, OOPD does not rely on either of the two statutory exceptions to ODE set forth in section 527(b)(1)-(2). OOPD also conceded that the clinical superiority provision in section 527(c) does not provide a third exception to ODE or otherwise give the agency authority to break Xywav's ODE. *See id.* at 6 & 17 n.118. OOPD further conceded that Lumryz and Xywav contain the same active moiety (oxybate) and are treatments for the same rare disease. *See id.* at 17. OOPD also recognized that Xywav is safer than Lumryz "due to reduced sodium." *Id.* at 31; *id.* at 32 (acknowledging "safety risk associated with sodium for Lumryz").

24. OOPD nevertheless claims that the unexpired ODE for Xywav is irrelevant because Lumryz and Xywav are not "the same drug" within the meaning of section 527(a). According to OOPD, the controlling consideration is ***dosing schedule***. OOPD asserts that, at least for some patients, once-nightly dosing "outweighs the safety concern" posed by increased sodium intake. Exhibit A at 31. OOPD thus construes once-nightly dosing as a "major contribution to patient care" within the meaning of section 527(c)(2), which in turn allegedly renders Lumryz "clinically superior" within the meaning of section 527(c)(1).

25. As a last step, and to get around its concession that section 527(c) does not provide cause to break unexpired ODE, OOPD invoked a 1992 regulation that had also used the phrases "clinically superior" and "major contribution to patient care." *See* 21 C.F.R. § 316.3(b)(3). According to OOPD, that regulation allows a finding of clinical superiority to "overcome ODE," by way of a conclusion that a clinically superior drug is not the "same drug" as the drug that enjoys

unexpired ODE, even if the two drugs have the same active moiety and are intended to treat the same rare disease. Exhibit A at 18. On that basis, OOPD broke Xywav's ODE, approved Lumryz, and granted Lumryz its own ODE through May 1, 2030.

26. For five broad reasons, OOPD's decision to break the unexpired ODE protecting Xywav was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. 5 U.S.C. § 706(2)(A). Because that decision was unlawful, FDA's final approval and ODE for Lumryz must be vacated and set aside.

27. ***First***, OOPD's decision was *ultra vires*. Congress provided two and only two statutory exceptions to ODE and neither of those exceptions is relevant here. FDA simply does not have the authority to use a clinical superiority finding to break or otherwise "overcome" ODE because doing so would rewrite the statute to include a third exception to section 527(a)'s restriction barring FDA from granting new drug approvals during the ODE period. Furthermore, Congress directly considered the role that clinical superiority should play in 2017, and the legislature chose ***not*** to include clinical superiority as a third reason to break ODE. Congress also addressed FDA's rulemaking authority in light of observations by the courts that pre-amendment section 527 "contain[ed] no express delegation from the Congress to promulgate regulations under that section." *Eagle II*, 952 F.3d at 334 n.14. Congress responded by pointedly granting FDA authority to "promulgate regulations for the implementation of [**527**]**(c)**," 21 U.S.C. § 360cc(d) (emphasis added), but not section 527(a)—the provision that OOPD purports to interpret in the Decision Letter. In all events, the statutory phrase "the same drug" is not ambiguous and does not require clarification from FDA.

28. Nor is this the first time that FDA has ignored the plain language of section 527. This Court has ruled in three separate cases that FDA lacks authority to promulgate regulations

that change the meaning of section 527. *See Depomed*, 66 F. Supp. 3d at 233 ("This Court will not impute to Congress an intention to authorize an exception that Congress itself did not think worth enacting."); *Eagle I*, 2018 WL 3838265, at *6 (the statute "leaves no room for the FDA's imposition of its clinical-superiority requirement"); *see also United Therapeutics Corp.*, 2020 WL 6498619. The D.C. Circuit reached the same conclusion. *See Eagle II*, 952 F.3d at 331 ("The fact that the Congress chose not to include an additional requirement, limitation or exception for successive or subsequent exclusivity holders does not make the provision ambiguous."). Most recently, the Eleventh Circuit vacated FDA's approval of an NDA where FDA had sought to narrowly interpret the phrase "the same disease or condition" in section 527(a) in order to break an unexpired period of ODE. *See Catalyst*, 14 F.4th at 1301-02.

29. ***Second***, OOPD's determination is inconsistent with FDA regulations, which require that comparative effectiveness claims be supported by substantial evidence, *i.e.*, one or more adequate and well-controlled clinical trials. *See* 21 C.F.R. § 201.57(c)(2)(iii) (rule for drug labeling); 21 C.F.R. § 202.1(e)(6)(ii) (rule for drug advertising). FDA's Orphan Drug regulations impose similar requirements for claims of clinical superiority based on claims of greater efficacy. *See* 21 C.F.R. § 316.3(b)(3)(i) (greater efficacy must be based on "a clinically meaningful endpoint in adequate and well controlled clinical trials," *i.e.*, "the same kind of evidence needed to support a comparative effectiveness claim").

30. No such evidence exists here because Avadel never conducted a clinical trial comparing Lumryz to Xywav. Indeed, OOPD conceded that there is "no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav." Exhibit A at 27.

31. Despite the concession, OOPD proceeded to claim that once-nightly dosing renders Lumryz more effective than Xywav. For example, the online summary of OOPD's clinical

superiority finding claims that "not having to awaken to take a second dose" will provide "***medical*** benefits" to narcolepsy patients by improving their "sleep architecture" and reducing "disrupt[ed] or fragment[ed] sleep." FDA, *Clinical Superiority Findings*, *supra* p. 4. (emphasis added). The Decision Letter similarly claims that Lumryz is more effective because it allows "narcolepsy patients to achieve normal sleep architecture." Exhibit A at 29. Those are greater efficacy claims, and they are not supported by any evidence whatsoever.

32. ***Third***, likely because the evidence needed to support greater efficacy claims does not exist, OOPD attempts to reframe Lumryz's alleged effects on sleep architecture as reasons why Lumryz provides a "major contribution to patient care." 21 U.S.C. § 360cc(c)(2). The reframing fails, however, because it is inconsistent with established FDA policy.

33. By regulation, the "major contribution to patient care" parameter of clinical superiority is reserved for "unusual cases." 21 C.F.R. § 316.3(b)(3)(iii). It "is intended to constitute a narrow category" and "is not intended to open the flood gates to FDA approval." 56 Fed. Reg. at 3343. One way in which the major contribution to patient care pathway could "open the flood gates" is if it allowed sponsors to sacrifice safety in the name of increased convenience or other minor improvement. To prevent such tradeoffs, FDA stated that the major contribution to patient care standard "is meaningful only when the subsequent drug provides safety or effectiveness ***comparable to the approved drug***." 76 Fed. Reg. 64868, 64871 (proposed Oct. 19, 2011) (emphasis added). Thus, for a subsequent drug to provide a major contribution to patient care, the proposed changes must not "render[] the [subsequent] drug less safe or less effective than the approved drug." *Id.* According to FDA, the comparable safety requirement is "longstanding policy." *Id.* at 68476.

34. OOPD plainly flouted that policy here. OOPD conceded, as it must, that Xywav is safer than Lumryz due to lower sodium. *See* Exhibit A at 31. That should have been the end of the matter. Because Lumryz does not achieve comparable safety to Xywav, under FDA's longstanding policy, it cannot provide a major contribution to patient care.

35. OOPD's only response is to try to deny that FDA's longstanding policy exists. OOPD concedes, as it must, that it is "aware of certain language in agency documents that could be interpreted as suggesting FDA has such a policy." Exhibit A at 23 n.147. OOPD nonetheless contends that "it is clear that those statements do not reflect such an agency policy" because OOPD allegedly could not identify any "past precedents" that "manifest application of such a policy" in this exact scenario. *Id.*

36. OOPD's denial amounts to revisionism and is unlawful. As an initial matter, OOPD violated a separate FDA regulation, 21 C.F.R. § 10.85, laying out the process that must be followed to modify a policy published in the *Federal Register*. FDA did not follow that process here.

37. OOPD also violated the Administrative Procedure Act ("APA") principle that an agency must openly acknowledge and cogently explain a departure from past policy. *See, e.g.*, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("[T]he requirement that an agency provide reasoned explanation for its action would ordinarily demand that it display awareness that it ***is*** changing position. An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books."); *Ciox Health, LLC v. Azar*, 435 F. Supp. 3d 30, 59 (D.D.C. 2020) (Mehta, J.) (the APA requires "clear recognition and articulation of a policy change") (citing *Fox Television*, 556 U.S. at 515). That requirement carries extra force when, as here, a policy change affects a party's investment-backed expectations. In those settings, the

agency also must address the "serious reliance interests" that the shift undermines. *Fox Television*, 556 U.S. at 515. OOPD provided no such explanation.

38. OOPD also failed to present its "past precedents" in a fair manner. As an initial problem, there is no public compilation of OOPD decisions, and industry must rely on disclosures through litigation or the Freedom of Information Act ("FOIA"). But even subject to that informational disadvantage, Jazz has identified at least three prior examples of OOPD insisting on a showing of comparable safety before being willing to consider whether a proposed drug provides a major contribution to patient care.

39. ***Fourth***, the Decision Letter fails to disclose (let alone explain) at least three prior determinations in which FDA rejected Avadel's claim that once-nightly dosing could establish a major contribution to patient care.

40. OOPD appears to have first considered that question in 2016. At the time, the only approved oxybate product on the market was Jazz's older product, Xyrem. OOPD staff concluded that although "the elimination of the second nightly dose provides convenience … OOPD does not consider this reduction in dosing frequency [to have] risen to the level of major contribution to patient care." FDA, Review of Request for Orphan Drug Designation, FT218, at 5 (July 26, 2016) ("2016 OOPD Review") (Exhibit B). On that basis, OOPD informed Avadel that a once-nightly dosing regimen failed to "provide a plausible hypothesis for the possible clinical superiority" of Lumryz over Xyrem. Ltr. From OOPD to Marla Scarola, The Weinberg Grp., at 1 (Aug. 23, 2016) ("2016 Ltr. To Avadel") (Exhibit C).

41. The Division of Neurology 1, formerly the Division of Neurology Products (the "Review Division") also evaluated Avadel's request for approval and exclusivity. The physicians and other officials in the Review Division have had primary responsibility for approving and

regulating oxybate since the late 1990s. In that role, they have overseen the development of oxybate as a treatment for narcolepsy, including idiopathic hypersomnia, disrupted nighttime sleep, and other sleep disorders. OOPD thus describes the employees of the Review Division as the "clinical experts" regarding oxybate. Exhibit A at 16.

42. On at least two occasions, the Review Division appears to have rejected Avadel's arguments regarding once-nightly dosing. First, when Avadel originally submitted the NDA for Lumryz in December 2020, Avadel requested a "priority review," which is reserved for new drugs that represent a "significant improvement" over existing therapies. Although the relevant documents and communications have not yet been disclosed, FDA rejected Avadel's priority review request in February 2021. The Review Division later observed that Avadel's arguments in support of a claim of "clinical superiority" were essentially the same as the arguments that the Review Division had rejected when it determined that Avadel's product was not likely to be a "significant improvement." *See* Memo. From Eric Bastings, DN1, FDA to Dir. of OOPD re: OOPD Consult Request #16-5302, at 8-9 (Aug. 30, 2021) (Exhibit D).

43. Second, the Review Division formally evaluated Lumryz's request for orphan-drug exclusivity in August 2021, and it concluded that Lumryz ***is not*** clinically superior to Xywav. The Review Division reached the same conclusion that OOPD had reached in 2016 regarding the potential for a major contribution to patient care: "While the once-nightly regimen of Lumryz will be more convenient for patients than a twice-nightly regimen, that attribute cannot be considered a major contribution to patient care." Exhibit D at 10. Overall, the Review Division found that there was "no evidence … that Lumryz is clinically superior." *Id.* at 12.

44. The Decision Letter never addresses these adverse determinations. While there are circumstances in which a federal agency may change its mind, the agency is obliged to

acknowledge and explain its about-face. *See, e.g.*, *MISO Transmission Owners v. FERC*, 45 F.4th 248, 264 (D.C. Cir. 2022) (An agency is "entitled to change its mind. But to do so, it must provide a 'reasoned explanation' for its decision to disregard 'facts and circumstances that' justified its prior choice.") (quoting *Fox Television*, 556 U.S. at 515-16). Rather than provide such an explanation, the Decision Letter conceals the existence of all three prior determinations.

45. It is true that the Review Division appears to have reversed its position in a second memo dated May 1, 2023, the same day Lumryz was approved. Although OOPD described the Review Division's reconsidered opinion as an "integral" part of its clinical superiority finding, Exhibit A at 2, OOPD has not disclosed how it managed to convince the Review Division to reconsider. However, the Review Division's second memo suggests that OOPD spent the better part of two years pressing the issue. *See* Memorandum from Ranjit Mani & Teresa Buracchio, DN1, FDA to Dir. of OOPD re: OOPD Consult Request #16-5302, at 4 (May 1, 2023) (Exhibit E) (describing undisclosed communications in which OOPD presented "scientific, legal, and regulatory" arguments in favor of approving Lumryz). Part of that pressure campaign involved OOPD taking the apparently unprecedented step of seeking a second opinion from two physicians working in the Center for Devices and Radiological Health ("CDRH").

46. On information and belief, the CDRH doctors are not experts in narcolepsy, have never prescribed oxybate to any patient, have no prior experience regulating drugs, and have no prior experience applying the Orphan Drug Act. Instead, they appear to be physicians focusing on obstructive sleep apnea who review regulatory submissions for ***devices***, such as continuous positive airway pressure ("CPAP") machines.

47. In seeking a second opinion, OOPD appears to have departed from FDA procedures for internal dispute resolution. FDA policy states that if staff in one center (like OOPD) disagree

with a conclusion reached by staff in another center (like the Review Division), disappointed staff may pursue their disagreement up either center's chain of command, with the Office of the Commissioner having ultimate decision authority. *See* FDA, *Staff Manual Guide 9010.2: Cross-Center Dispute Resolution at the FDA*, § 4 (June 21, 2019).[10] Alternatively, when a cross-center dispute arises regarding orphan-drug exclusivity, either team can request that the issue be resolved by FDA's Orphan Drug Products Policy Council. *See* FDA, *Staff Manual Guide 2010.19: FDA Orphan Drug Products Policy Council*, §§ 3(A), 3(B), 3(F) (Sept. 17, 2020).[11] FDA policy does not appear to allow disappointed staff to seek a new opinion from a third center and then use that opinion to pressure dissenting staff into agreement. *Cf. Tummino v. Torti*, 603 F. Supp. 2d 519, 548 (E.D.N.Y. 2009) (describing FDA's obligation to "come forward with an adequate explanation" for apparent departures from normal process).

48. In addition, OOPD appears to have predetermined the outcome of the CDRH opinion by preventing CDRH from considering all of the relevant issues. The CDRH memo indicates that OOPD asked for an opinion on the ultimate question whether Lumryz "is 'clinically superior' … based on being a 'major contribution to patient care.'" Memo from Mahadevappa Hunasikatti & Nargues Weir, Sleep Team, CDRH-FDA to Sandra Retzky, OOPD re: Consult request on Lumryz (extended-release sodium oxybate) administered as an oral solution once at bedtime for treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy, at 1 (Apr. 29, 2023) (Exhibit F). However, the CDRH "memo considers solely Lumryz's once nightly dosing" even though CDRH was aware "that other factors may also inform" the clinical superiority question. *Id.* The memo thus gives the impression that OOPD affirmatively instructed CDRH to

[10] https://www.fda.gov/media/87229/download.

[11] https://www.fda.gov/media/109167/download.

ignore Xywav's greater safety due to reduced sodium. Whether so instructed or not, CDRH's failure to consider the comparative safety of the two products "is a 'major shortcoming.'" *Cigar Ass'n of Am. V. FDA*, 436 F. Supp. 3d 70, 89 (D.D.C. 2020) (Mehta, J.) (quoting *Humane Soc'y v. Zinke*, 865 F.3d 585, 614 (D.C. Cir. 2017)). "'The court must vacate a decision that entirely failed to consider an important aspect of the problem.'" *Id.* (quoting *SecurityPoint Holdings, Inc. v. TSA*, 867 F.3d 180, 185 (D.C. Cir. 2017) (cleaned up).

49. ***Finally***, OOPD's decision was arbitrary and capricious because it failed to give "reasoned consideration to all the material facts and issues." *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 851 (D.C. Cir. 1970). In some respects, that failure was a consequence of FDA's informal process for exclusivity determinations. Although FDA appears to have spent years on this issue, at no point did it seek input from Jazz or, apparently, Avadel. Both companies attempted to be heard, but neither could comment on FDA's thinking because FDA did not share it. That, in turn, meant that OOPD made its determination without the benefit of informed comment on the bases of its eventual decision from the affected stakeholders, an indispensable feature of well-reasoned agency decisionmaking. *See Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1816 (2019) (informed comment "affords the agency a chance to avoid errors"). It was perhaps inevitable that OOPD would "entirely fail[] to consider [several] important aspect[s] of the problem." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

50. At its core, OOPD's decision reflects a conclusion that the convenience associated with once-nightly dosing "outweighs" the established safety benefit of lower sodium. Both sides of the alleged balancing were arbitrary and capricious. On the lower sodium side of the scale, the record reflects no effort to consult with the agency's experts on cardiovascular risk or those responsible for the agency's many ongoing efforts to reduce sodium intake. OOPD also

understated the risks associated with elevated sodium intake (and the benefits of sodium reduction) by unrealistically suggesting that narcolepsy patients can achieve an equivalent sodium reduction through other means. OOPD's suggestion is directly contrary to FDA's repeated recognition that consumers often cannot achieve clinically meaningful reductions in sodium through dietary choices alone.

51. On the other side of the scale, OOPD exaggerated the importance of once-nightly dosing. CDRH concluded that Lumryz should be considered clinically superior based on speculation that an "oxybate product that is dosed once nightly ***provides an opportunity for narcolepsy patients to achieve normal sleep architecture***, which is not a possibility for a patient on Xyrem or Xywav." Exhibit F at 8 (emphasis added). That speculation was then repeated by OOPD and further described by OOPD as a "benefit" that is "medically relevant" to narcolepsy patients. Exhibit A at 29. Any claim that Lumryz enables narcolepsy patients to achieve "normal" sleep is scientifically baseless and wholly unsupported.

52. OOPD claims its conclusion is based on its "expertise and consultation of the literature." Exhibit A at 39. However, the literature—including sources cited by CDRH—reflects a consensus that most narcolepsy patients already have disrupted sleep architecture and endure frequent arousals every night. Studies published by Avadel, Jazz, and others all suggest a baseline of ***about 80 nighttime arousals per night*** among untreated narcolepsy patients. Oxybate therapy can improve sleep architecture and reduce the symptoms of disrupted nighttime sleep, including the number of nighttime disruptions. But no oxybate therapy can cure narcolepsy, normalize sleep architecture, or eliminate nighttime disruptions.

53. Currently, there is no evidence suggesting that any oxybate product is more effective than any other at improving sleep. Neither OOPD or CDRH has cited any literature or

data suggesting such a difference. Moreover, Jazz and Avadel have published data reflecting the improvements that their products provided on sleep measures during clinical trials, including observed decreases in nighttime arousals. The data show remarkably similar results, and they indicate that narcolepsy patients continue to experience ***about 40 nighttime arousals*** every night after successful treatment with oxybate regardless of dosing schedule. Because OOPD's claim that once-nightly dosing normalizes sleep for narcolepsy patients is belied by the literature, "the court must undo its action." *Cigar Ass'n of Am.*, 436 F. Supp. 3d at 84 (quoting *Cnty. Of L.A. v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999)).

54. Even OOPD's statements about the general convenience of once-nightly dosing providing a major contribution to patient care were arbitrary and capricious. As acknowledged by OOPD in 2016 and the Review Division in 2021, the convenience associated with once-nightly dosing is not a major contribution within the meaning of the statute.

55. OOPD's unsupported statements about Lumryz have led to concerning confusion in the marketplace. Based on OOPD's major contribution to patient care finding, Avadel has begun to broadly disseminate claims that Lumryz provides greater efficacy by improving or even normalizing sleep. For instance, Avadel's press release announcing FDA's approval of Lumryz included the false and misleading claims that Lumryz provides narcolepsy patients with "the opportunity for an uninterrupted night sleep" and that Lumryz "may help restore a more natural sleep-wake cycle." Avadel, *Press Release: Avadel Pharmaceuticals Announces Final FDA Approval of LUMRYZ™ (sodium oxybate) for Extended-Release Oral Suspension as the First and Only Once-at-Bedtime Oxybate for Cataplexy or Excessive Daytime Sleepiness in Adults with*

Narcolepsy, 1 (May 1, 2023).[12] Avadel also has threatened litigation against Jazz on the theory that it is now unlawful for Jazz to promote the safety benefit that Xywav provides through dramatically reduced sodium. Avadel thus seeks to use OOPD's scientifically baseless assertions to mislead healthcare providers, narcolepsy patients, and their caregivers about the benefits and risks of oxybate therapy.

PARTIES

56. Plaintiff Jazz Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3170 Porter Drive, Palo Alto, California 94304. Jazz is the owner of new drug applications 021196 for Xyrem® (sodium oxybate) and 212690 for Xywav® (calcium, magnesium, potassium, and sodium oxybates). Jazz markets and distributes its products in this district and nationwide.

57. Defendant Xavier Becerra is the Secretary of Health and Human Services and is sued in his official capacity only. Secretary Becerra is responsible for activities at HHS, including the actions described in this complaint. He maintains an office and carries out official duties in this district, although he oversees governmental activities that occur nationwide.

58. Defendant Department of Health and Human Services ("HHS") is an Executive Department and Agency of the United States. Its headquarters and principal place of business are at 200 Independence Avenue, S.W., Washington, D.C. 20201. Its governmental activities occur nationwide.

[12] https://investors.avadel.com/news-releases/news-release-details/avadel-pharmaceuticals-announces-final-fda-approval-lumryztm.

59. Defendant Robert Califf is the Commissioner of Food and Drugs and is sued in his official capacity only. Commissioner Califf is responsible for activities at FDA, including the actions described in this complaint. He oversees governmental activities that occur nationwide.

60. Defendant Food and Drug Administration ("FDA") is an Agency of the United States and a component of HHS. FDA's headquarters and principal place of business are at 10903 New Hampshire Ave., Silver Spring, MD 20903. Its governmental activities occur nationwide.

JURISDICTION AND VENUE

61. This Court has subject matter jurisdiction under 28 U.S.C. § 1331.

62. 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.

63. Sovereign immunity has been waived for the declaratory and injunctive relief sought in this Complaint pursuant to 5 U.S.C. § 702. *See Trudeau v. FTC*, 456 F.3d 178, 185-86 (D.C. Cir. 2006).

64. FDA's decision to approve Lumryz and grant ODE to Lumryz on or about May 1, 2023 is a final agency action that is reviewable under the APA. *See* 5 U.S.C. § 704; *Stauber v. Shalala*, 895 F. Supp. 1178, 1188 (W.D. Wis. 1995).

65. This dispute is ripe for judicial review because the issues presented are fit for judicial decision and Jazz would incur substantial hardship were judicial review withheld. *See Schering Corp. v. Sullivan*, 782 F. Supp. 645, 646 n.3 (D.D.C. 1992), *vacated as moot sub nom. Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

66. Jazz has standing to challenge this action because FDA's approval decision has deprived Jazz of its statutory right to seven years of exclusivity under the Orphan Drug Act. *See Teva Pharms. USA., Inc. v. Azar*, 369 F. Supp. 3d 183, 196 (D.D.C. 2019). In addition, FDA's

approval decision has injured Jazz by subjecting it to unlawful competition. *See Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1498-99 (D.C. Cir. 1996).

67. No statute or regulation imposes any administrative exhaustion requirement relevant to this dispute, and the D.C. Circuit recently held that the issue exhaustion doctrine does not apply to circumstances where company submissions are reviewed, without an adjudicator, under FDA's internal review procedures. *See Sandoz Inc.*, 57 F.4th at 278-79. Regardless, from 2021 to 2023, Jazz attempted to engage with FDA regarding the issues presented in this litigation.

GENERAL ALLEGATIONS

I. REGULATORY BACKGROUND

68. With few exceptions, none of which are relevant here, no "new drug" may be introduced or delivered for introduction into interstate commerce in the United States without prior approval from FDA. 21 U.S.C. §§ 331(d), 355(a). To obtain approval for an innovative drug product, a manufacturer must submit a new drug application ("NDA") under section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). 21 U.S.C. § 355(b)(1). An NDA is an extensive filing. *See id*. § 355(b)(1)(A)-(G) (setting forth the filing requirements for a full NDA); 21 C.F.R. § 314.50 (same). Among many other things, an NDA must include 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)(1); *see* 21 C.F.R. § 314.126.

69. Upon approval, some innovative drug products earn periods of non-patent, regulatory exclusivity. Relevant here, drugs used to treat rare diseases may earn seven years of market exclusivity under the Orphan Drug Act.

70. In 1983, Congress recognized that market forces may not always provide the incentive necessary for companies to develop therapies to treat rare diseases and conditions. The Orphan Drug Act was intended to create the incentive needed to develop drugs for such "rare diseases." *See* Pub. L. No. 97-414, § 1(b), 96 Stat. 2049 (1983) ("The Congress finds that … it is in the public interest to provide such changes and incentives for the development of orphan drugs."). Under the Orphan Drug Act, a "rare disease" is generally one that affects 200,000 or fewer people. 21 U.S.C. § 360bb(a)(2).

71. A manufacturer or sponsor of a new drug may seek to "designate the drug as a drug for a rare disease or condition." 21 U.S.C. § 360bb(a)(1). The manufacturer or sponsor must seek "orphan drug designation" ("ODD") before it seeks FDA approval. *See id.* ODD enables the manufacturer or sponsor to obtain certain tax advantages, obtain financial and other assistance for its clinical trials, claim exemptions from user fees, and eventually earn exclusivity if the product is approved. ODD can also have important implications for a drug's reimbursement under the federal healthcare programs.

72. When a proposed drug would be the first of its kind to treat a particular rare disease, obtaining ODD can be relatively straightforward. But more is required if the same drug has been previously approved to treat the same disease or condition. In such cases, the sponsor must also provide a ***medically plausible hypothesis*** that its product will be clinically superior to all previously approved versions of the drug by providing greater efficacy, greater safety, or a major contribution to patient care.

73. When a drug with ODD is approved by FDA, the drug can be eligible for the Orphan Drug Act's primary incentive: a seven-year period of exclusivity known as "orphan drug exclusivity" ("ODE"). As amended in 2017, section 527(a) provides that FDA "may not approve

another application" by another company "for the same drug for the same disease or condition" until ODE has expired. 21 U.S.C. § 360cc(a)(2). This is a prohibition directed at FDA that limits its authority to approve competing drugs. *See Depomed,* 66 F. Supp. 3d at 233 (ODE "operates by removing FDA discretion to approve the marketing of certain other drugs"). During the seven-year period, FDA lacks authority to approve another company's version of the same drug to treat the same rare disease unless an exception applies.

74. The statute contains only two narrow exceptions. The prohibition in section 527(a) applies "[e]xcept as provided in subsection (b)." 21 U.S.C. § 360cc(a). Subsection (b) in turn provides narrow exceptions for shortages and consent. Thus, "[d]uring the 7-year period described in subsection (a)," FDA "may approve an application … for a drug that is otherwise the same … as the already approved drug for the same rare disease" only if (1) the agency finds, after notice and an opportunity to be heard, that the sponsor of the drug with ODE "cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated"; or (2) the sponsor of the drug with ODE provides written consent to the "approval of other applications … before the expiration of such seven-year period." *Id*. § 360cc(b)(1)-(2).

75. In 2017, Congress amended the Orphan Drug Act to revise subsection (a) and to add new subsections (c) and (d) to section 527. *See* Pub. L. No. 115-52, Tit. VI, § 607(a)(3), 131 Stat. 1005, 1049-50 (Aug. 18, 2017).

76. The revisions to subsection (a) were intended to clarify the scope of ODE by simplifying the language used to describe the prohibition on subsequent approvals:

FDCA Section 527(a), 21 U.S.C. § 360cc(a)

2016 Ed.	**2018 Ed.**
FDA "may not approve another application … for *such* drug for *such* disease or condition for a person who is not the holder of such approved application"	FDA "may not approve another application … for ***the same*** drug for ***the same*** disease or condition for a person who is not the holder of such approved application"

In doing so, Congress eliminated the need for FDA to interpret the phrase "such drug," which had previously been found to be ambiguous. *See Baker Norton Pharms., Inc. v. FDA*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001); *see also* 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) ("Congress left it to FDA to define 'such drug'").

77. New subsection (c) addressed the issue of serial exclusivity. The new provision confirmed a drug that "is otherwise the same … as an already approved or licensed drug" can earn a new "exclusive approval" for "the same rare disease," but must demonstrate, "as a condition of such exclusive approval," that the proposed drug will be "clinically superior to any already approved or licensed drug that is the same drug." 21 U.S.C. § 360cc(c)(1). "Clinically superior" is in turn defined to "mean[] that the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care." *Id.* § 360cc(c)(2).

78. Subsection (c) thus clarifies that not every drug with ODD is automatically entitled to ODE upon approval. If the drug is the first of its kind approved to treat a particular rare disease, then the exclusivity accrues automatically. But if one or more prior versions of the same drug was approved to treat that disease, ODE does not accrue unless the sponsor also ***demonstrates*** that its drug will be clinically superior to all previously approved products. This demonstration differs

from the hypothesis supporting ODD—at the approval stage, clinical superiority requires actual proof by competent evidence.

79. As Representative Mimi Walters explained, this new subsection would provide a "new statutory authority to require the sponsor of an orphan-designated drug, which has certain similarities to an already approved drug, to demonstrate 'clinical superiority' compared to the already approved drug as a condition of receiving seven years of market exclusivity." 163 Cong. Rec. H5483 (July 12, 2017) (statement of Rep. Walters). The new provision was intended to "limit the number of drugs that are automatically entitled to seven years of exclusivity, while maintaining incentives for the development of innovative treatments for rare diseases." *Id.*

80. Importantly, subsection (c) was not intended to and does not allow FDA to break unexpired ODE. Even though it specifically addresses "clinical superiority," subsection (c) does not authorize FDA to use a determination of clinical superiority as a basis to find that two drugs are not "the same drug" for purposes of subsection (a).

81. New subsection (d) addressed FDA's interpretive authority related to ODE. The original Orphan Drug Act did not grant FDA interpretive authority over any aspect of section 527. As added in 2017, subsection (d) allows FDA to issue regulations only "for the implementation of ***subsection (c)***." 21 U.S.C. § 360cc(d) (emphasis added). Until FDA exercises that authority, FDA may implement ***subsection (c)*** using the "definitions set forth in [the prior regulations from 1992]" but only "to the extent such definitions are not inconsistent with the terms of this section, as amended." *Id.* Even after the amendments, FDA lacks interpretive authority regarding section 527(a) or section 527(b).

82. Section 527(d) refers to pre-existing regulations that further define the three prongs of the definition of clinical superiority set out in section 527(c). Per those regulations, greater

efficacy requires a showing that the drug will have greater effect "on a clinically meaningful endpoint in adequate and well controlled clinical trials." 21 C.F.R. § 316.3(b)(3)(i). The level of proof required is generally the same as the "evidence needed to support a comparative effectiveness claim"; thus, "in most cases, direct comparative clinical trials" are required. *Id.*; *see id*. § 201.57(c)(2)(iii) (labeling comparing the "effectiveness of the drug with other agents for the same indication must … be supported by substantial evidence …"); *id.* § 202.1(e)(6)(ii) (advertising claims that a drug is "more effective than another drug in some particular" are false and misleading unless the drug has been shown to be "more effective in such particular by substantial evidence or substantial clinical experience").

83. The regulations also state that greater safety requires proof of a safety benefit that will be experienced by "a substantial portion of the target population[]." 21 C.F.R. § 316.3(b)(3)(ii). The only specific example provided is "the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects." *Id.* For some other claims, the regulation indicates that "direct comparative clinical trials will be necessary." *Id.*

84. The third category – major contribution to patient care – is reserved for "unusual cases, where neither greater safety nor greater effectiveness has been shown." 21 C.F.R. § 316.3(b)(3)(iii). According to FDA, the major contribution to patient care pathway "is intended to constitute a narrow category, and … is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated." 56 Fed. Reg. at 3343; *see* 78 Fed. Reg. 35117, 35125 (June 12, 2013) ("In FDA's experience, showings of major contribution to patient care remain unusual."). "[C]omparative trials are, of course, preferred and will usually be required." 57 Fed. Reg. at 62079.

II. FACTUAL BACKGROUND

A. Oxybate and Narcolepsy

85. Oxybate is a "new drug" for purposes of the FDCA and cannot lawfully be marketed in the United States without FDA's prior approval.

86. Oxybate is also known as gamma-hydroxybutyric acid and/or gamma-hydroxybutyrate ("GHB"), an infamous drug of abuse that is often associated with drug-facilitated sexual assault. When approved by FDA, oxybate is a Schedule III controlled substance. When not approved by FDA, oxybate is a Schedule I controlled substance. Abuse or misuse of oxybate is associated with a number of serious adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death. In addition, oxybate is a central nervous system ("CNS") depressant even when used in accordance with its labeling.

87. For these reasons, among others, oxybate is marketed in the United States with a boxed warning and through a restricted distribution program known as a risk evaluation and mitigation strategy ("REMS") with elements to assure safe use ("ETASU"). Nevertheless, oxybate is a safe and effective treatment for cataplexy and EDS in narcolepsy, among other conditions, when used in accordance with its labeling.

88. Narcolepsy, a form of hypersomnia, is a rare disease within the meaning of 21 U.S.C. § 360bb(a)(2). It is a debilitating, chronic neurological condition that has no known cure. One common symptom of narcolepsy is cataplexy, a sudden loss of muscle tone while awake, leading to a loss of voluntary muscle control. Cataplexy can be triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. A universal symptom of narcolepsy is excessive daytime sleepiness ("EDS"), which generally is defined as an irresistible need to sleep during the day and a constant feeling of fatigue.

89. People with narcolepsy have high rates of comorbidities. For instance, one retrospective study of more than 9,000 narcolepsy patients found that diseases of the circulatory system, including hypertension, are more prevalent in narcolepsy patients than in the general population (excess prevalence of 16.6%). *See* J. Black et al., *Medical Comorbidity in Narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) Study*, 33 Sleep Medicine 13, 15 Tbl. 2 (2017). The study further found statistically significant increases in the rate of stroke, myocardial infarction, cardiac arrest, and heart failure among patients with narcolepsy. *See id.* at 17 Tbl. 4. Another retrospective study of more than 12,000 narcolepsy patients similarly found increased frequencies of a wide variety of cardiovascular comorbidities. *See* Rami Ben-Joseph et al., *Cardio-Vascular Burden of Narcolepsy Disease (CV-BOND): A Real-World Evidence Study*, 44(2) Sleep A198 (May 2021). Smaller studies have likewise found higher rates of hypertension and other cardiovascular conditions among narcolepsy patients. *See, e.g.*, Alexander Cohen et al., *Comorbidities in A Community Sample of Narcolepsy*, 43 Sleep Med. 14 (2018); Maurice M. Ohayon, *Narcolepsy is Complicated By High Medical and Psychiatric Comorbidities: A Comparison With the General Population*, 14 Sleep Med. 488 (2013).

B. Xyrem® (sodium oxybate) and Xywav® (calcium, magnesium, potassium, and sodium oxybates)

90. Jazz is the sponsor of NDA No. 021196 for Xyrem® (sodium oxybate) oral solution and NDA No. 212690 for Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution. Both products are approved for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. Xywav is also approved to treat idiopathic hypersomnia.

91. Xyrem was originally approved in 2002, and it was the first oxybate product to be approved by FDA. In 2018, Xyrem also became the first oxybate product to be approved by FDA for pediatric use.

92. At the largest dose approved by FDA, patients taking Xyrem ingest 1,640 mg of sodium each night. In contrast, medical and scientific consensus generally recommends that most individuals over the age of 14 consume no more 2,300 mg of sodium per day. *See, e.g.*, FDA, *Final Guidance for Industry: Voluntary Sodium Reduction Goals*, 3-4 (Oct. 2021).[13] The American Heart Association ("AHA") actually "recommends … an ideal limit of less than 1,500 mg per day for most adults." AHA, *Answers by Heart: Why Should I Limit Sodium?*, *supra* p. 7. Nevertheless, "Americans consume on average 3,400 milligrams (mg) of sodium per day," FDA, *Sodium Reduction*, *supra* p. 6—an amount that is well in excess of all health organization recommendations.

93. At the highest approved dose, sodium oxybate represents an increase of 48% in daily sodium for the average American, contains more than 71% of the recommended upper daily limit for sodium, and is more than 109% of the ideal daily limit for sodium.

94. Excess sodium is of particular clinical concern given the significant association, discussed above, between narcolepsy and cardiovascular comorbidities. Accordingly, the approved labeling for Xyrem has always warned that patients sensitive to salt intake (including those with heart failure, hypertension, or renal impairment) should consider the amount of daily sodium intake associated with therapy with Xyrem.

95. As FDA recently reemphasized, "Sodium reduction is a critically important public health issue." FDA, *Constituent Update: FDA Issues Sodium Reduction Final Guidance* (Oct. 13,

[13] https://www.fda.gov/media/98264/download.

2021)[14]; *see also* Susan T. Mayne et al., *Reducing Sodium Intake in the US, Healthier Lives, Healthier Future*, 326(17) JAMA 1675-76 (Nov. 13, 2021)[15] ("[E]xcess sodium is a key contributor to high rates of hypertension and cardiovascular disease. Hypertension is epidemic in the US and affects more than an estimated 100 million adults, approximately half the adult population." (footnote omitted)). "Reducing sodium in the diet is the single most effective public health action related to nutrition." FDA, *Nutrition Innovation Strategy*, 3 (June 2021);[16] *accord* Scott Gottlieb, Comm'r of Food and Drugs, *Reducing the Burden of Chronic Disease* (Mar. 29, 2018)[17] ("There remains no single more effective public health action related to nutrition than the reduction of sodium in the diet. … [R]educing sodium intake by one-half teaspoon a day could prevent nearly 100,000 premature deaths a year, and up to 120,000 new cases of coronary heart disease, 66,000 strokes, and 99,000 heart attacks.").

96. Consistent with that public health goal, Jazz spent many years developing a new oxybate product, Xywav, that would drastically lower the amount of sodium ingested by patients. Xywav was approved on July 21, 2020 for the treatment of cataplexy and EDS in patients with narcolepsy aged 7 years or older.

97. Xywav contains a mixture of calcium, potassium, magnesium, and sodium salts of oxybate. At the largest approved dose, patients taking Xywav ingest only 131 mg of sodium each night, a reduction of more than 1,500 mg (or 92%) versus Xyrem. That reduction is clinically meaningful.

[14] https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-sodium-reduction-final-guidance.

[15] https://jamanetwork.com/journals/jama/article-abstract/2785289.

[16] https://www.fda.gov/media/152678/download.

[17] https://www.fda.gov/news-events/speeches-fda-officials/reducing-burden-chronic-disease-03292018.

98. Because it does not involve significant sodium intake, the package insert for Xywav does not contain a warning regarding high sodium.

99. In light of its lower sodium burden, FDA has recognized that Xywav achieves greater safety than, and is clinically superior to, sodium oxybate:

> Xywav (calcium, magnesium, potassium, and sodium oxybates) is clinically superior to Xyrem by means of greater safety because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem. The differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.

FDA, *Clinical Superiority Findings*, *supra* p. 4.

100. In a related memorandum, the Review Division expounded on the patient population expected to benefit from a low sodium version of oxybate. The Review Division observed that Xywav would be "the medication of choice" for "patients who concomitantly have conditions such as cardiac failure, hypertension, and renal impairment." Memo. From Eric Bastings, DN1, FDA to Dir. of OOPD re: Orphan Products Consult Request #2020-00029-EC, at 9-10 (Nov. 27, 2020). The Review Division also observed that such patients, "especially those with hypertension, may constitute a significant proportion of those with cataplexy and [EDS] in narcolepsy." *Id.* But given the need for virtually all Americans to reduce sodium, the Review Division also acknowledged that the "difference in sodium content … is also very likely to be clinically meaningful in all patients with narcolepsy." *Id.* at 10.

101. In a contemporaneous letter to Avadel, OOPD explained that "the sodium reduction from Xyrem to Xywav is significant" and that the "reduction in chronic sodium burden … [was] expected to be beneficial to all patients with narcolepsy, especially those with comorbidities that put them at increased risk of cardiovascular disease." Ltr. from OOPD to Jennifer Gudeman, Avadel Pharms. re: Sodium Oxybate for the Treatment of Narcolepsy, at 3 (June 24, 2021).

102. In sum, as a clinically superior and safer product, Xywav earned exclusive approval pursuant to 21 U.S.C. § 360cc(a) and (c) for the treatment of cataplexy and EDS in narcolepsy patients aged seven years or older. The orphan drug exclusivity protecting Xywav will not expire until July 2027.

C. Avadel and Lumryz™ (sodium oxybate)

103. Non-party Avadel CNS Pharmaceuticals LLC ("Avadel") is headquartered in Dublin, Ireland (NASDAQ: AVDL). Avadel has developed its own sodium oxybate product, originally referred to as the investigational candidate "FT218" and more recently approved by FDA under the proprietary name "Lumryz."

104. Avadel's efforts to show clinical superiority for its sodium oxybate product date to at least July 2016, when OOPD ***denied*** Avadel's request for an orphan drug designation because once-nightly dosing did not support even a hypothesis of a major contribution to patient care. At the time, OOPD staff reviewing Avadel's request wrote:

> The sponsor claims that FT218 is superior to Xyrem® by providing major contribution to patient care. While OOPD acknowledges that the reduction in nighttime dosing frequency is convenient, it has not risen to the level which OOPD considers as major contribution to patient care.

2016 OOPD Review, Exhibit B at 5.

105. Based on that review, OOPD wrote to Avadel informing Avadel that its arguments and evidence did not amount to a plausible hypothesis that once-nightly dosing would provide a major contribution to patient care:

> The OOPD acknowledges that the proposed dosing regimen of FT218 is more convenient to the patient and/or caregivers than that of Xyrem®. However, based on your current submission, this reduction in dosing frequency is not considered as providing a major contribution to patient care. You have also not submitted a plausible

> hypothesis for superior efficacy or safety for your product over the approved product.

2016 Ltr. to Avadel, Exhibit C, at 1.

106. About a year and a half later, OOPD reversed course. A letter from OOPD dated January 8, 2018, indicates that Avadel submitted an amended designation request. In response to that amendment, OOPD apparently determined that Avadel had established a plausible hypothesis of greater safety (but not a major contribution to patient care) due to the alleged "ramifications associated with the dosing regimen for [Xyrem]." Ltr. from OOPD to Marla Scarola, The Weinberg Grp., at 1 (Jan. 8, 2018). The assertion was not further explained in OOPD's letter to Avadel, and no documents supporting that assertion have been disclosed as of this writing.

107. The January 2018 letter did caution that a hypothesis would not be enough to support exclusivity for FT218. OOPD informed Avadel that "to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to any already approved version of the same drug for the same indication. Failure to demonstrate clinical superiority over the already approved same drug(s) will result in your drug not receiving orphan-drug exclusivity." *Id.* at 2.

108. When Avadel submitted its NDA for Lumryz in December 2020, Avadel included a request for priority review. An application is entitled to priority review only if the proposed drug will be "a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of [serious conditions] compared to available therapies." FDA, *Manual of Policies and Procedures 6020.3: Review Designation Policy: Priority (P) and Standard (S)*, Center for Drug Evaluation and Research, 6 (June 25, 2013).[18] Although the relevant documents have not been disclosed, the Review Division rejected Avadel's request in February 2021. The Review Division

[18] https://www.fda.gov/media/72723/download.

later observed that Avadel's arguments in support of its clinical superiority claim were essentially the same as the arguments that the Review Division had rejected in the priority review context. *See* Exhibit D at 8-9.

109. In July 2021, OOPD appears to have asked the Review Division to formally assess Avadel's claims that Lumryz is clinically superior to Xywav. OOPD told the Review Division that, given the unexpired ODE protecting Xywav, the only way "for Lumryz to receive marketing approval" was to establish clinical superiority. *Id.* at 4. In presenting the issue to the Review Division, OOPD appears to have prejudged the question and to be seeking the Review Division's concurrence. *See id.* at 6 ("Among the arguments provided by Avadel, the OOPD finds most persuasive the argument for greater safety due to reduced fall potential . … Does the review division agree that Lumryz provides greater safety in a substantial portion of the target population when compared to Xyrem and Xywav?"). Despite the thumb that OOPD had placed on the scale, the Review Division disagreed. The Review Division concluded that once-nightly dosing "cannot be considered a major contribution to patient care," *id.* at 10, which is essentially the same conclusion that OOPD had reached in 2016. Overall, the Review Division concluded that Avadel had provided "***no evidence*** … that Lumryz is clinically superior to Xyrem or Xywav as defined in the orphan drug regulations." *Id.* at 12 (emphasis added).

110. FDA tentatively approved Lumryz in July 2022. The tentative approval reflected FDA's assessment that Avadel had failed to include a patent certification regarding one of the patents covering Xyrem, and that such a certification was necessary to obtain a full approval. *See Avadel CNS Pharms., LLC v. Becerra*, No. 22-cv-02159 (D.D.C. July 21, 2022), ECF No. 2-41 ("TA Letter"). According to the materials FDA has released to date, at the time of the tentative

approval, the Review Division had not yet changed its August 2021 determination that Lumryz was not clinically superior to Xywav and was blocked by Xywav's ODE.

111. On May 1, 2023, some ten months later, the Review Division apparently reconsidered its position and agreed with OOPD that Lumryz was clinically superior. That reversal appears to have been the result of a lengthy pressure campaign by OOPD. None of the relevant communications from OOPD to the Review Division have been disclosed, but the May 1, 2023 Review Division memorandum indicates that OOPD raised "several factors, including scientific, legal, and regulatory considerations." Exhibit E at 4. In those undisclosed communications, OOPD apparently dictated to the Review Division, among other things, the factors that are relevant for major contribution to patient care determinations, the meaning of FDA regulations and policies, and which precedents should be considered relevant. *Id.*

112. OOPD's pressure campaign appears to have violated FDA's internal policies and procedures. There is no question that the physicians and other officials in the Review Division are the primary regulators at FDA for all oxybate products. They have decades of experience reviewing applications for Xyrem and Xywav (and now Lumryz) as treatments for narcolepsy, idiopathic hypersomnia, and disrupted nighttime sleep.

113. The Review Division is supervised in that role by the Office of Neuroscience, which in turn is supervised by the Office of New Drugs, by the Center for Drug Evaluation and Research, and finally by the Office of the Commissioner.

114. OOPD has a different chain of command. OOPD is supervised by the Office of Clinical Policy, which reports to the Office of the Commissioner. In FDA parlance, OOPD and the Review Division are therefore considered to be different "review teams" that are situated within different "centers" of the agency.

115. FDA has an established policy regarding how to resolve disputes among review teams situated in different centers:

> Cross-center disagreements that cannot be resolved at the review team level may be pursued either through an informal or a formal scientific or regulatory dispute resolution (SDR) process. This process moves the issue through sequential levels of management (i.e., chain of command) for the affected teams, up to and including the Center Director, as needed.

FDA, *Staff Manual Guide 9010.2: Cross-Center Dispute Resolution at the FDA*, *supra* p. 17, § 4. Under that policy, if OOPD did not agree with the Review Division's recommendation, OOPD had the option of pursuing the matter up either of the relevant chains of command, both of which terminate with the Office of the Commissioner.

116. Alternatively, FDA has established the Orphan Drug Products Policy Council, which "serve[s] as a forum to resolve disagreements among centers, the Office of Orphan Products Development (OOPD), additional relevant FDA offices, and/or sponsors on activities and policies related to [the Orphan Drug Act]." FDA, *Staff Manual Guide 2010.19: FDA Orphan Drug Products Policy Council*, *supra* p. 17, § 2.

117. OOPD does not appear to have pursued either option. Once again, the relevant documents and communications have not been disclosed. But it appears that OOPD responded to the Review Division's disagreement by seeking input from two doctors employed by a ***third*** center, the Center for Devices and Radiological Health ("CDRH").

118. On information and belief, the CDRH doctors are not neurologists and are not experts either in narcolepsy as a general matter or in the specific practice of treating narcolepsy patients with a powerful central nervous system depressant like oxybate. Based on a review of the records contained in the REMS for Xyrem and Xywav, Jazz is confident that neither CDRH doctor has ever enrolled in the REMS as a prescriber of oxybate. Based on public information, both

CDRH doctors appear to be pulmonologists with expertise in obstructive sleep apnea and to work at CDRH as reviewers of medical device submissions seeking approval or clearance of continuous positive airway pressure ("CPAP") machines.

119. Notably, the Orphan Drug Act does not apply to medical devices at all. On information and belief, as medical device reviewers, CDRH medical officers generally have no cause or opportunity to consider issues related to orphan drug exclusivity, clinical superiority, or the major contribution to patient care standard. In contrast, evaluating those issues is a routine responsibility for the experts in the Review Division.

120. CDRH appears to have concluded its consult on Saturday, April 29, 2023, *see* Exhibit F, some six hundred days after the Review Division's decision in August 2021 that Lumryz was not clinically superior to Xywav. Armed with a favorable memorandum from CDRH, OOPD was able to convince the Review Division to reconsider its position, which it did two days later in a new memorandum dated May 1, 2023. *See* Exhibit E.

121. That same day, in a 42-page letter, OOPD issued its determination that Lumryz could break the unexpired ODE protecting Xywav, *see* Exhibit A. OOPD identified both the CDRH memorandum and the new memorandum from the Review Division as "integral" parts of the clinical superiority finding. *See id.* at 2. Later that day, the Office of Neuroscience issued a final approval for Lumryz, *see* Exhibit G (Approval Ltr., NDA 214755 (May 1, 2023)).

D. Avadel's Actions Following Approval of Lumryz

122. Emboldened by OOPD's decision, Avadel has begun to promote Lumryz based on the alleged medical benefit that once-nightly dosing has on sleep architecture. For instance, Avadel issued a press release containing the false and misleading claims that Lumryz provides narcolepsy patients with "the opportunity for an uninterrupted night sleep" and that Lumryz "may help restore a more natural sleep-wake cycle." Avadel, *Press Release: Avadel Pharmaceuticals Announces*

Final FDA Approval of LUMRYZ™, *supra* p. 20, at 1. As another example, Avadel issued a presentation claiming that patients taking Lumryz "will have the opportunity for an uninterrupted night sleep" and further claiming that Lumryz makes "improvements in disturbed nocturnal sleep." *Avadel, Avadel Pharmaceuticals plc (NASDAQ: AVDL)*, 8 (May 2023) ("May 2023 Presentation").[19]

123. In addition, Avadel has made clear that it intends to minimize the health benefit of reduced sodium impact. For instance, its recent presentation indicates that Avadel continues to rely on a 2020 article that it sponsored claiming that treatment with high sodium oxybate "does not confer additional CV risk in patients with narcolepsy." *Id.* at 30. In doing so, Avadel notably ignores the fact that FDA previously informed Avadel that the article in question was not reliable. Ltr. from OOPD, FDA to Jennifer Gudeman, Avadel Pharms., re: Sodium Oxybate for the Treatment of Narcolepsy (June 24, 2021).

124. Avadel also has attempted to silence Jazz and prevent it from communicating the cardiovascular health benefits associated with lower sodium. In the weeks since FDA approved Lumryz, Avadel has sent two letters threatening to sue Jazz if Jazz continues to publicly discuss the established safety benefit provided by Xywav.

125. Finally, Avadel has confirmed that it intends to price Lumryz at "parity" with Xyrem and Xywav. *See* May 2023 Presentation, *supra* p. 40, at 19 ("Planning for parity pricing and coverage with branded 2x-nightly oxybates"). Thus, FDA's approval of Lumryz is unlikely to have any appreciable impact on the cost of treating narcolepsy.

[19] https://investors.avadel.com/static-files/7c1ce79e-0215-4e4b-8a66-281e61030bdb.

E. Prior Related Case

126. In 2022, Avadel sued FDA in this Court seeking a declaration that it was not required to certify to one of Jazz's patents. Jazz intervened as a defendant and asserted, *inter alia*, that ongoing patent litigation between it and Avadel provided an adequate remedy regarding the patent certification question. The Court agreed with Jazz and entered summary judgment dismissing Avadel's claims. *Avadel CNS Pharms., LLC v. Becerra*, No. 22-cv-02159 (APM), -- F. Supp. 3d --, 2022 WL 16650467 (D.D.C. Nov. 3, 2022). Thereafter, the district court hearing the patent litigation directed Jazz to seek delisting of the patent. *Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, No. 21-cv-691-GBW, -- F. Supp. 3d --, 2022 WL 17084371 (D. Del. Nov. 18, 2022). Jazz appealed and, after granting a stay pending appeal, the Federal Circuit affirmed the district court on February 24, 2023. *Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, 60 F.4th 1373, 1382 (Fed. Cir. 2023). Jazz requested that FDA remove the patent from the Orange Book on or about February 28, 2023.

III. APPROVAL OF LUMRYZ MUST BE VACATED AND SET ASIDE.

127. FDA's approval of Lumryz was unlawful and must be set aside for five broad reasons. First, OOPD's clinical superiority determination is based on a misreading of the statute and wrongfully engrafted a third exception to ODE that goes beyond the authority Congress provided. FDA's use of this additional, non-statutory exception to break Xywav's ODE and approve Lumryz was therefore contrary to law.

128. Second, OOPD's clinical superiority determination is not consistent with FDA regulations. OOPD's conclusion that Lumryz is "clinically superior" is based on an assertion that Lumryz provides "medical" benefits to narcolepsy patients not achievable by Xywav—in other words, an assertion that Lumryz provides greater efficacy for those patients. That assertion is not based on any relevant evidence, much less the type of proof required by FDA regulations. The

assertion also is contrary to OOPD's own admission that "[t]here is no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav." *See* Exhibit A at 27.

129. Third, OOPD deviated from established agency policy. FDA's longstanding policy, as set out in the *Federal Register* is that a new drug must be comparable in safety to prior versions of the same active moiety before it can be considered a major contribution to patient care. Rather than provide a reasoned explanation for why it would be appropriate to depart from the policy in this case, OOPD denied that FDA had ever established such a policy, even while acknowledging that agency documents assert exactly that policy.

130. Fourth, OOPD failed to even disclose, much less explain, three prior agency decisions indicating or finding that Lumryz ***does not*** provide a major contribution to patient care. Moreover, the available record indicates that OOPD departed from FDA's established procedures as it went about convincing the Review Division to reconsider and approve Lumryz.

131. Finally, OOPD's decision was arbitrary, capricious, and an abuse of discretion. OOPD's attempt to "balance" Avadel's speculative claims regarding once-nightly dosing against the established benefit of dramatically lower sodium was not evidence-based and ignored several relevant considerations, including the relevant scientific literature.

A. FDA Lacked Authority to Break the Unexpired Orphan Drug Exclusivity Protecting Xywav.

132. Xywav was approved on July 21, 2020. As reflected on FDA's website, Xywav earned exclusive approval for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. *Supra* p. 5.

133. Xywav and Lumryz are the same drug for purposes of ODE. The two drugs contain the same active moiety (oxybate) and Xywav's exclusivity-protected indication entirely subsumes the only indication for which Lumryz was approved. They are, in the words of the statute, "the

same drug for the same disease or condition." 21 U.S.C. § 360cc(a). As a result, FDA is not permitted to approve Lumryz "until the expiration of seven years from the date of the approval" for Xywav. *Id.*

134. Per the statute, there are only two circumstances in which FDA could break that exclusivity and approve Lumryz as a treatment for the symptoms of narcolepsy. Those circumstances are (1) if FDA makes a formal finding after notice and an opportunity to be heard that oxybate is in shortage, or (2) Jazz provides its express written consent. 21 U.S.C. § 360cc(b). Because neither circumstance exists, the decision to approve Lumryz was contrary to the statute and must be set aside.

135. In response, OOPD relies on a regulation from 1992 stating that two drugs are not considered the "same"—even if they are the same active moiety and have the same intended use—if one has been found to be clinically superior to the other. *See, e.g.*, Exhibit A at 6 (citing 21 C.F.R. § 316.3(b)(14)). Because it claims that Lumryz is clinically superior to Xywav, OOPD construed the two products to be "different drugs" and therefore concluded that Lumryz was not blocked by Xywav's unexpired ODE.

136. This "different drug" fiction is the linchpin of OOPD's analysis, and it is inconsistent with the statute for a number of reasons.

1. Using Clinical Superiority to "Overcome" Orphan Drug Exclusivity Impermissibly Creates a Third Exception to Exclusivity That Congress Did Not Authorize.

137. OOPD summarized its legal argument as "**Clinical superiority can overcome ODE**." Exhibit A at 18 (boldface in the original). OOPD thus asserts that its approach to clinical superiority functions as a *de facto* third exception to section 527(a).

138. That position is *ultra vires*. As discussed, the prohibition in section 527(a) applies "[e]xcept as provided in subsection (b)," section 527(b) creates two discrete exceptions, and

neither is applicable here. *See* 21 U.S.C. § 360cc(a)-(b). Where Congress speaks so clearly, agencies lack authority to imply additional exceptions. *See, e.g.*, *United States v. Johnson*, 529 U.S. 53, 58 (2000) ("When Congress provides exceptions in a statute … [t]he proper inference, and the one we adopt here, is that Congress considered the issue of exceptions and, in the end, limited the statute to the ones set forth."); *Andrus v. Glover Constr. Co.*, 446 U.S. 608, 616-17 (1980) ("Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent."); *In re England*, 375 F.3d 1169, 1178 (D.C. Cir. 2004) (Roberts, J.) ("Where a statute contains explicit exceptions, the courts are reluctant to find other implicit exceptions.").

139. OOPD contends that the limiting language in section 527(a) and the exceptions in section 572(b) are irrelevant. *See* Exhibit A at 19-20. Attempting to draw an analogy to the treatment of hearsay in the Federal Rules of Evidence, OOPD contends that there is a meaningful distinction "familiar to most law students" between "an ***exception*** to ODE" and an "***exclusion*** from the term 'same drug.'" *Id.* at 19 n.130 (emphasis added). The analogy misses completely. For starters, the evidence rules expressly spell out both the hearsay exceptions and the hearsay exclusions – the exclusions are not implied from thin air. More to the point, the law precludes federal agencies from expanding their own powers in this way. Cases like *Johnson*, *Andrus*, and *England* recognize that when Congress has established a comprehensive framework, agencies lack authority to alter it because—as most law students know—agencies cannot rewrite statutes. *See Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 213-14 (1976) ("The rulemaking power granted to an administrative agency charged with the administration of a federal statute is not the power to make law. Rather, it is the power to adopt regulations to carry into effect the will of Congress as expressed by the statute.") (quotation marks and citation omitted); *see also Util. Air Regul. Grp.*

v. EPA, 573 U.S. 302, 328 (2014) ("We reaffirm the core administrative-law principle that an agency may not rewrite clear statutory terms to suit its own sense of how the statute should operate."). It does not matter whether OOPD thinks that clinical superiority "overcomes" ODE as an "exclusion" or an "exception." All that matters is that Congress gave FDA authority to "overcome" ODE in only two narrowly defined situations, and neither of those situations exist with respect to oxybate.

140. Indeed, this question was effectively asked and answered in the *Depomed* case. Then-Judge Jackson summarized the regulation at issue as follows:

> [FDA's] regulations define the term 'same drug' … to mean, in relevant part, 'a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug,' with the exception 'that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.'
>
> ***The insertion of the 'same drug' concept into the exclusivity regulations effectively limits the scope of exclusivity protection*** because under the regulations, only if a new drug uses the same active ingredient ('active moiety') to treat the same disease or condition as a drug that already has orphan-drug exclusivity ***and*** the new drug is also not found to be 'clinically superior' to the existing orphan drug will the FDA consider the new drug to be the 'same' as the drug with exclusivity and thereby forbid its marketing within the exclusivity period.

Depomed, 66 F. Supp. 3d at 222 (citation omitted; first emphasis added). Judge Jackson then rejected FDA's definition of "same drug" as inconsistent with Congress's enumeration of two exceptions to ODE. *Id.* at 233 ("This Court will not impute to Congress an intention to authorize an exception that Congress itself did not think worth enacting.").

141. *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013), also is instructive. There, the Court of Appeals construed section 801(a) of the FDCA, which states that certain imports "shall be refused admission, except as provided in subsection (b)." 21 U.S.C. § 381(a). The Court of Appeals held

that this language would be rendered "'insignificant, if not wholly superfluous'" if FDA could use its (generally unreviewable) enforcement discretion to allow covered imports to enter the country without complying with subsection (b). *See Cook*, 733 F.3d at 8 (quoting *TRW, Inc. v. Andrews*, 534 U.S. 19, 31 (2001)). An agency's authority is at its zenith when invoking enforcement discretion—enforcement is one of only a handful of issues that the Supreme Court has found "committed to agency discretion by law." 5 U.S.C. § 701(a)(2); *see Heckler v. Chaney*, 470 U.S. 821, 834-35 (1985). If enforcement discretion could not justify FDA's effort to create additional exceptions to section 801(a), it should follow *a fortiori* that OOPD cannot use a regulation to create additional exceptions to ODE.

2. Congress Addressed Clinical Superiority in 2017 and Chose Not to Recognize Clinical Superiority as a Third Exception to Orphan Drug Exclusivity.

142. OOPD's position also fails to account for the evolution of section 527(a). When the 1992 regulation was created, the statute did not include the phrase "the same drug." Rather, the statute prohibited FDA from approving "another application … for such drug for such disease or condition." 21 U.S.C. § 360cc(a) (2016 ed.). In 1992, FDA promulgated a regulation purporting to implement that prohibition, and the regulation replaced the phrase "such drug for such disease or condition" with the phrase "same drug for the same use or indication" *See* 21 C.F.R. § 316.31(a) ("FDA will not approve another sponsor's marketing application for the same drug for the same use or indication before the expiration of 7 years."). The regulation also contained a definition for the ***regulatory*** phrase "same drug," and it specified that a product found to be clinically superior would be considered a different drug. *See id.* § 316.3(b)(14)(i).

143. FDA claimed at the time that it was the ambiguity of the phrase "such drug" that left a gap for the agency to fill:

> Congress left it to FDA to define 'such drug' as used in 21 U.S.C. § 360cc and provided no guidance on the meaning of this term. Thus, it is within FDA's authority to define what is the 'same' and what is a 'different' drug. 'Clinical superiority' is a rational and permissible means of making this distinction.

57 Fed. Reg. at 62078.

144. FDA's construction was rejected in the *Depomed* decision, both of the *Eagle* opinions, and in the *United Therapeutics* case. Those decisions all recognize that FDA used the concept of clinical superiority in the regulatory definition of "same drug" to accomplish two different objectives. First, the agency used clinical superiority to break unexpired ODE and approve a competing product and break the seven-year period of exclusivity established by section 527(a). *See, e.g.*, *Eagle II*, 952 F.3d at 326 ("when determining whether it can approve another drug for marketing during an orphan drug's seven-year exclusivity period"). Second, FDA required a demonstration of clinical superiority as a condition for granting a serial exclusivity. *See, e.g.*, *id.* ("in deciding whether to grant a subsequent drug its own period of exclusive approval after the seven years have expired").

145. In response to FDA's loss in *Depomed*, Congress amended the statute, but it chose to codify only ***one*** of the two ways in which FDA had used clinical superiority. Congress added new section 527(c) to grant FDA the authority to require a demonstration of clinical superiority as a condition for serial exclusivity. Congress did not authorize FDA's separate practice of using clinical superiority to break unexpired ODE. FDA concedes as much. *See* Exhibit A at 6 ("As the text demonstrates, section 527(c) only concerns potential eligibility of a subsequent drug for its own period of ODE and does not address whether a subsequent drug's approval is blocked by another drug's ODE….").

146. Congress's decision to codify ***only one aspect*** of FDA's prior practice is confirmation that the legislature did not intend for clinical superiority to function as a third

exception to section 527(a) or otherwise provide a basis for the agency to break an unexpired period of ODE. *See, e.g., Prestol Espinal v. Att'y Gen.*, 653 F.3d 213, 222 (3d Cir. 2011) (where "Congress specifically codified other regulatory limitations already in existence," but not the regulatory exception at bar, "[n]either we nor the agency should be permitted to override Congress' considered judgment"); *see also Jama v. Immigr. & Customs Enf't*, 543 U.S. 335, 341 (2005) ("We do not lightly assume that Congress has omitted from its adopted text requirements that it nonetheless intends to apply, and our reluctance is even greater when Congress has shown elsewhere in the same statute that it knows how to make such a requirement manifest.").

3. FDA Lacks Authority to Promulgate Regulations Interpreting the Phrase "the Same Drug" in Section 527(a).

147. The original Orphan Drug Act required FDA to establish regulations governing the process by which sponsors obtain orphan drug ***designation***, *i.e.*, a formal recognition from FDA that an investigational drug is a treatment for a rare disease or condition. *See* 21 U.S.C. § 360bb(d) ("[FDA] shall by regulation promulgate procedures for the implementation of subsection (a)."). The original statute provided no corresponding authority for FDA to interpret the orphan drug ***exclusivity*** provision, which was archly noted by Judge Jackson. *See Depomed*, 66 F. Supp. 3d at 222 ("While Congress did not direct the FDA to promulgate implementing regulations for the Act's exclusivity provision … the FDA did so nonetheless.").

148. Judge Jackson also indicated that FDA's assertion of interpretive authority over the exclusivity provision was inappropriate. After reviewing the relevant provisions of the statute, Judge Jackson found that "the intent of Congress was to provide the FDA with a merely ministerial role in the exclusivity process." *Id.* at 233. Further, because section 527(a) operates as a prohibition directed to FDA, it is "exactly the kind of 'thou shalt not' statute that the D.C. Circuit has found expressly negates the existence of a claimed administrative power to interpret the circumstances

in which the provision applies." *Id.* (cleaned up). In other words, Judge Jackson suggested that FDA has no authority to interpret section 527(a). *Cf. City of Kansas City v. HUD*, 923 F.2d 188, 191 (D.C. Cir. 1991) (there must be a "delegation of interpretive authority" before an agency can "advance its own statutory construction").

149. The 2017 amendments addressed this question in two different ways. First, the amendments updated section 527(a) to remove the phrase "such drug" and replace it with the phrase "the same drug." *See supra* pp. 24-26. In doing so, Congress removed the precise language that FDA had identified as ambiguous in 1992 and used to justify its assertion of interpretive authority over section 527(a). *See supra* pp. 46-47.

150. Then, for the avoidance of doubt, the 2017 amendments added new section 527(d), which authorizes FDA to "promulgate regulations for the implementation of ***subsection (c)***." 21 U.S.C. § 360cc(d) (emphasis added). Until FDA exercises that authority (which it has not yet done), the agency may continue to interpret ***subsection (c)*** according to the definitions set forth in the 1992 regulations, but only "to the extent such definitions are not inconsistent with the terms of this section, as amended." *Id.*

151. The obvious implication is that FDA ***does not*** have interpretive authority regarding either the prohibition in section 527(***a***) or the two specific exceptions in section 527(***b***). *See, e.g.*, *Am. Fin. Servs. v. FTC*, 767 F. 2d 957, 965 (D.C. Cir. 1985) ("The extent of [the agency's] powers can be decided only by considering the powers Congress specifically granted it in the light of the statutory language and background."); *see also Agudas Chasidei Chabad of U.S. v. Russian Fed'n*, 528 F.3d 934, 948 (D.C. Cir. 2008) ("Congress's inclusion of a provision in one section strengthens the inference that its omission from a closely related section must have been intentional.").

152. In short, the changes to section 527(a) and the inclusion of new section 527(d) confirm that Congress did not intend for FDA to use its 1992 regulations to interpret the phrase "the same drug" as it appears in amended section 527(a).

4. "The Same Drug" Is Not Ambiguous.

153. Even when an agency does have interpretive authority, it cannot change the meaning of an unambiguous statutory provision. Here, the statutory phrase "the same drug" presents no ambiguity requiring clarification from FDA.

154. To be sure, the isolated word "drug" can have multiple meanings in the FDCA. Sometimes, "drug" means a finished product. *See, e.g.*, *United States v. Generix Drug Corp.*, 460 U.S. 453, 454 (1983) ("drug" in section 505(a) refers to a specific finished product, such that every product requires its own approval from FDA). Alternatively, "drug" can refer to the active ingredient contained in one or more finished products. *See, e.g.*, 21 C.F.R. § 314.3(b) (definition of "drug substance"). As a third alternative, "drug" can refer to the active moiety, which is the portion of the drug substance that is "responsible for [its] physiological or pharmacological action." *See id.* (definition of "[a]ctive moiety").

155. "Drug" can have only one meaning in section 527(a). For section 527(a) to provide the incentive envisioned by Congress, orphan drug exclusivity must actually provide a period of exclusive marketing. And for that to occur, "drug" must mean "active moiety." *See, e.g.*, *Nat'l Pharm. All. v. Henney*, 47 F. Supp. 2d 37, 39-40 (D.D.C. 1999) (upholding FDA's interpretation of "drug" as "active moiety" in the FDCA's pediatric exclusivity provision, which extends the duration of ODE by six months). Indeed, FDA has never suggested that "drug" can mean anything other than "active moiety" in section 527(a).

156. Because the active moiety of a product is an objective and knowable fact, the statutory phrase "the same drug" just means "the same active moiety." There is no ambiguity that

requires clarification from FDA. *See, e.g.*, *Hunter v. Town of Mocksville*, 897 F.3d 538, 550 (4th Cir. 2018) ("The word 'same,'… is nontechnical and unambiguous. … In its ordinary usage, same means '[i]dentical or equal; resembling in every relevant respect.'" (quoting Black's Law Dictionary (10th ed. 2014)).

B. OOPD's Determination that Lumryz Provides Additional Medical Benefits Was Inconsistent With FDA Regulations.

157. FDA regulations state that comparative efficacy claims—that is, a claim that one drug performs better than another—must be supported by substantial evidence. *See* 21 C.F.R. § 201.57(c)(2)(iii) (establishing that requirement for drug labeling); 21 C.F.R. § 202.1(e)(6)(ii) (similar rule for drug advertising). Substantial evidence is a term of art meaning one or more adequate and well-controlled clinical trials. *See* 21 U.S.C. § 355(d).

158. The Orphan Drug regulations impose similarly stringent standards on claims of greater efficacy. *See* 21 C.F.R. § 316.3(b)(3)(i) (greater efficacy must be based on "a clinically meaningful endpoint in adequate and well controlled clinical trials," *i.e.*, "the same kind of evidence needed to support a comparative effectiveness claim").

159. There is ***zero*** evidence that Lumryz is more effective than Xywav or Xyrem. The absence of such evidence is the result of Avadel's development program. Avadel chose to study Lumryz only ***against placebo***. Avadel chose not to conduct any clinical trials directly comparing Lumryz to any other drug product.

160. Likely because no competent evidence exists, OOPD denied that it was making a greater efficacy finding for Lumryz. The Decision Letter thus concedes that there is "no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav." Exhibit A at 27. The Decision Letter also concedes that "Avadel has not demonstrated that Lumryz provides greater safety than either Xyrem or Xywav." *Id.*

161. Despite those concessions, OOPD's clinical superiority conclusion rests heavily on speculation that Lumryz will be more effective than Xywav. OOPD thus claims that Lumryz provides "medical benefits" by allowing narcolepsy patients to achieve normal sleep. For instance, the agency's website summarizes the clinical superiority finding as follows:

> The active moiety, oxybate, was previously approved as Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) for the treatment of cataplexy or EDS in adults with narcolepsy. The benefits of Lumryz's once-nightly dosing rise to the level of making a major contribution to patient care because ***Lumryz's dosing provides for oxybate therapy that does not involve disrupting or fragmenting sleep***, whereas Xyrem and Xywav necessitate a nocturnal awakening to take a second dose, which disrupts sleep architecture in patients with a known sleep disorder. Aside from ***the medical benefits of not having to awaken to take a second dose***, it is inherently more convenient, easier, and less burdensome for patients to forgo awakening to take a second dose on a nightly basis. Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment.

FDA, *Clinical Superiority Findings*, *supra* p. 4 (emphasis added). "Medical benefits" is a shorthand referring to the efficacy of Lumryz. *See, e.g.*, *E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 681-82 (D.C. Cir. 1989) (affirming FDA's view that substantial evidence of effectiveness requires proof that a drug will provide a "medical benefit").

162. The Decision Letter also asserts that Lumryz provides greater efficacy. For example, OOPD asserts that Lumryz is more effective than Xywav because it allegedly "provides an opportunity for narcolepsy patients to achieve normal sleep architecture, which is not a possibility for a patient on Xyrem or Xywav." Exhibit A at 29.

163. As another example, the Decision Letter asserts that "the benefit offered by once-nightly dosing would ***outweigh the risk*** of increased sodium intake." Exhibit A at 32 (emphasis added). It is a foundational principle of FDA's regulation of prescription drugs that only a therapeutic (i.e., efficacy) benefit can outweigh a safety risk. *Cf. FDA v. Brown & Williamson*

Tobacco Corp., 529 U. S. 120, 140 (2000) ("Several provisions in the Act require the FDA to determine that the product itself is safe as used by consumers. That is, the product's probable therapeutic benefits must outweigh its risk of harm.").

164. The above claims are baseless from a scientific perspective and are not supported by any relevant evidence.

C. OOPD's Assertion That Once-Nightly Dosing Is a Major Contribution to Patient Care Departed From Longstanding FDA Policy.

165. Throughout the Decision Letter, OOPD describes its unsupported greater efficacy claims about Lumryz as reasons why Lumryz allegedly makes a "major contribution to patient care" per 21 U.S.C. § 360cc(c)(2) and 21 C.F.R. § 316.3(b)(3)(iii). In doing so, OOPD departed from longstanding FDA policy interpreting the major contribution to patient care parameter of clinical superiority. OOPD did not acknowledge the departure, let alone provide the sort of reasoned explanation required by the APA.

166. FDA has stated that the major contribution to patient care parameter of clinical superiority is reserved for "unusual cases" where "neither greater safety nor greater effectiveness has been shown." 21 C.F.R. § 316.3(b)(3)(iii). The major contribution to patient care pathway "is intended to constitute a narrow category" and "is not intended to open the flood gates to FDA approval." 56 Fed. Reg. at 3343.

167. The major contribution to patient care pathway would "open the flood gates" if it allowed sponsors to sacrifice safety in the name of increased convenience. To prevent such tradeoffs, FDA has stated that clinical superiority based on a major contribution to patient care "is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug." 76 Fed. Reg. at 64871. For a major contribution to patient care to exist, the changes made by the new product must not "render[] the drug less safe or less effective than the

approved drug." *Id.* Indeed, the requirement that a drug allegedly providing a major contribution to patient care must first achieve "safety and effectiveness comparable to the approved drug" is the agency's "longstanding policy." *Id.* at 64876.

168. OOPD appears to have recognized as much in this very case. When it first requested input from the Review Division regarding Avadel's request for orphan-drug exclusivity, OOPD apparently described clinical superiority as follows:

> For the purpose of orphan drug exclusivity, clinical superiority can be based on greater effectiveness, greater safety in a substantial portion of the target population, or a major contribution to patient care (MCTPC), ***with all else being equal*** (see definition below).

Exhibit D at 3-4 (quoting OOPD's July 6, 2021 consultation request) (emphasis added). In recognizing that a major contribution to patient care finding would be appropriate only if "all else" were "equal," OOPD appears to have been referring to FDA's longstanding requirement that a drug providing a major contribution to patient care must first achieve at least comparable safety and efficacy.

169. OOPD's subsequent decision obviously violated that policy. OOPD conceded, as it must, that Xywav is safer than Lumryz due to its dramatically lower sodium content, which reduces the risk of hypertension and cardiovascular disease for all patients. *See* Exhibit A at 31. That should have been the end of the matter.

170. Because the comparable safety requirement is an insurmountable obstacle preventing the approval of Lumryz, OOPD was forced to deny that it exists:

> We are aware of certain language in agency documents that could be interpreted as suggesting FDA has such a policy. … [D]espite these statements, none of FDA's past precedents that OOPD reviewed manifest application of such a policy upon approval when FDA is determining eligibility for ODE or when it is considering whether a drug may be approved in light of another sponsor's ODE.

> Given the quantum of information suggesting otherwise, it is clear that those statements do not reflect such an agency policy.

Exhibit A at 23 n.147.

171. That statement is the very definition of administrative caprice. Rather than acknowledge that its desired outcome is facially inconsistent with FDA policy statements (not to mention its own prior statement to the Review Division regarding Lumryz) and then explain why the policy should change, OOPD claims the right to ***disavow*** policy statements on the fly, as though they never existed. No agency has that power. *See Fox Television*, 556 U.S. at 515 ("[T]he requirement that an agency provide reasoned explanation for its action would ordinarily demand that it display awareness that it ***is*** changing position. An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books.").

172. What is more, the policy statements in question were made in a preamble published in the *Federal Register*. As such, they carry special legal significance. Any agency's preamble statements are relevant as compelling evidence regarding the meaning of the corresponding regulation. *See, e.g.*, *Wyo. Outdoor Council v. United States Forest Serv.*, 165 F.3d 43, 53 (D.C. Cir. 1999). But ***FDA*** long ago promulgated a separate regulation that elevates all ***FDA*** preamble statements to the status of "advisory opinions." 21 C.F.R. § 10.85(d)(1). Advisory opinions are binding on FDA until revoked through a subsequent *Federal Register* notice. *See* 21 C.F.R. § 10.85(e), (g). That regulation is an independent reason why OOPD cannot disavow an FDA policy in the manner attempted in the Decision Letter.

173. OOPD also claims that the policy statements identified above reflect only a proposal that was never adopted. *See* Exhibit A at 22. This is revisionism. The relevant policy statements were made in the preamble to a 2011 proposed rule:

> As described in § 316.3(b)(3)(i) and (b)(3)(ii), a drug that is otherwise the same drug as a previously approved drug, and for

> which a clear showing of greater effectiveness or greater safety has not been made, may still be considered clinically superior within the meaning of § 316.3(b)(3)(iii) if it makes a major contribution to patient care. FDA believes that such clinical superiority is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug. For example, to claim that a drug makes a major contribution to patient care through a new formulation or a different route of administration, the sponsor must also address whether the change renders the drug less safe or less effective than the approved drug. For these reasons, FDA proposes that § 316.3(b)(3)(iii) be revised.

76 Fed. Reg. at 64871. The specific proposed revision was to revise the regulatory definition of a major contribution to patient care to provide:

> In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug provides safety and effectiveness comparable to the approved drug and otherwise makes a major contribution to patient care.

See id. at 64878 (redline shown against current regulation). However, the 2011 preamble also made clear that the proposed revision was a clarification to recognize and codify an extant policy, and not a proposal to adopt a new approach:

> We propose ***to clarify*** the definition of clinical superiority ***to make explicit*** that a drug shown to be clinically superior to an approved drug for making a major contribution to patient care would also have to be demonstrated to provide safety and effectiveness comparable to the approved drug (§ 316.3(b)(3)(iii)). ***This revision is consistent with longstanding policy*** and would impose no new costs.

Id. at 64876 (emphases added).

174. FDA received a number of comments on that proposal that apparently misunderstood the proposal to suggest that a major contribution to patient care determination "would require direct proof of comparability to the already approved drug … (e.g., through non-inferiority trials)." 78 Fed. Reg. at 35118. In light of the confusion, FDA withdrew the proposed edit to the regulation, but did not in any way question or withdraw the "longstanding policy" identified in the 2011 preamble:

> In response to these comments, FDA is deleting the 'safety and effectiveness comparable to the approved drug' language from the final rule because of the confusion this language engendered. FDA did not intend to propose a new standard for major contribution to patient care with this language; ***in particular, FDA did not mean to suggest that direct proof of comparability to the already approved drug would be required*** (e.g., through non-inferiority trials).

Id. at 35124 (emphasis added). In sum, the 2013 final rule ultimately chose not to revise the regulation to avoid the misconception that "direct proof of comparability … through non-inferiority trials" would be required to support every major contribution to patient care finding. But that did not in any way affect FDA's "longstanding policy" that a major contribution to patient care finding must be predicated on a showing that the drug "provide[s] safety and effectiveness comparable to the approved drug." 76 Fed. Reg. at 64871, 64876.

175. Precedent also does not help OOPD. As an initial matter, it is important to be clear about what "precedent" means in this context. OOPD is not referring to judicial decisions or even public FDA pronouncements. Instead, OOPD is referring to its own internal memoranda that are usually kept confidential. Such memoranda generally become public only through litigation or Freedom of Information Act ("FOIA") requests, and OOPD's reasoning is frequently redacted from the public copies. The result is an enormous informational disparity where OOPD has unfettered access to a body of "precedents" that are often unknown or available to regulated entities only subject to heavy redactions.

176. Regardless, OOPD does not present its precedent in a fair or reasoned manner. OOPD places primary emphasis on two prior decisions related to interferon and cysteamine products, respectively. OOPD claims that those two examples are sufficient to disprove the existence of the longstanding policy that FDA described in the *Federal Register*. However, the interferon example is not relevant at all, and the cysteamine example actually followed FDA's policy of insisting on comparable safety.

177. OOPD first points to a series of internal memoranda related to interferon products. Exhibit A at 7-9, 23, 27, 30-32, 36-37 & nn.31-36, 42, 148, 170, 202, 208, 212, 246. OOPD presents interferon as a situation where OOPD "determined that a subsequent drug is clinically superior … even though the drug was less safe in one measure." *Id.* at 7. OOPD's reliance is misplaced for two reasons. First, the most recent interferon decision cited by OOPD was made in 2002. An internal memorandum from 2002 proves little about a policy statement made in the *Federal Register* nine years later. Second, interferon was a case where the sponsor had demonstrated ***greater efficacy*** through a head-to-head comparative trial. The policy that FDA described in the *Federal Register* applies only to the major contribution to patient care pathway. *See* 76 Fed. Reg. at 64871, 64,876. OOPD concedes that none of the interferon decisions were "based on a [major contribution to patient care] finding." Exhibit A at 23.

178. OOPD next invokes its decision regarding PROCYSBI® (cysteamine bitartrate). *See* Exhibit A at 24-25, 29-30, 37, 41 & nn.154-157, 161, 197-201, 250. OOPD's description of that precedent appears to have played a causal role in convincing the experts in the Review Division to reverse their position. *See* Exhibit E at 4 ("OOPD has also made the Division aware of a previous [major contribution to patient care] determination with delayed release cysteamine (PROCYSBI) for the treatment of cystinosis."). OOPD claims that the PROCYSBI decision reflects a major contribution to patient care finding even though the "drug was potentially less safe in at least one respect," Exhibit A at 25, but a review of the source documents shows that description to be incorrect.

179. The sponsor of PROCYSBI received ODD in 2006 based on a hypothesis of greater safety. *See* FDA, Review of Request for Orphan-Drug Designation, Enteric-coated cysteamine, at 3 (Oct. 16, 2006). In 2008, the sponsor changed course and informed OOPD that it was "planning

to demonstrate ***similar efficacy and safety***" and requested that OOPD accept a major contribution to patient care theory instead. *See* Ltr. from Ted Daley, Bennu Pharms. to OOPD re: Orphan Drug Exclusivity Determination for Delayed-release Cysteamine Bitartrate Capsules (i.e., enteric-coated beads) for Treatment of Cystinosis, at 1 (June 27, 2008) (emphasis added). When OOPD rejected the major contribution to patient care theory in 2009, it observed that an "[i]nherent" part of a major contribution to patient care finding was a threshold requirement that the new drug "would maintain a ***similar or improved*** adverse event profile and ***similar*** efficacy." Memo. from Peter Vaccari to Orphan Drug Application 06-2310 re: Request for OOPD Op., at 1 (Mar. 3, 2009) (emphases added). In 2012, the sponsor offered several new theories on major contribution to patient care, which OOPD also rejected. But in doing so, OOPD emphasized that the sponsor had provided "a clinical and safety update which demonstrates non-inferiority" and that there had been no observed "increase in cysteamine toxic effects." FDA, Review of an Amended Request for Orphan Drug Designation re: Procysbi, at 2, 7 (Nov. 29, 2012). Throughout this lengthy back-and-forth, both the sponsor and OOPD were following FDA's comparable safety requirement, and no one suggested that PROCYSBI was not at least as safe as the prior drug.

180. The sponsor finally prevailed in 2013 when OOPD agreed at last to award ODE to PROCYSBI based on a major contribution to patient care finding. At the time, OOPD staff indicated that PROCYSBI had a "Favorable Tolerability Profile" and noted that "treatment-emergent adverse events (TEAEs) showed continuous decline." FDA, Review of Amended Request for Orphan Drug Designation, Procysbi (June 13, 2013). OOPD staff also quoted the responsible review division as follows:

> The reviewer's overall conclusions with the review of all the safety information submitted in support of the NDA were that ***the safety profile for the delayed-release cysteamine product was similar to***

> [that of the prior drug] although a higher incidence of GI AEs were observed in the pivotal trial [for PROCYSBI].

Id. (emphasis added). Thus, even at the approval stage for PROCYSBI, comparable safety was found as part of the major contribution to patient care analysis, which is consistent with the longstanding FDA policy described in the *Federal Register*.

181. OOPD next attempts to prove a negative by asserting that its precedents are "devoid of instances in which we refused to find [a major contribution to patient care] for a drug based on a failure to show comparable safety…." Exhibit A at 23. As a threshold problem, there is no way for anyone outside OOPD to realistically verify that claim because there is no public compilation of OOPD's decisions. In any event, OOPD's insistence on a prior precedent in the same exact posture as the present dispute is overly narrow—examples of OOPD applying FDA's comparable safety requirement are easy to find. As just shown, PROCYSBI is one such example.

182. RAVICTI® (glycerol phenylbutyrate) is a second example. RAVICTI was a new version of phenylbutyrate and was intended to treat the same rare disease as prior phenylbutyrates. When its sponsor sought an orphan-drug designation based on an anticipated major contribution to patient care, FDA rejected the request because there was "a lack of objective evidence to support [the sponsor's] claim that [RAVICTI] would have comparable safety and effectiveness profiles as those of [the existing phenylbutyrate products]." FDA, Review of Request for Orphan-Drug Designation, Glyceryl tri (4-phenylbutryate), at 5 (Sept. 2, 2005). FDA further explained that before it would even "consider" the sponsor's major contribution to patient care hypothesis, the sponsor would have to "first demonstrate with reasonable certainty that [RAVICTI] would be at least as safe and as effective as [existing products]." *Id.*

183. OOPD relegates the RAVICTI precedent to a footnote and tries to distinguish it by observing that OOPD was reviewing a request for ODD, as opposed to deciding whether to grant

or break ODE. *See* Exhibit A at 25 n.158 ("This is another example of FDA considering whether there is a plausible hypothesis of clinical superiority, not a demonstration of clinical superiority."). The distinction cuts against OOPD. As discussed, the standard at the ODD stage (a hypothesis) is significantly lower than the standard at the ODE stage (a demonstration). Indeed, the standard at the designation stage is so low that OOPD claims to "generally ***assume*** that the drug provides comparable safety and efficacy." *Id.* at 25 (emphasis added). However, as the RAVICTI decision demonstrates, the assumption of comparable safety can be set aside when it is unreasonable, ***and ODD can be denied on that basis***. If a lack of comparable safety can be cause for FDA to deny a designation based on a major contribution to patient care (where only a hypothesis is required), it follows *a fortiori* that a failure to demonstrate comparable safety is grounds to deny exclusivity based on a major contribution to patient care (where an affirmative demonstration of clinical superiority is required).

184. A third example involves treprostinil, which OOPD entirely failed to address. Treprostinil is an orphan drug that was approved by FDA as an injection in 2002 and as an inhaled product in 2009. Subsequently, the same sponsor sought ODD for an oral version based on a hypothesis that the oral route of administration would provide a major contribution to patient care. OOPD denied that request in March 2012. Paraphrasing FDA's statements in the *Federal Register*, OOPD's denial letter stated that the major contribution to patient care pathway "is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug." Ltr. from Gayatri Rao, OOPD to Rex Mauthe, United Therapeutics Corp. re: Designation request #11-3621 at 2 (Mar. 9, 2012). The rest of OOPD's reasoning is redacted in the public copy of the letter, *see id.*, but context suggests that the major contribution to patient care hypothesis was rejected because the sponsor had not shown comparable safety or efficacy.

185. The OOPD memorandum supporting the treprostinil denial likewise states that the major contribution to patient care pathway "is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug." FDA, Review of Request for Orphan Drug Designation, trepronstinil diethanolamine at 7-8 (Feb. 27, 2012). The public version is also heavily redacted, but it reveals enough to know that OOPD concluded that, although "the oral tablet formulation may be more convenient to patients, it does not appear to provide [a major contribution to patient care] over the inhaled formulation." *Id.* at 8.

186. In short, a fair presentation of OOPD's "past precedents" confirms the longstanding policy that FDA described in the *Federal Register*. OOPD's effort to pretend that the policy does not exist is a stark violation of the APA.

187. Equally stark is OOPD's failure to identify any relevant agency precedent for the policy standard that the agency did apply in the Decision Letter.

188. According to OOPD, "[f]or a drug to make a [major contribution to patient care], the drug should provide adequate safety to meet the approval standard (not necessarily the same or greater safety as a previously approved drug)." Exhibit A at 32. By appearances, that is a brand new standard, created and applied to break Xywav's ODE. And as above, it is a new standard created without forthright acknowledgment of the prior standard, without adherence to the procedures FDA must follow when it modifies an advisory opinion, without any discussion or acknowledgment of the reliance interests affected by the change, and without any discussion or acknowledgment of how the new policy affects the breadth of what, until now, has been a "narrow category." Exhibit A at 9. Under the new rule, through the mechanism of interpreting its own regulation, FDA has conferred on itself very broad discretion to break ODE, or grant a serial

exclusivity, by deeming clinically superior essentially any new drug that offers new convenience to patients and is safe enough to be approved.

D. OOPD Failed to Address Prior Agency Determinations That Once-Nightly Dosing Does Not Provide a Major Contribution to Patient Care.

189. FDA has released only a fraction of the documents relevant to its decision to break Xywav's exclusivity and approve Lumryz. However, the records released to date reflect at least three prior determinations by FDA staff indicating that Avadel had not demonstrated that Lumryz would provide a major contribution to patient care.

190. ***First***, in 2016, OOPD itself rejected Avadel's claim that once-nightly dosing provides a major contribution to patient care. OOPD staff found that Avadel's arguments and evidence could not even support a hypothesis that once-nightly dosing would provide a major contribution to patient care over Xyrem (the only marketed oxybate product at that time). OOPD sent Avadel a letter stating as much. *See supra* p. 14 (discussing 2016 OOPD Review, Exhibit B, and 2016 Ltr. to Avadel, Exhibit C).

191. The Decision Letter does not acknowledge that determination at all. The Decision Letter describes OOPD's letter to Avadel merely as a request that Avadel "provide additional support for its hypothesis for clinical superiority." *See* Exhibit A at 16 & n.109. The Decision Letter does suggest that Avadel's hypothesis was accepted by both OOPD and the Review Division in January 2018, *see id.* at 17, but the key documents from 2017 have not been disclosed, and the 2018 letter accepted only a hypothesis of greater safety. *See* Jan. 8, 2018 Ltr. from OOPD to M. Scarola, *supra* p. 35. Avadel's announcement of the 2018 decision likewise stated only that ODD was granted based on a hypothesis that its drug "may be safer." Avadel, *Press Release: Avadel Pharmaceuticals Receives Orphan Drug Designation from FDA for FT 218 for the Treatment of*

Narcolepsy (Jan. 10, 2018).[20] The available records thus indicate that FDA never accepted a hypothesis that once-nightly dosing would provide a major contribution to patient care.

192. ***Second***, when Avadel submitted its NDA for Lumryz in December 2020, Avadel included a request for priority review. Although the relevant documents have not been disclosed, the Review Division rejected Avadel's request in February 2021. The Review Division later observed that Avadel's arguments in support of its clinical superiority claim were essentially the same as the arguments that the Review Division had rejected in the priority review context. *See* Exhibit D at 8-9.

193. In the Decision Letter, OOPD addressed the relationship between priority review and clinical superiority. *See* Exhibit A at 41. OOPD even conceded that there is "some practical overlap" in the standards for clinical superiority and priority review. *Id.* But OOPD entirely failed to disclose the fact that the Review Division had pointed to the overlap in standards and arguments as a reason to reject Avadel's arguments.

194. ***Third***, OOPD failed to disclose that the Review Division rejected Avadel's major contribution to patient care theory "*after* [it] conducted a full and substantive review of the relevant marketing application." Exhibit A at 41 (emphasis in the original). The Review Division was unequivocal that Avadel had failed to discharge its burden. *See* Exhibit D at 10 ("While the once-nightly regimen of Lumryz will be more convenient for patients than a twice-nightly regimen, that attribute cannot be considered a major contribution to patient care."); *see id.* at 12 (Avadel provided "no evidence … that Lumryz is clinically superior").

[20] https://investors.avadel.com/news-releases/news-release-details/avadel-pharmaceuticals-receives-orphan-drug-designation-fda-ft.

195. Given this record, the APA required OOPD to candidly acknowledge its prior adverse determination in 2016, acknowledge the Review Division's prior adverse determinations in February 2021 and August 2021, and provide a reasoned explanation for reversing all three decisions. *See, e.g.*, *MISO Transmission*, 45 F.4th at 264 (An agency is "entitled to change its mind. But to do so, it must provide a 'reasoned explanation' for its decision to disregard 'facts and circumstances that' justified its prior choice.") (citation omitted).

196. The need for a reasoned explanation is particularly acute here because Avadel's burden ***increased over time*** between 2016 (when a hypothesis would have been sufficient but was found lacking) and 2023 (when actual proof by competent evidence was required). *See* 21 U.S.C. § 360cc(c)(1) (FDA "shall require such sponsor … to demonstrate" clinical superiority "as a condition of such exclusive approval."). Avadel's burden also increased during that period due to the introduction of a safer product in Xywav. OOPD has not explained how Avadel's evidence and arguments in 2023 could satisfy a more demanding standard than the one Avadel failed to meet in 2016 and 2021.

197. Separately, the need for a reasoned explanation is heightened given the apparent violation of FDA's internal procedures. Because disagreements between FDA components with shared responsibility for important regulatory decisions are foreseeable, FDA has adopted policies establishing both a general process for resolving cross-center disagreements, *see supra* p. 17, and a specific process for resolving cross-center disagreements that pertain to orphan-drug exclusivity, *see supra* p. 17. So far, there has been no public indication that OOPD followed either procedure. Instead, OOPD appears to have indulged in forum shopping, ultimately settling on a second opinion from a device review team in CDRH.

198. That choice appears unprecedented. Jazz has not identified any prior example where a ***device*** team in CDRH was asked to opine on the potential clinical superiority of a ***drug***. Indeed, Jazz has not identified any prior example of CDRH being involved in the implementation of the Orphan Drug Act. Nor has Jazz been able to identify a prior instance where the opinion of medical device reviewers was given precedence over that of the Review Division with jurisdiction over the class of drugs in question. *Cf. Tummino*, 603 F. Supp. 2d at 523-24 (FDA acted arbitrarily and capriciously where it "wrested control over the decision-making" on a new drug application from the "staff that normally would issue the final decision").

E. OOPD's Weighing of the Speculative Impacts of Once-Nightly Dosing Against The Established Benefits of Lowered Sodium Was Arbitrary, Capricious, and an Abuse of Discretion.

199. "One of the basic procedural requirements of administrative rulemaking is that an agency must give adequate reasons for its decisions. An agency therefore must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made. … And while the agency action under review is entitled to a presumption of regularity, that presumption is not to shield an action from a thorough, probing, and in-depth review. Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, the court must undo its action." *Cigar Assoc. of Am.*, 436 F. Supp. 3d at 84 (cleaned up) (citations omitted). OOPD's decision to break Xywav's ODE cannot satisfy that standard.

200. OOPD's desire to approve Lumryz notwithstanding Xywav's ODE led it to declare that a ***less safe*** drug can nonetheless be considered the ***superior*** product. In doing so, OOPD claimed to be balancing the established cardiovascular benefits of dramatically lowered sodium against the hypothetical impact that once-nightly dosing would have in this patient population.

According to OOPD, the "medical" benefits to be gained from once-nightly dosing "outweigh" the greater safety associated with lower sodium.

201. OOPD's balancing was arbitrary and capricious. As an initial matter, OOPD's balancing was not evidence-based. OOPD conceded that there "is no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav," Exhibit A at 27, which means that there is no evidence that Lumryz provides additional medical benefits for narcolepsy patients. OOPD also disclaimed reliance on the materials submitted by Avadel and claimed to rely solely on its own "expertise and consultation of the literature." *Id.* at 39. However, it is well-established that the APA requires more than "puffery about agency expertise." *NRDC v. Regan*, 67 F.4th 397, 412 (D.C. Cir. 2023) (Pan, J., concurring).

202. It is questionable whether FDA actually brought its expertise to bear. The experts in the Review Division appear to have concluded that the relevant standards were not met. In response, OOPD appears to have (1) gone around the agency's established chain of command; (2) departed from FDA's established procedure for cross-center dispute resolution; (3) obtained a second opinion from device reviewers in a different center; and (4) used that second opinion to strong arm the actual subject matter experts into reversing their position.

203. In all events, OOPD's assertion that once-nightly dosing is more important than eliminating nightly consumption of more than 1,500 mg of sodium is ***not*** supported by "the literature." As described below, OOPD had to cheat on both sides of the scale to reach that conclusion. On one side, OOPD minimized the importance of reducing chronic sodium intake. On the other, OOPD exaggerated the importance of once-nightly dosing. The result is an alleged "balancing" that is not based on evidence or science and ignores the clinical realities of narcolepsy and how the disease impacts patients.

1. OOPD Wrongly Minimized the Established Benefits of Lower Sodium Therapy for Narcolepsy Patients.

204. The Decision Letter does not reflect any serious consideration of the harms associated with elevated sodium intake. There is no evidence, for instance, of any effort by OOPD to consult with the officials at the agency with expertise in cardiovascular health or cardiovascular risk. Nor is there any evidence that OOPD consulted with those in the agency responsible for FDA's ongoing efforts to reduce sodium intake. *See, e.g.*, 88 Fed. Reg. 21148 (proposed Apr. 10, 2023) (proposing to authorize the use of salt substitutes in standardized foods); 86 Fed. Reg. 57156 (Oct. 14, 2021) (finalizing sodium reduction goals for commercially processed, packaged, and prepared foods).

205. In particular, the Decision Letter failed to address the magnitude and clinical impact of the sodium reduction achieved by Xywav. At the highest approved dose of oxybate, switching to Xywav eliminates more than 1,500 mg of daily sodium. Authoritative publications show that reducing daily sodium by 1,000 mg per day is clinically meaningful and will improve health. In 2019, the National Academy of Sciences, Engineering, and Medicine (NASEM) committee on *Dietary Reference Intakes for Sodium and Potassium* comprehensively reviewed the relevant literature and concluded that a 1,000 mg reduction in daily sodium intake reduced the risk of cardiovascular disease and hypertension by 27% and 20% in individuals without preexisting disease, respectively. *See* NASEM, *Dietary Reference Intakes for Sodium and Potassium*, *supra* p. 68. This evidence was used to establish the Chronic Disease Risk Reduction recommended upper limit of sodium intake of 2,300 mg/day, which was jointly adopted by HHS and the U.S. Department of Agriculture in their *Dietary Guidelines for Americans*. That recommended daily limit was subsequently accepted and endorsed by both FDA and the Centers for Disease Control. In particular, FDA found that more than 90% of Americans exceed this limit.

206. OOPD also minimized the safety benefit provided by Xywav by asserting that clinically meaningful reductions in daily sodium are easily achieved through other means. After conceding that even "patients who are not sensitive to sodium could also benefit from a reduction in sodium," OOPD claimed that the benefit is outweighed by once-nightly dosing because "there are other ways such patients may reduce sodium in their diet." Exhibit A at 32. That assertion is not further explained by OOPD, but it is contradicted by numerous prior FDA statements recognizing that consumers often ***cannot*** achieve clinically significant reductions in sodium through dietary changes alone.

207. For instance, a recent FDA guidance states, "Multiple public health efforts have attempted to reduce sodium intake over the past 40 years. However, these efforts, which mainly included education initiatives, have generally not been successful." FDA, *Final Guidance for Industry: Voluntary Sodium Reduction Goals*, *supra* p. 31, at 6 (citation omitted). The guidance also states that "without an overall reduction of the level of sodium in the food supply, consumers will not be able to reach intakes recommended by the *Dietary Guidelines*." *Id.* Similar statements by FDA abound. *See, e.g.*, FDA Statement, *To Improve Nutrition and Reduce the Burden of Disease, FDA Issues Food Industry Guidance for Voluntarily Reducing Sodium in Processed and Packaged Foods* (Oct. 13, 2021)[21] ("Although many consumers may want to reduce their sodium intake, about 70% of the sodium we eat comes from packaged, processed and restaurant foods, making it challenging to limit sodium."); FDA News Release, *FDA Issues Draft Guidance to Food Industry for Voluntarily Reducing Sodium in Processed and Commercially Prepared Food* (May

[21] https://www.fda.gov/news-events/press-announcements/improve-nutrition-and-reduce-burden-disease-fda-issues-food-industry-guidance-voluntarily-reducing.

31, 2016)[22] ("Because the majority of sodium in our diets comes from processed and prepared foods, consumers are challenged in lowering their sodium intake themselves.").

208. Like the food supply, prescription drugs are often a significant source of dietary sodium that cannot easily be eliminated. *See, e.g.*, Chao Zeng et al., *Sodium-Containing Acetaminophen and Cardiovascular Outcomes in Individuals With and Without Hypertension*, 43 Eur. Heart J. 1743, 1744 (2022) ("In addition to dietary sodium intake, sodium-containing drugs are another source of sodium intake as it is widely used in drug preparations for enhancing solubility or disintegration."). For that reason, public health advocates (including FDA officials) have long urged the development and use of low sodium alternative medications. *See, e.g.*, *FDA Sodium Labeling Requirements for Prescription Drugs Recommended*, The Pink Sheet (Aug. 12, 1991)[23] (quoting comments from FDA officials that healthcare providers "need to be cognizant of the amounts of sodium in prescribing medications" and that manufacturers "should be encouraged to voluntarily produce drug products with lower sodium content"); Ana Szarfman et al., *Letter to the Editor: Declaring the Sodium Content of Drug Products*, 333 N. Engl. J. Med. 1291 (1995) (noting that FDA "will be working with pharmaceutical organizations to develop voluntary sodium labeling for prescription drugs"); Jacob George et al., *Association Between Cardiovascular Events and Sodium-Containing Effervescent, Dispersible, and Soluble Drugs: Nested Case-Control Study*, 347 BMJ, 4 (2013) ("Our results suggest that physicians should prescribe sodium-containing formulations with caution and only if there are compelling reasons to do so."); Aletta Shutte & Bruce Neal, *The Sodium Hidden in Medication: A Tough Pill to Swallow*, 43 Eur. Heart J. 1756, 1758 (2022) ("The weight of the evidence makes ongoing inaction on sodium-containing

[22] https://www.fda.gov/news-events/press-announcements/fda-issues-draft-guidance-food-industry-voluntarily-reducing-sodium-processed-and-commercially.

[23] https://pink.pharmaintelligence.informa.com/PS019569/FDA-SODIUM-LABELING-REQUIREMENTS-FOR-PRESCRIPTION-DRUGS-RECOMMENDED.

medications untenable. … [T]he enormous doses of sodium that can be consumed inadvertently by unsuspecting consumers requires urgent action.").

209. OOPD thus ignored an important aspect of the problem—one that FDA itself and a raft of medical experts have recognized. It is difficult for many consumers to reduce dietary sodium. And sodium-containing medications are a significant part of that dietary sodium problem. Thus, in many cases, the only practicable way for a narcolepsy patient taking sodium oxybate to eliminate 1,500 mg of daily sodium is to make the switch to Xywav.

2. OOPD Had No Basis to Conclude that Once-Nightly Dosing Provides Additional Medical Benefits for Narcolepsy Patients.

210. In addition to minimizing the risks of elevated sodium, OOPD clearly overstated the supposed benefits of once-nightly dosing.

211. Broadly speaking, OOPD and CDRH made four fundamental errors. They first failed to objectively describe the sleep experience of narcolepsy patients. They then compounded the problem by failing to discuss the literature demonstrating the significant sleep improvements that narcolepsy patients experience once they are successfully on twice-nightly oxybate therapy. They also failed to acknowledge the complete absence of evidence that Lumryz is any more effective at improving sleep architecture than any other oxybate product. Finally, they failed to ensure that their position aligned with FDA's prior decisions regarding disrupted nighttime sleep. Each error was independently arbitrary and capricious.

212. On the first point, the established medical consensus is that narcolepsy patients generally report much poorer sleep quality and significantly more frequent nocturnal awakenings than the general population:

Table 3—The number of nightly awakenings reported by patients with narcolepsy and by comparator groups

	Nightly Awakenings		
Study	Patients with Narcolepsy	Comparator	p value
Parkes et al., 1998[31]	4.5	1.4	0.01
Rosenthal et al., 1990[33]	4.6	1.3	< 0.001
Bruck et al., 1996[22]	3.3	1.3	< 0.005

In each study, the number of awakenings among patients with narcolepsy was more than twice that reported by the comparator.

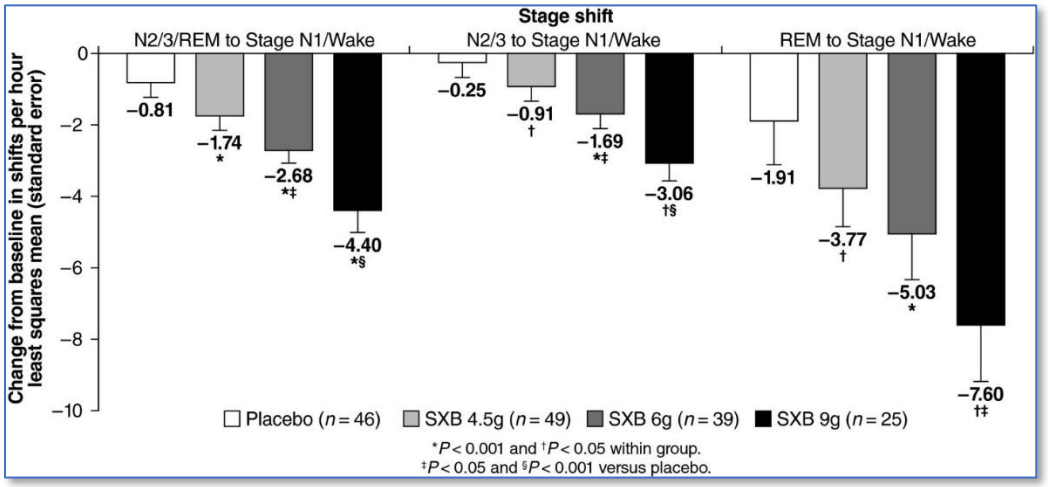
Thomas Roth et al., *Disrupted Nighttime Sleep in Narcolepsy*, 9(9) J. Clin. Sleep Med. 955, 960 Tbl. 3 (2013). Narcolepsy patients also experience significantly more nighttime "arousals" (also called "mini-awakenings") than the general population:

	Arousal Index		Number of Arousals	
Study	Patients with Narcolepsy	Normal Controls	Patients with Narcolepsy	Normal Controls
Frauscher et al., 2011[23]	21.6	8.7[a]	–	–
Jiménez-Correa et al., 2009[26]	–	–	78.38	29.13[b]
Mukai et al., 2003[30]	–	–	–	–
Khatami et al., 2007[27]	–	–	–	–
Khatami et al., 2008[28]	–	–	–	–

Id. at Tbl. 4. Studies showing that narcolepsy patients experience around four full awakenings and around 80 arousals each night provide critical context that should have informed OOPD's assessment of the value of once-nightly dosing.

213. OOPD also failed to address the ways in which twice-nightly oxybate improves these and other measures of sleep quality. "Sleep architecture" refers to a broad set of quantitative parameters that can be measured by polysomnography ("PSG"). OOPD asserts that twice-nightly oxybate therapy "disrupts sleep architecture." Exhibit A at 32-33. That assertion is not true, and it ignores abundant literature showing that twice-nightly oxybate therapy significantly ***improves*** sleep architecture in narcolepsy patients.

214. For example, the CDRH consult describes the number of shifts between stages of sleep as an important measure of sleep architecture and identifies reducing the number of stage shifts as an important goal. *See* Exhibit F at 6. Treatment with twice nightly oxybate has been shown to significantly reduce stage shifts relative to placebo in narcolepsy patients:



Thomas Roth et al., *Effect of Sodium Oxybate on Disrupted Nighttime Sleep in Patients With Narcolepsy*, 26(4) J. Sleep Rsch. 407, Figure 2 (2017).

215. Jazz is not aware of any data or literature suggesting that once-nightly oxybate is more effective at reducing stage shifts than twice-nightly oxybate, and OOPD cited none.

216. Another relevant metric is the amount of time spent awake after sleep onset ("WASO"). OOPD suggests that twice-nightly dosing harms sleep quality because waking up to take a second dose will "increase WASO." Exhibit A at 12 & n.65 (citing Exhibit F at 6). Once again, OOPD failed to provide critical context. Studies have shown that narcolepsy patients already experience significantly elevated WASO:

	WASO	
Study	**Patients with Narcolepsy**	**Normal Controls**
Frauscher et al. 2011	41.3 min	33.1 min
Mukai et al. 2003	3.9%	1.0%
Khatami et al. 2007	31.5 min	10.4 min
Khatami et al. 2008	39.5 min	11.2 min

Roth 2013, *supra* p. 72, at 960 Tbl. 4.

217. Similar WASO data was actually in the literature reviewed by CDRH. The CDRH consult cites to a 2021 summary of PSG measures in narcolepsy patients. *See* Exhibit F at 6 n.36. That summary reports average WASO for type 1 narcolepsy patients of more than 60 minutes per night. Ye Zhang et al., *Polysomnographic Nighttime Features of Narcolepsy: A Systematic Review and Meta-Analysis*, 58 Sleep Med Revs. 101488, 9 Tbl. 3 (Apr. 5, 2021). That narcolepsy patients have significantly elevated WASO is another fact that should have informed OOPD's assessment of once-nightly dosing.

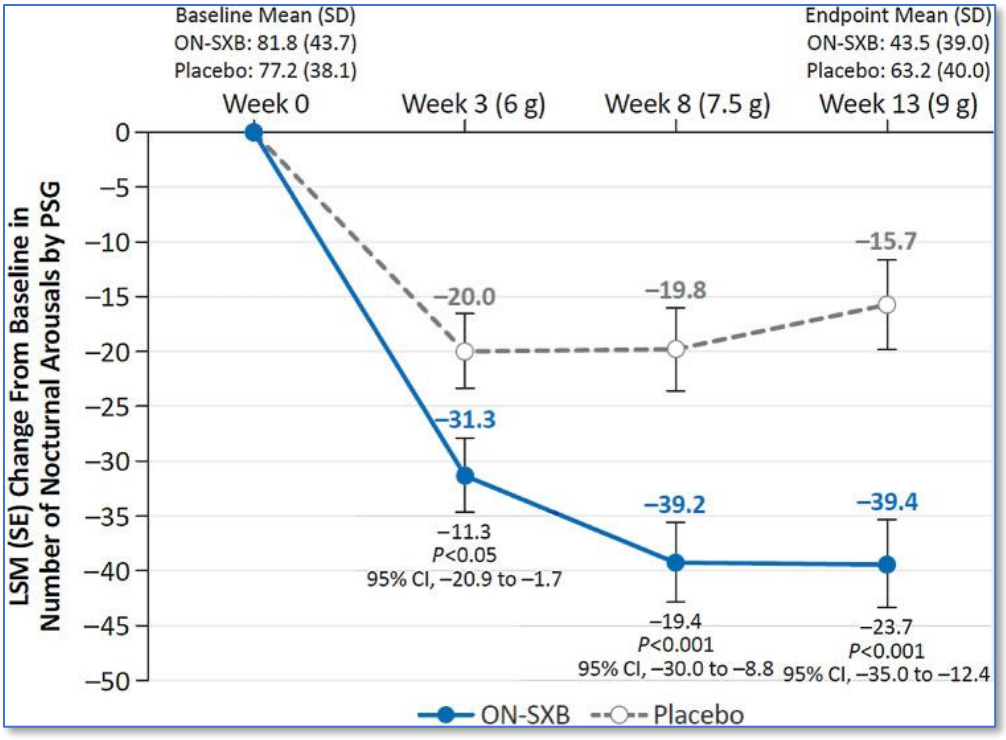
218. More importantly, OOPD entirely ignored data in the literature demonstrating that twice-nightly oxybate therapy does not increase, but significantly ***reduces*** WASO in narcolepsy patients. *See, e.g.*, Jed Black et al., *The Nightly Use of Sodium Oxybate Is Associated with a Reduction in Nocturnal Sleep Disruption: A Double-Blind, Placebo-Controlled Study in Patients with Narcolepsy*, 6(6) J. Clin. Sleep Med. 596, 599 (2010) ("WASO was significantly decreased in the 9 g/night group at 8 weeks [by an average of 22 minutes]. There was a significant dose relationship for the decrease in WASO at 8 weeks as well ($p = 0.0075$).").

219. Again, Jazz is not aware of any data or literature suggesting that once-nightly oxybate is more effective at reducing WASO in narcolepsy patients than twice-nightly oxybate. And again, OOPD cited none.

220. OOPD also focuses on nighttime arousals, noting that "nocturnal arousals should be avoided." Exhibit A at 28. OOPD suggests that eliminating the arousal associated with a second

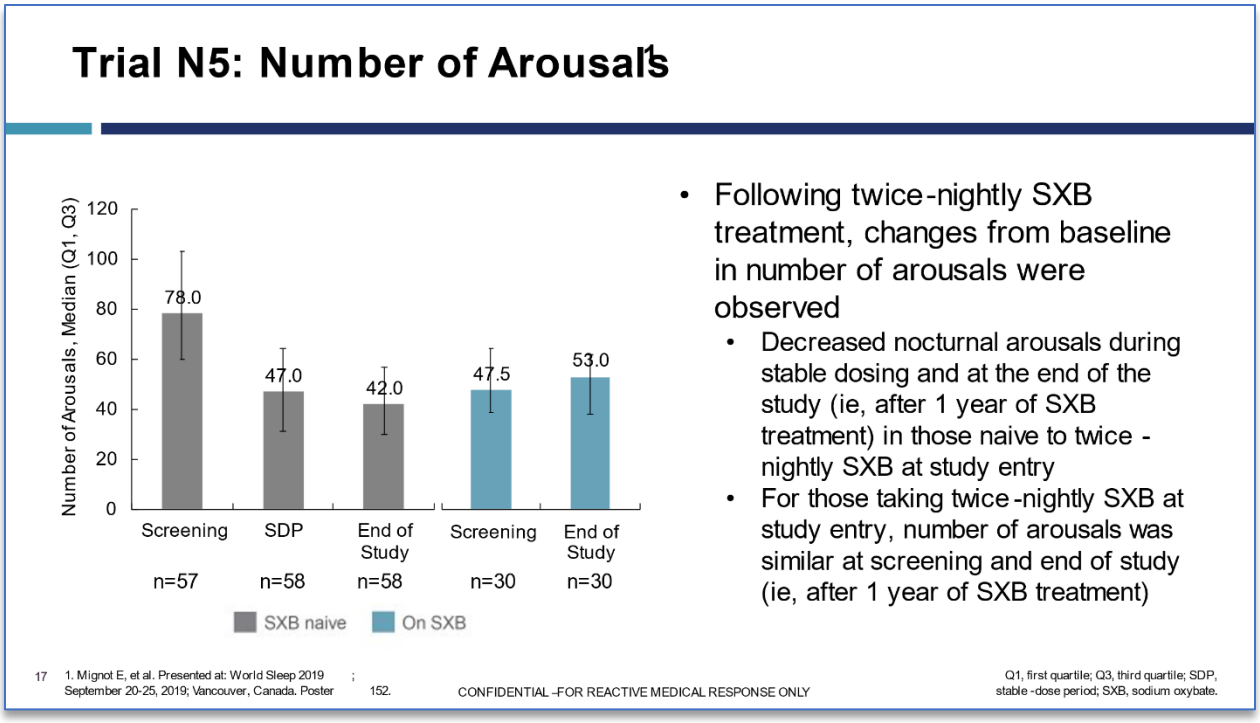
dose is a "medically relevant" benefit for narcolepsy patients. *Id.* at 29. OOPD goes so far as to assert that once-nightly dosing will allow narcolepsy patients taking oxybate to enjoy "normal" sleep. *See, e.g.*, *id.* ("The dosing regimen of Lumryz provides an opportunity for narcolepsy patients ***to achieve normal sleep architecture***, which is not a possibility for a patient on Xyrem or Xywav.") (emphasis added; quotation marks omitted).

221. OOPD's suggestion that Lumryz will allow narcolepsy patients to achieve "normal" sleep is egregiously wrong. Avadel itself recently published an article on this point. Avadel's pivotal trial compared Lumryz to placebo. One of the secondary endpoints measured in the trial was the number of nocturnal arousals as measured by PSG data. All participants were adult patients diagnosed with narcolepsy. At baseline (*i.e.*, the start of the trial), PSG data indicated that the participants averaged ***about 80 arousals*** each night. After thirteen weeks of treatment, the placebo group showed minor improvement, while patients on Lumryz did significantly better. But the Lumryz patients did not achieve "normal" sleep. Rather, as shown in the below figure—which, again, was published by Avadel—after 13 weeks of treatment with Lumryz, narcolepsy patients still experienced ***about 40 arousals*** each night:



Thomas Roth et al., *Effect of FT218, a Once-Nightly Sodium Oxybate Formulation, on Disrupted Nighttime Sleep in Patients with Narcolepsy: Results from the Randomized Phase III REST-ON Trial*, 36(4) CNS Drugs 377, 380 (2022). Although it claimed to have reviewed "the literature," OOPD failed to acknowledge this Avadel-published evidence.

222. Studies of Xyrem show remarkably similar results. For instance, in a study that compared narcolepsy patients who had never before received oxybate with a group of established oxybate patients, PSG data indicated that the "naïve" patients experienced about 78 nocturnal arousals at baseline, whereas established patients experienced about 47 nocturnal arousals. After a full year of treatment with Xyrem, the number of nocturnal arousals observed in the "naïve" group had dropped to about 42 nocturnal arousals, while the number of arousals experienced by the established patients had not changed:



See Emmanuel Mignot et al., *Effects of Sodium Oxybate Treatment on Sleep Architecture in Paediatric Patients with Narcolepsy*, 64 Sleep Med. S256 (2019). Again, OOPD and CDRH completely failed to discuss the data showing the reductions in arousals associated with twice-nightly oxybate therapy.

223. Articles published by both companies thus show that narcolepsy patients treated with oxybate continue to experience ***roughly 40 nighttime arousals every night***, regardless of which drug is used. Given that reality, there was no legitimate basis for OOPD to claim that avoiding the awakening needed to take a second dose of medicine will somehow return narcolepsy patients to "normal" sleep.

224. Finally, OOPD's position that avoiding a single awakening is a medically relevant benefit cannot be squared with FDA's past statements to Jazz. Over the years, Jazz has consulted with the Review Division about the possibility of developing oxybate as a treatment for disrupted nighttime sleep many times, but the Review Division denied all of Jazz's requests.

225. For instance, in a 2007 letter, the Review Division acknowledged that Xyrem "has a reproducible beneficial effect on the duration of Stage 1 sleep, the duration of Stage 3 and 4 sleep, the duration of non-REM sleep, and delta power," which are all well-known, important parameters of sleep architecture. Ltr. from Russel Katz, DN1, FDA to Jennifer Ekelund, Jazz Pharms., at 1 (2007). The Review Division nevertheless refused to approve Xyrem as a treatment for disrupted nighttime sleep given "uncertainty" about which sleep measures are clinically relevant and a lack of "knowledge" regarding "the clinical meaning of a change in any of these specific PSG measures." *Id.* at 2.

226. In a 2013 letter, the Review Division reiterated that it still did not consider the improvements in sleep architecture caused by oxybate therapy to be "clinically meaningful" for narcolepsy patients. Ltr. from Billy Dunn, DN1, FDA to Joel Selcher, Jazz Pharms. re: Meeting Request-Written Responses, at 4 (Dec. 7, 2013).

227. Most recently, in December 2020, the Review Division discouraged Jazz from conducting a planned clinical trial to objectively measure the impact of Xywav on the sleep architecture of narcolepsy patients and told Jazz that FDA would not allow the results of any such trial to even be disclosed in the Clinical Studies section of the Prescribing Information for Xywav. Ltr. from Eric Bastings, DN1, FDA to Arthur Merlin d'Estreux, Jazz Pharms. re: Meeting Request-Written Responses, at 5-6 (Dec. 10, 2020).

228. That the Review Division has for the past 15 years overseen Jazz's efforts to develop oxybate as a treatment for disrupted nighttime sleep underscores that the physicians and other officials in that Review Division are the actual sleep experts within FDA when it comes to oxybate. That, in turn, underscores the extraordinary nature of OOPD's decision to seek a second opinion from CDRH and then to rely on the CDRH opinion and the Review Division's about-face

without even acknowledging any of the statements the Review Division had made to Jazz regarding disrupted nighttime sleep.

229. Moreover, the Review Division's repeatedly stated position that statistically significant and reproducible improvements in multiple sleep architecture measures are not clinically meaningful for narcolepsy patients is entirely at odds with the speculation from CDRH and OOPD that the elimination of a single nighttime awakening will be a "medically relevant" benefit for narcolepsy patients.

3. OOPD's Assessment of the Convenience Associated with Once-Nightly Dosing Was Also Arbitrary and Capricious.

230. OOPD also claims that a major contribution to patient care exists because once-nightly dosing is "significantly more convenient for patients." Exhibit A at 29. It is not clear whether OOPD intended to present convenience as an independent ground for its conclusion. To the extent it did, the suggestion is arbitrary and capricious.

231. As an initial matter, OOPD originally found in 2016 that the convenience of once-nightly dosing could not even support a hypothesis of a major contribution to patient care. *See* 2016 OOPD Review, Exhibit B; 2016 Ltr. to Avadel, Exhibit C. The Review Division similarly concluded in 2021 that Avadel had failed to prove that the convenience associated with once-nightly dosing would provide a major contribution to patient care. Exhibit D. OOPD has not adequately explained its reversal of those determinations.

232. In addition, OOPD's assessment of the convenience provided by once-nightly dosing was based in part on an unreasonable overstatement of the difficulty of taking a second dose. OOPD contends that "it usually takes ***at least*** 5 to 15 minutes to fall back asleep after taking the second dose." Exhibit A at 28 (emphasis added). OOPD claims that the 5-to-15 minute timeframe is the "minimum" amount of time needed to fall back asleep. *Id.* at 29. That assertion

is not based on any evidence. Instead, it is based on a misleading and out-of-context reading of a warning contained in the labeling for oxybate products.

233. Oxybate has strong hypnotic (*i.e.*, sleep inducing) effects, and patients can fall asleep abruptly after taking oxybate. If patients do not understand that effect, they could be hurt. To guard against harm, the Medication Guides for Xyrem and Xywav both provide:

> [Xyrem / Xywav] can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night. Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.

Notably, the Medication Guide for Lumryz contains the exact same warning.

234. That warning appears to be the sole support for OOPD's estimate of the time needed to fall back asleep. *See* Exhibit A at 28 ("Both Xyrem and Xywav labeling explain that after a dose, it usually takes at least 5 to 15 minutes to fall asleep, ***which means*** it usually takes at least 5 to 15 minutes to fall back asleep after taking the second dose"). Obviously, the warning was not intended to, and does not, address the amount of time it takes to fall back asleep after consuming a second dose of oxybate. Indeed, the message conveyed by the labeling for all three products is that sleep occurs "very quickly" after dosing and can occur "within 5 minutes." There is no basis for CDRH or OOPD to describe 5 to 15 minutes as a "minimum."

235. OOPD's convenience argument is based primarily on the PROCYSBI precedent discussed above, which also appears to have helped sway the Review Division. *See supra* pp. 58-60. It is true that PROCYSBI reduced dosing frequency from four times a day to twice a day, thereby eliminating an overnight dose. However, OOPD rejected the idea that this improved dosing schedule constituted a major contribution to patient care in 2009. *See* Memo from Vaccari, *supra* p. 59, at 1 ("A FDA-approved cysteamine product that allows every 12 hour dosing instead of

every 6 hours would be a contribution to patient care. However, this type of change in administration schedule does not meet the regulatory definition of a 'major' contribution to patient care.").

236. It is also true that OOPD eventually reversed itself and found a major contribution to patient care in 2013. *See* 2013 Procysbi Review, *supra* p. 59, at 9-10. But that reversal was based on "the unique nature of the drug and the disease," *id.* at 9, including three factors not present here.

237. First, the sponsor of PROCYSBI submitted data to show that the pharmacokinetic and pharmacodynamic profile of the prior drug was such that 6-hour dosing was "absolutely key" to maintaining blood concentrations at a therapeutic level.

238. Second, the sponsor submitted data showing that 67 to 77% of patients taking the prior product were unable to maintain 6-hour dosing. In other words, the sponsor of PROCYSBI submitted ***data*** to ***prove*** that up to three quarters of all patients were likely not receiving a therapeutic dose. That proof removed the need to speculate about the impact of the new dosing schedule, as OOPD does here.

239. Third, PROCYSBI is approved for pediatric use in children as young as a year old. OOPD appears to have been swayed by an in-person meeting with two families with elementary-school aged children, 2013 Procysbi Review, *supra* p. 59, at 5, and reports from two adolescents, *id.* at 9. It may be appropriate for OOPD to be give special weight to the needs of pediatric patients and their care-givers when making a major contribution to patient care decision. But Lumryz has not even been studied in a pediatric or adolescent population, and it is only approved for adult use. The special consideration that OOPD gave to the sponsor of PROCYSBI is plainly not appropriate for an adult-only product like Lumryz.

240. Finally, it bears repeating that increased convenience cannot justify the increased cardiovascular risk posed by nightly intake of up to 1,640 mg of sodium. FDA's decision to elevate convenience over cardiovascular health was arbitrary and capricious.

* * *

241. For all of the above reasons, FDA's approval of Lumryz violated section 527(a) and the unexpired ODE protecting Xywav.

CAUSES OF ACTION

COUNT ONE – Unlawful Agency Action, 5 U.S.C. § 706(2)

242. Jazz repeats and incorporates paragraphs 1 through 241 as if fully stated herein.

243. Xywav obtained and is protected by orphan drug exclusivity until July 2027. Xywav and Lumryz are the "same drug for the same disease or condition" because they contain the same active moiety and are intended for the same use for the treatment of narcolepsy. 21 U.S.C. § 360cc(a). As a result, FDA lacked authority to approve Lumryz unless one of the statutory exceptions to ODE applies.

244. Neither statutory exception to ODE applies. There is no oxybate shortage and Jazz did not consent to FDA's approval of Lumryz. *See* 21 U.S.C. § 360cc(b).

245. The Orphan Drug Act does not permit FDA to break through Xywav's unexpired orphan drug exclusivity on the ground that a different sponsor is seeking approval for an allegedly clinically superior drug. *See* 21 U.S.C. § 360cc(c). Thus, the agency's determination of clinical superiority regarding Lumryz is irrelevant.

246. In the alternative, FDA's determination of clinical superiority is inconsistent with FDA's own regulations and reflects an unexplained departure from multiple agency policies. It is also arbitrary and capricious because it relies on unsupported speculation, minimizes the risks associated with elevated sodium intake, exaggerates the impact of once-nightly dosing, and

fundamentally fails to account for the reality of narcolepsy as reflected in the literature on which the agency purported to rely (including articles published by Avadel).

247. FDA's approval of Lumryz is final agency action for which Jazz has no other adequate remedy and is subject to review under 5 U.S.C. § 704.

248. Any regulations or policies FDA may cite to justify this unlawful action are inconsistent with the Orphan Drug Act and thus invalid.

249. For all of these reasons, FDA's approval of Avadel's application must be held unlawful and set aside.

PRAYER FOR RELIEF

WHEREFORE, Jazz respectfully asks the Court to order the following relief:

A. Declare that Defendants' approval of Lumryz was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law;

B. Declare that Defendants' approval of Lumryz was in excess of FDA's statutory authority and was made without observance of procedure required by law;

C. Hold unlawful and set aside Defendants' approval of Lumryz;

D. Award costs and reasonable attorney fees to the extent permitted by law; and

E. Grant such other relief as this Court may deem just and proper.

Dated: June 22, 2023

Respectfully submitted,

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