UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

JAZZ PHARMACEUTICALS, INC.,	
Plaintiff,	
v.	
XAVIER BECERRA, et al.,	
Defendants,	**Case No. 23-cv-01819 (APM)**
and	
AVADEL CNS PHARMACEUTICALS, LLC,	
Defendant-Intervenor.	

MEMORANDUM OPINION

I. INTRODUCTION

The Orphan Drug Act ("ODA") encourages pharmaceutical companies to develop drugs to treat rare diseases or conditions through various economic incentives, including marketing exclusivity for seven years upon final approval from the Food and Drug Administration ("FDA"). Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") and Defendant-Intervenor Avadel CNS Pharmaceuticals, LLC ("Avadel") each manufacture an "orphan drug" for the rare sleep disorder narcolepsy. Jazz was first to bring its narcolepsy drug, Xywav, to market. The FDA approved Xywav in July 2020 and granted Jazz marketing exclusivity for seven years. During an exclusivity period, the ODA generally bars the FDA from approving another orphan drug that is the "same drug for the same disease or condition" as the approved drug. In this case, that meant the ODA generally prohibited the FDA from approving another drug that was the "same drug" as Xywav for a seven-year period.

Approximately three years later, in May 2023, the FDA approved Avadel's narcolepsy drug, Lumryz. Lumryz and Xywav are similar in that they have the same active moiety (oxybate) and treat the same disease or condition, but Lumryz is taken in a single dose before the user goes to sleep. Xywav, on the other hand, requires the user to ingest a second dose within four hours of falling asleep, thereby disrupting the sleep cycle. Under the FDA's longstanding regulatory definition of "same drug" (a term that is not defined by the ODA), an orphan drug is *not* the "same drug" if it is "clinically superior" to an approved drug. The FDA determined that, because of its once-nightly dosing regimen, Lumryz was "clinically superior" to Xywav. The FDA therefore concluded that the two drugs were not the "same drug," and for that reason, the ODA did not bar the FDA from approving Lumryz during Xywav's ongoing exclusivity period. The Agency thus approved Lumryz. It also granted Lumryz its own seven-year period of marketing exclusivity.

Jazz then brought this action challenging the FDA's approval of Lumryz under the Administrative Procedure Act. Jazz asserts that the FDA committed three errors. First, it contends that the Agency incorrectly concluded that Lumryz and Xywav are not the "same drug" and, because they are in fact the "same," the Agency lacked authority under the ODA to approve Lumryz before Xywav's period of exclusivity expired. Second, Jazz asserts that the FDA's approval was arbitrary and capricious because it departed, without explanation, from longstanding agency policy requiring a new orphan drug like Lumryz to have "comparable safety" to the previously approved drug to receive approval. All parties agree that Lumryz contains far more sodium than Xywav and, in that respect, presents a greater health risk to all narcolepsy patients. Third, Jazz argues that the FDA's clinical superiority determination was arbitrary and capricious both because the Agency did not comply with internal dispute resolution procedures and because its findings are inconsistent with the scientific literature.

Now before the court are the parties' cross-motions for summary judgment. The court concludes that (1) the FDA did not err in determining that Lumryz and Xywav are not the "same drug"; (2) the Agency did not inexplicably depart from a "comparable safety" policy because there is no such policy; and (3) the FDA's approval of Lumryz was not arbitrary and capricious. Accordingly, the court denies Jazz's motion and grants the FDA's and Avadel's cross-motions.

II. BACKGROUND

A. Statutory and Regulatory Background

1. The ODA and the FDA's Implementing Regulations

In 1983, Congress passed the ODA as an amendment to the Food, Drug, and Cosmetic Act of 1938. *See* Pub. L. No. 97–414, 96 Stat. 2049 (Jan. 4, 1983). Its purpose was to encourage the development of so-called "orphan drugs," that is, drugs that are "designed to treat a rare disease or condition that historically received little attention from pharmaceutical companies." *Spectrum Pharms., Inc. v. Burwell*, 824 F.3d 1062, 1064 (D.C. Cir. 2016). "When the potential market for a drug is small because the target market is relatively small, it is difficult for a pharmaceutical manufacturer to recover the large research and development costs, and even more difficult to realize a worthwhile return on that investment." *Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30, 31 (D.D.C. 2001). Congress therefore devised the ODA to "reduce the costs" and "provide financial incentives" to develop orphan drugs. 96 Stat. at 2049, § 1(b)(5).

These inducements operate at two stages. A drug in development first must be designated as an "orphan drug" by the FDA. 21 U.S.C. § 360bb.[1] Designation provides the drug sponsor certain financial benefits, including tax credits, assistance with investigations and the approval

[1] Congress made the Secretary of Health and Human Services responsible for carrying out the ODA, but the Secretary does so through the FDA Commissioner. *See Eagle Pharms. v. Azar*, 952 F.3d 323, 325 n.2 (D.C. Cir. 2020) (citing 21 U.S.C. § 393(d)(2)). For ease of reference, the court refers to the FDA throughout this opinion, instead of the Secretary.

process, and monetary grants to offset the costs of development. *Id.* § 360aa(a), 360ee; 26 U.S.C. § 45C.

Then, before an orphan drug can be sold, the FDA must approve it. 21 U.S.C. § 355(a), (b). An orphan drug that obtains such approval can receive an important benefit: a seven-year period of marketing exclusivity. As originally enacted, and as relevant here, the ODA provided that "if the [FDA] approves an application" for a drug designated as an orphan drug "for a rare disease or condition," "the Secretary may not approve another application . . . for *such drug* for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved application[.]" 21 U.S.C. § 360cc(a) (1983) (emphasis added). Thus, Congress generally barred the FDA from approving another orphan drug application "for such drug for such disease or condition" until the earlier-approved drug's seven-year period of marketing exclusivity ended.

The ODA, as originally enacted, contained two limited exceptions to this prohibition. Congress authorized the FDA to approve another application for "such drug for such disease or condition" if the previously approved drug's sponsor (1) could not assure the availability of the drug in sufficient quantities or (2) consented to approval of other applications. *Id*. § 360cc(b) (1983).

The ODA does not define the term "such drug." *See Orphan Drug Regulations*, 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) (observing that Congress "provided no guidance on the meaning of this term"). The FDA filled that void in 1992, when it "promulgated a regulation defining when a second drug is considered the same as a previously approved drug under the [ODA]." *Baker Norton*, 132 F. Supp. 2d at 34. The regulation provided: The Agency "will not approve another sponsor's marketing application for the *same drug* before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA[.]" 21 C.F.R. § 316.31(a)

(1992) (emphasis added). By dint of that regulation, the FDA "interpreted 'such drug' to mean 'same drug'" for purposes of § 360cc. *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323, 326 (D.C. Cir. 2020) (citing 21 C.F.R. § 316.31(a)).

The FDA also defined "same drug." 21 C.F.R. § 316.3(b)(14). That definition turns on whether the drug is composed of "small molecules" or "large molecules." *Id.* If, as here, the drug consists of small molecules, "same drug" means "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, . . . *except* 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." *Id.* § 316.3(b)(14)(i) (emphasis added).

The FDA also defined the two key terms "active moiety" and "clinically superior." "Active moiety" means "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance." *Id.* § 316.3(b)(2). And a subsequent drug is "[c]linically superior" if that drug "is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug)." *Id*. § 316.3(b)(3). Such an advantage may arise from "[g]reater effectiveness," "[g]reater safety," or, "[i]n unusual cases, . . . a demonstration that the drug otherwise makes a major contribution to patient care." *Id*.

Putting this all together, the FDA treats a subsequent drug to be the "same drug" as an already approved drug if it has "the same active moiety and is not otherwise clinically superior" and is intended for the same use. *Eagle Pharms.*, 952 F.3d at 326. But if the subsequent drug is "clinically superior" to the first, then they are not the "same drug," even if both drugs have the same active moiety and are used to treat the same disease or condition. *See id.* (explaining that the FDA "considers the [subsequent] drug to be different—and thus entitled to its own seven-year exclusivity period upon designation and approval—if it does not have the same active moiety or

is clinically superior"). Under this framework, the FDA has long believed that the ODA grants it the authority to approve a "clinically superior" drug, even during an ongoing exclusivity period, because a "clinically superior" drug is not the "same drug" as a previously approved drug for purposes of § 360cc. *See Baker Norton Pharms.*, 132 F. Supp. 2d at 37 (agreeing with the FDA that nothing in the ODA "prevents subsequent applicants from obtaining FDA approval for . . . a clinically superior drug with the same active moiety for the same use").

2. Relevant Case Law

Predictably, litigation ensued over the FDA's enforcement of the ODA. The court summarizes two key cases. These rulings are important because, in response to one of them, Congress in 2017 changed "such drug for such disease or condition" in § 360cc(a) to "same drug for the same disease or condition." *See* FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607, 131 Stat. 1005, 1049–50 (2017) (amending 21 U.S.C. § 360cc). The meaning and significance of that amendment lies at the heart of the parties' dispute. The cases discussed below frame their disagreement.

a. <u>*Baker Norton Pharmaceuticals, Inc. v. FDA*</u>

The first significant case came in 2001, when a court in this District addressed the FDA's interpretation of "such drug." *Baker Norton Pharms.*, 132 F. Supp. 2d at 30, 34–35. *Baker Norton* involved a race for approval by two companies who had received orphan drug designation for the same active moiety for treatment of the same disease less than a month apart. *Id.* at 32. The FDA approved Baker Norton's competitor's new drug application first. It then advised Baker Norton that, because the two drugs had the same active moiety, they were the "same drug," which meant that the ODA barred the Agency from approving Baker Norton's new drug application for the next seven years. *Id.*

Baker Norton challenged the FDA's decision, asserting that the agency had improperly defined "same drug" based on the "activity moiety," as opposed to the "finished drug product" as Congress had intended. *Id.* at 35. According to Baker Norton, the term "drug" in § 360cc(a) should have been understood as the new drug "application" under § 355, a provision that governs applications for approval of new drugs and is expressly referenced in § 360cc(a)(1). *Id.* Because an application for a drug under § 355 contemplates the entire drug product, including inactive ingredients and manufacturing processes, Baker Norton argued that § 360cc(a) could not have limited the term "drug" to only mean "active moiety." *Id*.

The court disagreed. It reasoned that "Sections 355 and 360cc(a) [were] different statutory provisions with different purposes," and the meaning of the term "drug" depends on context. *Id.* The court thus could not "find that the definition of 'drug' in § 360cc(a) is clear and unambiguous," and "it [is] more likely that Congress left it to the FDA to determine which definition fits a particular statutory section." *Id.* at 36. The court held that the FDA's decision to define the term "drug" in terms of "activity moiety" was a "permissible construction of the statute" and "bear[s] out the purpose behind the [ODA]." *Id*. at 37. "Nothing [in the ODA] prevents subsequent applicants from obtaining FDA approval for the same drug for a different use, or a different drug for the same use, or *a clinically superior drug with the same active moiety for the same use*." *Id.* (emphasis added). The Agency's interpretation was reasonable, the court explained, because otherwise "the period of market exclusivity . . . would be undermined if other companies could develop drugs with the same activity moiety but minor differences in inactive ingredients. The interests of patients who need such drugs are served by the approval of drugs which have the same active moiety but are clinically superior." *Id.* at 38 (citation omitted). The court therefore affirmed the FDA's definition of "same drug."

As a result of *Baker Norton*, the FDA continued to equate "such drug" with its regulatory definition of "same drug" for purposes of § 360cc. And it maintained that it could approve and grant exclusivity to a subsequent drug that is "clinically superior" to an approved drug because they are not the "same drug." *See* Def.'s Mot. to Dismiss or, in the Alternative, for Summ. J., *Depomed Inc. v. HHS*, 12-cv-1592 (RLW), ECF No. 22 (Feb. 8, 2013), at 29–30 ("Under this framework, if there is a previously approved drug, a sponsor may nevertheless get approval and exclusivity for a later drug if it can establish that it is not the 'same drug' as the previously approved drug because it is clinically superior to it. Thus, clinically superior drugs are not blocked from approval by another drug's exclusivity period, and are eligible for their own exclusivity period." (citation omitted)).

b. *Depomed, Inc. v. HHS*

More than a decade later, in 2014, then-Judge Jackson considered a challenge to the FDA's regulatory practice of considering "clinical superiority" in determining whether an orphan drug was entitled to marketing exclusivity. *Depomed, Inc. v. HHS*, 66 F. Supp. 3d 217, 226 (D.D.C. 2014). The FDA required new drug sponsors (1) to make a hypothetical showing of "clinical superiority" over an approved drug to receive orphan drug designation under § 360bb *and* (2) to make an actual showing of "clinical superiority" upon drug approval to secure a seven-year period of marketing exclusivity under § 360cc. *See id.* at 223, 226. The FDA had denied a seven-year exclusivity period for Depomed's drug Gralise, even though the FDA had designated it as an orphan drug and later approved its new drug application. *Id.* at 220. The FDA concluded that Gralise was not entitled to the period of exclusivity, because an earlier drug with the same active moiety, Neurontin, had been approved for use for the same disease and Depomed had not shown that Gralise was "clinically superior" to Neurontin. *Id.* The FDA rejected the exclusivity period

even though Neurontin's manufacturer had never sought, and thus never received, an orphan drug designation. *Id.* at 223–24, 226.

Depomed then filed suit, arguing that the statute's plain language provided that orphan-drug exclusivity followed automatically from designation and marketing approval. In other words, once the FDA designated a drug as an orphan drug and then approved it, marketing exclusivity necessarily followed, without regard to "clinical superiority." *Id.* at 226. Depomed pointed to the statutory text indicating that the FDA "may not approve another application" for a drug if it "approv[ed] an application" for a "drug designated" under the ODA. *Id*. at 228–30. By defining "same drug" to exclude one that is "clinically superior," the company argued, the FDA's regulation imposed an additional condition that was improper under the statute. *Id*. The FDA responded that its regulations were a reasonable construction of the ODA, to which the court owed deference under *Chevron*. *Id*. at 228–29. The FDA also argued that, if Depomed's reading were accepted, a drug sponsor could achieve serial periods of exclusivity merely by tweaking a drug's formulation and resubmitting the drug's application for new designation and approval, so as to ensure continuity of exclusivity. *Id.* at 235.

The court sided with Depomed. It explained that § 360cc(a)'s marketing exclusivity text "can only be interpreted as a *limitation* on the agency's authority [to approve a new drug application]." *Id.* at 230 (emphasis in original).

> In other words, although it is convenient to characterize orphan-drug marketing exclusivity as something in the nature of a benefit that the FDA confers or withholds . . . the text of section 360cc makes clear that the incentive Congress intended to create in the orphan drug context is not a thing to be "conveyed" to drug manufacturers at all; rather, it is a restriction of the FDA's ability to approve the marketing of other such drugs for the same rare disease or condition . . . when a drug that has been designated as an orphan drug is approved for marketing.

Id. Finding no ambiguity in the statutory text, the court concluded that "the Act's exclusivity provision does not permit or invite any discretion on the part of the FDA regarding whether or not to continue authorizing new such drug marketing applications once an orphan drug has been so designated and approved." *Id.* at 231. As for the FDA's concern about serial exclusivity, the court discounted it. It reasoned that the FDA could address that problem at the designation stage by demanding a more stringent hypothetical showing of "clinical superiority." *Id.* at 235. The court thus held that the FDA had acted contrary to law by denying Gralise a seven-year period of exclusivity based on the failure to make a "clinical superiority" showing.

The court also explained why *Baker Norton* was not relevant to its inquiry. Judge Jackson noted that *Baker Norton* "was concerned only with the permissibility of the FDA's interpretation of what counted as 'such drug' (and thus must not be approved within the seven-year preclusion period)." *Id*. at 232. That term, she observed, "operates only to define the scope of the limit on the FDA's approval authority once a 'designated drug' has been 'approved' as required for exclusivity to attach." *Id.* In other words, the term "such drug" constrained the FDA's authority to approve a subsequent orphan drug where there "exist[ed] . . . a drug that has previously been designated and approved." *Id*. But the question of what counted as "such drug" did not need to be addressed, she wrote, because there had been "no previously designated gabapentin product" for treatment of the same disease. *Id.* Put differently, because the question of "same drug" under § 360cc(a) arises only if there is an unexpired period of exclusivity, and there was no such unexpired period in that case, *Baker Norton*'s acceptance of the Agency's definition of "same drug" was not relevant to the court's inquiry.

The FDA declined to acquiesce to the *Depomed* ruling. *See Eagle Pharms.*, 952 F.3d at 328 (citing *Policy on Orphan-Drug Exclusivity; Clarification*, 79 Fed. Reg. 76888 (Dec. 23,

2014)). It followed the decision in that case, but otherwise announced that it would continue to apply current regulations and "require the sponsor of a designated drug that is the 'same' as a previously approved drug to demonstrate that its drug is 'clinically superior' to that drug upon approval in order for the subsequent approved drug to be eligible for orphan-drug exclusivity." 79 Fed. Reg. at 76888.

Years later, the Agency's practice of denying exclusivity based on the failure to show "clinical superiority" would be challenged in *Eagle Pharmaceuticals., Inc. v. Azar*, and rejected once more for the reasons explained in *Depomed*. In *Eagle*, the D.C. Circuit agreed that "the text [of § 360cc(a)] leaves no room for the FDA to place additional requirements on a drug that has been designated and approved before granting its manufacturer the right to exclusivity." 952 F.3d at 331. Thus, the FDA could not consider "clinical superiority" to deny exclusivity to a designated and approved orphan drug. *Id.*

3. The 2017 Amendments to the ODA

The consequence of the D.C. Circuit's eventual decision in *Eagle*, however, was blunted by congressional action. In 2017, before *Eagle* reached the D.C. Circuit, Congress "amended the ODA to codify a clinical superiority requirement for exclusivity and supersede *Depomed*'s holding." *Id.* at 329 n.9 (citation omitted). Had the *Eagle/Depomed* interpretation of § 360cc remained the law, the FDA would have been powerless to deny exclusivity to a designated and approved orphan drug, even if it provided no additional clinical benefit over an already approved drug.[2]

Depomed also arguably cast doubt on the FDA's power to approve a "clinically superior" drug *during* an approved drug's exclusivity period. *Baker Norton* had found the Agency's

[2] Because the D.C. Circuit deemed the 2017 amendments not to apply retroactively, it based its decision on the original statutory text. *See Eagle*, 952 F.3d at 329 n.9.

definition of "same drug" to be reasonable, thereby allowing the FDA to continue evaluating "clinical superiority" in the context of drug approvals. *Depomed* did not question that ruling. Still, its reasoning could be read to undermine the FDA's practice of approving "clinically superior" drugs during exclusivity periods. If, as *Depomed* held, the FDA could not deny marketing exclusivity to a later-approved drug based on the failure to show clinical superiority, then perhaps it likewise lacked the authority to approve a second drug during an ongoing exclusivity period, notwithstanding its clinically superiority.

It is in this context that Congress amended the ODA in 2017. Congress made five changes to § 360cc that are relevant to the present dispute. *See* FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 607, 131 Stat. 1005, 1049–50 (2017)

First, Congress struck "such drug for such disease or condition" in subsection (a) and replaced it with "the *same* drug for the *same* disease or condition." *Id.* § 607(a)(1) (emphasis added). The new statutory text now reads as follows (with deletions noted by strikethroughs):

> [I]f the Secretary . . . approves an application . . . for a drug designated . . . for a rare disease or condition, the Secretary may not approve another application . . . for ~~such~~ the same drug for ~~such~~ the same disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application or the issuance of the license.

21 U.S.C. § 360cc(a) (notation added). Subsection (a) therefore generally prohibits the FDA from approving a second drug that is the "same drug for the same disease or condition" as an already approved drug during that drug's seven-year exclusivity period.

Second, Congress reworded subsection (b) to simplify it and to make its text parallel to the changes made to subsection (a). The introductory paragraph in that subsection now states:

> During the 7-year period described in subsection (a) for an approved application under section 355 . . . the Secretary may approve an

> application . . . for a drug that is otherwise the same as determined by the Secretary, as the already approved drug for the same rare disease or condition . . . .

131 Stat. at 1049, § 607(a)(2) (codified at 21 U.S.C. § 360cc(b)). Congress otherwise left undisturbed the two exceptions contained in subsection (b).

Third, Congress added a new subsection (c), which reads as follows:

> If a sponsor of a drug that is designated under section [360bb] of this title and is otherwise the same, as determined by the Secretary, as an already approved or licensed drug is seeking exclusive approval or exclusive licensure described in subsection (a) for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a condition of such exclusive approval or licensure, to demonstrate that such drug is *clinically superior* to any already approved or licensed drug that is the same drug.

Id., § 607(a)(3) (codified at 21 U.S.C. § 360cc(c)(1) (emphasis added)). This new subsection expressly granted the FDA authority to enforce a clinical superiority condition for a later approved drug that is otherwise the same as a previously approved drug to secure marketing exclusivity. It codified the power that *Depomed* (and later *Eagle*) said that the FDA lacked, and it cured the FDA's serial exclusivity concerns, which courts had discounted. Congress defined "clinically superior" to track the FDA's existing regulatory definition of that term. *See id.* (codified at 21 U.S.C. § 360cc(c)(2)) ("[T]he term 'clinically superior' with respect to a drug means 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.").

Fourth, Congress authorized the FDA to make rules to implement subsection (c). It also recognized the Agency's existing regulatory scheme. Subsection (d) provides that, until new regulations go into effect, "the Secretary may apply any definitions set forth in regulations that were promulgated prior to [the 2017 amendments'] date of enactment, to the extent such

definitions are not inconsistent with the terms of this section[.]" 131 Stat. at 1049–50, § 607(a)(3) (codified at 21 U.S.C. § 360cc(d)).

Finally, Congress added subsection (e), titled "Demonstration of clinical superiority standard." It requires the FDA to provide notice of clinical superiority determinations at both the designation and approval stages. 131 Stat. at 1050, § 607(a)(3) (codified at 21 U.S.C. § 360cc(e)). "To assist sponsors in demonstrating clinical superiority as described in subsection (c)," the FDA must upon the designation of a drug notify the sponsor "of the basis for the designation, including, as applicable, any plausible hypothesis offered by the sponsor and relied upon by the [FDA] that the drug is clinically superior to the previously approved drug." 21 U.S.C. § 360cc(e)(1). In addition, "upon granting exclusive approval or licensure under subsection (a) on the basis of a demonstration of clinical superiority as described in (c)," the FDA "shall publish a summary of the clinical superiority findings." *Id.* § 360cc(e)(2).

B. Factual and Procedural Background

With this legislative and regulatory framework in place, the court turns to the facts of this case and its procedural history.

1. Narcolepsy

Narcolepsy is a rare sleep disorder that impairs the brain's ability to control natural wake and sleep cycles. AR39.[3] Narcolepsy patients commonly experience excessive daytime sleepiness ("EDS") featuring sudden onset episodes of sleepiness or "sleep attacks" with little warning. AR535. Some patients also suffer cataplexy, which is the sudden onset of muscle weakness while a person is awake. AR510. At night, persons with narcolepsy generally fall sleep quickly but awaken several times and have difficulty returning to sleep. AR509. Their sleep is often

[3] The parties' Joint Appendix contains the relevant portions of the administrative record ("AR") and can be found at ECF Nos. 81-2 through 81-5. For ease of reference, the court simply cites to the page number in the "AR."

interrupted by spontaneous arousals that impact their "sleep architecture," which is the cyclical pattern of sleep stages at night. AR505. The goal of narcolepsy therapeutics is to achieve "normal" alertness during the day and, "to the extent possible, promote normal sleep at night." AR535.

2. Jazz's Drug Products Xyrem and Xywav

Oxybate salts are a class of drugs that improve symptoms of EDS by consolidating nighttime sleep. AR536. Oxybate products are "intended to decrease nocturnal arousals" and help promote "sleep continuity through the normal stages of sleep architecture." AR536. In November 1994, the FDA granted orphan drug designation to Jazz's predecessor, Orphan Medical, Inc., for the active moiety oxybate for the treatment of narcolepsy. *Id.*

Jazz's first oxybate-based drug, Xyrem, received approval from the FDA on July 17, 2002, for the treatment of cataplexy associated with narcolepsy. AR536. On November 18, 2005, FDA approved Xyrem for a new indication, the treatment of EDS in patients with narcolepsy. *Id.* Finally, on October 26, 2018, the FDA approved Xyrem for the treatment of EDS or cataplexy in narcolepsy patients seven years or older. *Id.*[4]

Xyrem is taken in two doses at night, with the first taken at bedtime and the second taken 2.5 to 4 hours later. AR537. A maximum dose of Xyrem (9 grams) contains 1,640 milligrams of sodium. *Id.* That maximum dose represents a high percentage of the daily recommended amount of sodium (2,300 milligrams per day). *Id.* Xyrem's labelling accordingly includes a use warning for patients sensitive to high sodium intake. *Id.*

Jazz later developed a low-sodium alternative to Xyrem called Xywav. *Id.* Xywav is administered on the same two dose schedule as Xyrem, but a 9-gram dose of Xywav contains only 131 milligrams of sodium. AR537–38. The FDA determined that Xywav's reduced sodium

[4] Each of these approvals received seven-year periods of marketing exclusivity. *Id.* The first two periods have expired and the last extends until October 26, 2025. AR536–37. These periods of exclusivity are not implicated in this case.

content provided greater safety in a substantial portion of the target population and therefore was "clinically superior" to Xyrem. AR538. The FDA therefore approved Xywav and found that it was eligible for marketing exclusivity, effective as of July 21, 2020. *Id*. The exclusivity period for Xywav would run presumptively until July 21, 2027.

3. Avadel's Drug Product Lumryz

Avadel has developed its own oxybate-based drug for narcolepsy treatment called Lumryz. *Id.* Unlike Xyrem or Xywav, Lumryz is an extended-release oral suspension that is dosed once per night. Lumryz has the same high sodium content as Xyrem. AR539.

On April 20, 2016, Avadel requested orphan drug designation for "oxybate for the treatment of narcolepsy." *Id.* Almost two years later, on January 8, 2018, the FDA granted Avadel's request for orphan drug designation. AR540. The FDA determined that, as compared to a twice-per-night dosing, Lumryz's once-per-night dosing "would be much more convenient and less disruptive for patients, and that a drug administered once-per-night may present less risk to patients, for example risks from falls when waking up to take the second dose." AR539–40. The FDA thus concluded that "there was a plausible hypothesis that Lumryz may be clinically superior to Xyrem based on providing safety or providing a [major contribution to patient care] over Xyrem." AR540.

On December 15, 2020, Avadel requested full drug approval for Lumryz. *Id.* Over 18 months later, on July 18, 2022, the FDA tentatively approved Lumryz for the treatment of cataplexy or EDS for adult narcolepsy patients. *Id.* The Tentative Approval letter did not, however, address whether "any orphan drug exclusivity [ ] recognized for Xyrem . . . or for Xywav . . . affect[ed] the approvability of Avadel's application." *Id.* On March 1, 2023, Avadel submitted an amendment to its application requesting final approval of Lumryz. *Id.*

The FDA's Office of Orphan Products Development ("OOPD") makes orphan drug marketing exclusivity determinations. After Avadel sought approval of Lumryz, OOPD requested consults from other centers within the FDA as to whether Lumryz was "clinically superior" to Xywav and Xyrem. AR1344. One early consultation determined that Lumryz was *not* "clinically superior." In August 2021, the Division of Neurology ("Review Division") opined that "[w]hile the once-nightly regimen of Lumryz will be more convenient for patients . . . that attribute cannot be considered a major contribution to patient care." AR480. But the Review Division's consult was not the end of the road for Lumryz's approval hopes.

In 2023, OOPD sought input from a different center, the Center for Devices and Radiological Health. AR504. Within the Center is a group of board-certified sleep specialists known as the "Sleep Team." *Id.* The Sleep Team concluded that Lumryz provided "a significant therapeutic advantage over and above that of Xywav and Xyrem" and had therefore provided a major contribution to patient care. *Id.*

> The underpinning of [its] rationale [was] that patients with narcolepsy, a sleep disorder, will not need to awaken from sleep to take a second dose of Lumryz . . . . From a therapeutic perspective, it is highly desirable to eliminate, or at least minimize, nocturnal arousals from sleep—especially for patients who have a sleep disorder and seek treatment. A nocturnal arousal from sleep to take a second dose of sleep medication will fragment sleep and disrupt sleep architecture.

Id. at 504–05 (citations omitted).

Following the Sleep Team's evaluation, OOPD returned to the Review Division for another consultation. The Review Division reconsidered its earlier conclusion "in light of several factors." AR516. Among them were "the expert opinion of the FDA's sleep team," as well as certain clarifications about the factors to weigh in deciding whether a new drug provides a "major contribution to patient care." *Id.* Although acknowledging that "the sodium content of Lumryz

raises the same safety concern that was present for Xyrem and that is not present for Xywav," the Review Division believed that "the benefit of Lumryz's once nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients." *Id.* at 517. The Review Division "reconsidered its prior assessment dated August 31, 2021, and now conclude[d] that Lumryz provides a [major contribution to patient care] over Xywav and Xyrem." *Id.*

Thereafter, on May 1, 2023, FDA granted final approval to Lumryz notwithstanding Xywav's ongoing exclusivity period. The FDA acknowledged that Lumryz shared the same active moiety with Xywav and was intended for the same use, AR524–25, but determined that Lumryz was "clinically superior to both Xywav and Xyrem." AR525. Lumryz was "clinically superior" because it provided a "major contribution to patient care" insofar as its once-nightly dosing regimen presented a greater opportunity for normalized sleep. AR552. Once-nightly dosing also was "significantly more convenient for patients, an advancement in the ease of drug administration, and a reduction in the treatment burden" compared to twice-nightly dosing with Xywav. *Id.* The FDA thus approved Avadel's new drug application "for the use of Lumryz (sodium oxybate) for extended-release oral suspension for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy." AR258. It also recognized that Lumryz was entitled to its own seven-year period of marketing exclusivity because it was clinically superior to Xywav. AR525.

4. Procedural History

On June 22, 2023, Jazz filed this suit against various federal officials and the FDA asserting a single claim under the Administrative Procedure Act, alleging that FDA's approval of Lumryz was an unlawful agency action, 5 U.S.C. § 706(2). Compl., ECF No. 1, 82–83. According to Jazz,

the FDA had no authority to approve Lumryz during Xywav's unexpired exclusivity period. *Id.* It further claims that the FDA's "clinical superiority" determination "is inconsistent with FDA's own regulations and reflects an unexplained departure from multiple agency policies." *Id.* ¶ 246. It also asserts that the Lumryz approval decision was based upon "unsupported speculation." *Id.*

Thereafter, Avadel intervened as a defendant, Order, ECF No. 15, and the parties filed cross-motions for summary judgment. Pl.'s Mem. of P & A in Supp. of Pl.'s Mot. for Summ. J., ECF No. 34-2 [hereinafter Jazz's Mem.]; Mem. of P & A in Opp'n to Pl.'s Mot. & in Supp. of Avadel's Cross-Mot. for Summ. J., ECF No. 41-2 [hereinafter Avadel's Mem.]; Fed. Defs.' Mem. in Supp. of Their Cross-Mot. for Summ. J & in Opp'n to Pl.'s Mot., ECF No. 45-2 [hereinafter FDA's Mem.]. The court held oral argument on May 10, 2024.

III. LEGAL STANDARD

In cases that involve review of a final agency action under the APA, the district court "sits as an appellate tribunal," and "the entire case on review is a question of law." *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083 (D.C. Cir. 2001) (internal quotation marks omitted). The court's review is limited to the administrative record, and "its role is limited to determining whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did." *Philip Morris USA Inc. v. U.S. Food & Drug Admin*., 202 F. Supp. 3d 31, 45 (D.D.C. 2016) (cleaned up).

Under the APA, an agency action may be set aside if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). The arbitrary-and-capricious standard is "highly deferential" and "presumes the validity of agency action." *Nat'l Ass'n of Clean Air Agencies v. EPA*, 489 F.3d 1221, 1228 (D.C. Cir. 2007) (cleaned up). That deference does not, however, extend to matters of statutory construction. *See Loper Bright*

Enterprises v. Raimondo, 144 S. Ct. 2244 (2024). Instead, "[c]ourts must exercise independent judgment in determining the meaning of statutory provisions." *Id*. at 2273. Thus, to the extent Defendants have argued that the FDA's reading of § 360cc is a reasonable one and therefore entitled to deference, the court rejects that position as inconsistent with the court's obligations under *Loper Bright*. *See* FDA's Mem. at 15; Fed. Defs.' Reply Mem. in Supp. of Their Cross-Mot. for Summ. J [hereinafter FDA's Reply] at 13–15; Avadel's Mem. at 16–17. *See Pac. Gas & Elec. Co. v. FERC*, 113 F.4th 943, 948 (D.C. Cir. 2024) (rejecting an agency's request for deference after *Loper Bright*).

IV. DISCUSSION

Jazz advances three broadside attacks on the FDA's approval of Lumryz. First, it argues that the FDA lacked the statutory authority to approve Lumryz during Xywav's unexpired exclusivity period. Second, Jazz maintains that the Agency departed without explanation from longstanding policy requiring a drug approved under the major-contribution pathway to demonstrate comparable safety to an approved drug. Finally, Jazz contends that the FDA's "clinical superiority" determination was arbitrary and capricious because (1) the agency's decision-making deviated from internal rules and (2) the decision was contrary to the scientific literature.

A. The FDA's Authority to Approve Lumryz

1. Congress ratified the FDA's regulatory definition of "same drug" in the 2017 amendments

Recall, § 360cc(a) of the ODA provides that when the FDA "approves an application . . . for a drug designated under section 360bb," it "may not approve another application . . . for the same drug for the same disease or condition" during an approved drug's exclusivity period. 21 U.S.C. § 360cc(a). Jazz's principal argument is that the FDA lacked the statutory authority

under § 360cc(a) to approve Lumryz during its unexpired period of exclusivity because Xywav and Lumryz are the "same drug for the same disease or condition." Jazz's Mem. at 19.

According to Jazz, the term "drug" in § 360cc can only mean "active moiety" and that "same drug" means "same active moiety." Jazz's Mem. at 20–21. "Drug" must refer to "active moiety," says Jazz, because the only drug referenced in § 360cc(a) is the "drug designated under § 360bb" as an orphan drug. *See id.* And, it further claims, the FDA's "settled position" is that, in "'the orphan drug provisions of the statute,' the word 'drug' in the context of small molecule drugs like [oxybate] means 'active moiety.'" *Id.* at 20 (citing Memo from Elizabeth Dickson, Office of the Chief Counsel, FDA to Tan Nguyen, Director, Office of Orphan Products Development, FDA, at 3 (Apr. 25, 2006) (attached to Decl. of Sean C. Griffin [hereinafter Griffin Decl. I] as Ex. 9, ECF No. 36-8)). Under this straightforward reading, because Xywav and Lumryz share the same active moiety—oxybate—they are the "same drug," and because both are used "for the same disease or condition," the FDA lacked the authority to "approve" Avadel's application for Lumryz during Xywav's seven-year exclusivity period. *See* Combined Reply in Supp. of Pl.'s Mot. for Summ. J. and Opp'n to Defs.' Mots. For Summ. J., ECF No. 59-2, at 10–11, 13 [hereinafter Jazz's Opp'n].

The FDA and Avadel read the statute differently. They note that the ODA contains no definition of the term "same drug," and urge that "history and context provide the keys to unlocking the statutory meaning." FDA's Mem. at 13–14; *see also* Avadel's Mem. at 19–20. They argue that Congress effectively ratified the FDA's longstanding regulatory definition of "same drug" as part of the 2017 amendments to the ODA when it changed "such drug for such disease or condition" to "same drug for the same disease or condition." *See* FDA's Mem. at 14–15; Avadel's Mem. at 19–20. Defendants point to the fact that when Congress introduced "same

drug" into the statute, the term's definition "had been firmly established by a quarter century of regulatory practice and had survived judicial review." FDA's Mem. at 14 (citing *Baker Norton*, 132 F. Supp. 2d at 38); Avadel's Mem. at 19. Under that well-established regulatory definition, two drugs are not the "same drug" if the subsequent drug is "clinically superior" to the first, even if they share the same active moiety and are intended for the same use. FDA's Mem. at 14–15; Avadel's Mem. at 19–20. With Congress having codified the FDA's regulatory definition of "same drug," Defendants assert, the FDA appropriately considered whether Lumryz was "clinically superior" to Xywav. And, because it concluded that Lumryz is "clinically superior" to Xywav and therefore not the "same drug," § 360cc(a) did not prohibit approval of Lumryz during Xywav's exclusivity period.

The nub of the parties' dispute therefore boils down to the following question: Does § 360cc(a) authorize the FDA to conclude that two orphan drugs are not the "same" based on the second drug's "clinical superiority" over the first, even though the two drugs share the same active moiety and are used for the same disease or condition? If, as Defendants assert, the answer is "yes," then the FDA had the power to approve Lumryz during Xywav's unexpired exclusivity period because they are *not* the "same drug." If the answer is "no," as Jazz maintains, the FDA acted unlawfully.

Because "statutory language cannot be construed in a vacuum," "[i]t is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme." *Davis v. Mich. Dep't of Treasury*, 489 U.S. 803, 809 (1989). So, in addition to the text, the court must consider the statute's "structure, purpose and legislative history." *Genus Med. Techs. LLC v. FDA*, 994 F.3d 631, 637 (D.C. Cir. 2021). Here, the statute's words, structure, and historical context establish that, when Congress amended

the ODA in 2017, it ratified and incorporated the existing regulatory definition of "same drug" into the statute.

The court begins with the statute's text. "If a statute uses words or phrases that have already received authoritative construction by . . . a responsible administrative agency, they are to be understood according to that construction." *Washington All. of Tech. Workers v. Dep't. of Homeland Sec.*, 50 F.4th 164, 180–81 (D.C. Cir. 2022) (quoting Antonin Scalia & Bryan A. Garner, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 322 (2012)). For 25 years preceding the 2017 amendments, the term "such drug" in the context of the ODA had a well-established regulatory meaning. The FDA had equated the term "such drug" in § 360cc(a) with "same drug," *see Eagle Pharms.*, 952 F.3d at 326; 21 C.F.R. § 316.31(a), and it had defined "same drug" to mean two drugs with the same active moiety and intended for the same use, *unless* the second drug was "clinically superior" to the first. 21 C.F.R. § 316.3(b)(14)(i). The FDA considered a drug to be "different—and thus entitled to its own seven-year exclusivity period upon designation and approval—if it [did] not have the same active moiety or [was] clinically superior." *Eagle Pharms.*, 952 F.3d at 326. This was the well-trodden administrative terrain when Congress acted in 2017. It changed the phrase "such drug for such disease or condition" in § 360cc(a) to "same drug for the same disease or condition." "'[A]ll indications' here are that Congress was 'well aware' of [this] legal and administrative landscape," *Hikvision USA, Inc. v. FCC*, 97 F.4th 938, 947 (D.C. Cir. 2024) (quoting *Bragdon v. Abbott*, 524 U.S. 624, 645 (1998)), and "intended to give that position its active endorsement," *Bragdon*, 524 U.S. at 645.

Other textual clues support this conclusion. *See New York v. EPA*, 413 F.3d 3, 19 (D.C. Cir. 2005) ("We have (naturally) required indications in the statutory language or history to infer that Congress intended to incorporate into a statue a preexisting regulatory definition."). In two

places, the 2017 amendments expressly import or acknowledge the Agency's existing regulatory definitions. In subsection (c), Congress gave "clinical superiority" a meaning that closely mirrors the FDA's existing definition of that term. *Compare* 21 U.S.C. § 360cc(c)(2), *with* 21 C.F.R. § 316.3(b)(3). The concept of "clinical superiority" is, of course, at the heart of the FDA's definition of "same drug." Moreover, new subsection (d) authorizes the FDA to continue use of its existing regulatory definitions to implement subsection (c) until it adopts new regulations. 21 U.S.C. § 360cc(d). These provisions leave little doubt that Congress was "plainly [ ] aware" of the FDA's definition of "same drug" when it changed "such drug" to "same drug" in subsection (a). *Hikvision*, 97 F.4th at 946. Such awareness is "particularly strong" evidence that Congress intended to ratify the regulatory definition of "same drug" in § 360cc(a). *Cf. Jackson v. Modly*, 949 F.3d 763, 773 (D.C. Cir. 2020) (stating that an indication of congressional acquiescence to a judicial interpretation of a statute is "particularly strong if evidence exists of the Congress's awareness of and familiarity with such an interpretation").

The history and purpose of the 2017 amendments further supports Defendants' reading of § 360cc(a). Congress amended the ODA in 2017 to supersede *Depomed*, which had rejected the FDA's claimed authority to deny marketing exclusivity under § 360cc to a drug sponsor that had satisfied the designation and approval requirements but failed to demonstrate "clinical superiority." *See supra* Section II.A.3. Historically, the FDA had rooted its power to deny exclusivity in its regulations. The regulations provided that "such drug" under § 360cc(a) meant "same drug," and that two drugs were the "same drug" if they shared the same activity moiety and use, unless the second drug was "clinically superior" to the first. *See Eagle Pharms.*, 952 F.3d at 326. In practice that meant a later-approved drug that shared the same active moiety and use as an already approved drug could receive marketing exclusivity only by demonstrating its "clinical

superiority." *See id. Depomed* cast this approach into doubt. Congress's clear purpose in enacting the 2017 amendments was to supersede *Depomed* and to codify the agency's authority to make "clinical superiority" determinations. *See Eagle Pharm.*, 952 F.3d at 329 n.9. To be sure, *Depomed* concerned a "clinical superiority" inquiry only in the context of the FDA recognizing marketing exclusivity for a new orphan drug, not approving one during an existing exclusivity period. But it would be an odd result for Congress to have codified only the FDA's discretion as to exclusivity periods, but not approvals. The court must presume that Congress changed "such drug" to "same drug" in § 360cc(a) for a reason. *See Stone v. INS*, 514 U.S. 386, 397 (1995) ("When Congress acts to amend a statute, we presume it intends its amendment to have real and substantial effect."). Congress surely knew that, before the 2017 amendments, the FDA used the regulatory definition of "same drug" to administer § 360cc(a) *both* to deny exclusivity *and* to grant approvals during existing exclusivity periods. Under Jazz's reading of § 360cc(a), the 2017 amendments permit the FDA only to do the former, and not the latter. If accepted, it would mean that Congress *rolled back* the FDA's approval authority under § 360cc(a). That interpretation is at odds with the historical context in which Congress legislated.

In sum, statutory text, history, and purpose demonstrate that Congress meant to ratify and incorporate the FDA's existing definition of "same drug" in § 360cc(a) when it substituted "same drug" for "such drug." The FDA therefore was authorized to consider Lumryz's "clinical superiority" to Xywav when it decided to approve Lumryz during Xywav's unexpired period of exclusivity.

2. Jazz's Arguments

Jazz's response is four-fold. First, it argues that § 360cc(a) does not expressly incorporate the FDA's regulation and that Congress's "drafting choices" suggest an intent not to ratify. Jazz's

Opp'n, at 14–15. Second, Jazz points out § 360cc(c) references the concept of "clinical superiority," but § 360cc(a) does not, which suggests that Congress meant to exclude that concept from agency decisions under the § 360cc(a). *Id.* at 19. Third, Jazz asserts that "same drug" is "too common and context dependent" a term to carry the FDA's definitional meaning. *Id*. at 16. Finally, Jazz argues that the "old soil" canon, which Defendants say applies, has no purchase here because "same drug" lacks sufficient historical pedigree. *Id*. at 17. None of these arguments is persuasive.

a. The lack of express incorporation and Congress's "drafting choices"

First, Jazz maintains that § 360cc(a) cannot be read to adopt the FDA's definition of "same drug" because the section, as amended, nowhere mentions the regulatory definition, and "Congress knows how to expressly incorporate FDA regulations when it wants to." Jazz's Opp'n at 14. But Jazz is wrong to contend that the "usual rule" is that "'Congress' failure to use such an express incorporation of prior regulations . . . cuts against any suggestion that Congress intended to incorporate into the Act the preexisting regulatory definition.'" *Id.* (quoting *Env't Def. v. Duke Energy Corp.*, 549 U.S. 561, 576 (2007)). The question of ratification turns not on "express incorporation" but whether there are "indications in the statutory language or history to infer that Congress intended to incorporate into a statute a preexisting regulatory definition." *New York*, 413 F.3d at 19. As discussed, the text, history, and purpose of the 2017 amendments support reading "same drug" to have incorporated the FDA's existing regulatory definition of that term.

Environmental Defense does not compel a different result. In that case, the Supreme Court considered the meaning of the term "modification" across two provisions of the Clean Air Act enacted seven years apart. 549 U.S. at 566–67. The first included a definition of the term "modification," and the second cross-referenced to that earlier-enacted provision's definition. *Id.*

The question facing the Court was whether by including the cross-reference Congress intended for the EPA to conform the later-enacted provision's regulations on "modification" to its earlier counterparts. *Id.* The Court held that such conformity was not required, because "[n]othing in the text or legislative history . . . suggest[ed] that Congress had details of regulatory implementation in mind" based on "the cross-reference alone." *Id.* at 576.

That is simply not the case here. Congress's 2017 amendments to ODA involve far stronger evidence of ratification than a mere "cross-reference." The statute is clear on its face that Congress was well-aware of the FDA's longstanding regulatory definitions. *See* 21 U.S.C. § 360cc(d). Congress also sought to codify the Agency's longstanding practice of considering "clinical superiority" in exclusivity determinations, which *Depomed* had said the FDA did not have. Congress therefore unquestionably knew that the agency had for decades equated "such drug" and "same drug" and that "same drug" definitionally encompassed "clinical superiority," which itself carried a specific regulatory meaning. So, when it changed "such drug" to "same drug," the reason for doing so is likely the obvious one—to conform the ODA's text to the FDA's longstanding definition of "same drug."

Jazz further contends that Congress's "drafting choices" show that it did *not* intend to ratify the FDA's regulatory definition of "same drug." Jazz's Opp'n 14. It points out that Congress did more than "just swap" "same drug" for "such drug" in § 360cc(a); it struck the phrase "such drug for such disease or condition" and replaced it with "same drug for the same disease or condition." *Id* at 14–15. The FDA's regulations, on the other hand, use the phrase "same drug for the same *use or indication*." 21 CFR § 316.3(b)(12) (emphasis added). So, Jazz concludes, "Congress did not borrow the FDA's words," a decision which "must be honored." Jazz's Opp'n at 17 (citations omitted).

But that argument is too cute by half. The phrase "same drug for the same use or indication" appears not in the FDA's definitions of "same drug" or "clinically superior" but in the term "orphan-drug exclusive approval." *Compare* 21 C.F.R. § 316.3(b)(12), *with id.* § 316.3(b)(3), (14). Jazz does not explain why the appearance of "use or indication" in the definition of that term is relevant to interpreting the statutory change from "such drug" to "same drug." In addition, and more importantly, there is a clear textual reason why Congress used the phrase "same drug for the same disease or condition" (instead of "use or indication"): "same disease or condition" is a key term that appears elsewhere in the ODA. For instance, § 360bb, regarding designation of an orphan drug, provides that "[t]he manufacturer or the sponsor of a drug may request the Secretary to designate the drug as a drug for a rare *disease or condition*." 21 U.S.C. § 360bb(a)(1). That provision contains a definition for "rare disease or condition." *Id.* § 360bb(a)(2). "[R]are disease or condition" again appears in § 360cc(a). Thus, to ensure consistency of meaning, Congress's use of "same drug for the same disease or condition" as opposed to "same drug for the same use or indication" makes perfect sense.

Nor is this case, as Jazz argues, "on all fours" with the Eleventh Circuit's decision in *Catalyst Pharmaceuticals, Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021). Jazz's Opp'n at 11. In *Catalyst*, the parties agreed that the two drugs at issue were the same and treated the same disease. 14 F.4th at 1305. The question was whether the phrase "same disease or condition" was ambiguous. The FDA argued that it was and therefore its interpretation as allowing it to recognize exclusivity for the second drug based on its approval for a different "use or indication" was reasonable and entitled to deference. *Id.* at 1306–08. The court held otherwise. It concluded that "same disease or same drug" was not ambiguous and therefore the statute did not allow the FDA to grant a period of exclusivity based on a second drug's different "use or indication." *Id.* at 1311.

Part of the court's rationale was that Congress had not used the words "use or indication" in § 360cc when it had elsewhere used more limiting terms, such as "use" in § 355, which governs new drug applications. "If Congress wanted to make the 'use or indication' inquiry relevant to a holder's market exclusivity for an orphan drug, it could have done so by including such language in § 360cc(a). The fact that Congress did not include that language counsels against an interpretation that finds an ambiguity in § 360cc(a)'s language." *Id.* at 1309. Here, of course, just the opposite is true: Congress *did* amend § 360cc(a) to include the very term that the FDA had coined and defined—"same drug." Thus, the *inclusion* of a defined regulatory term in the statutory text makes this case fundamentally different than *Catalyst*.

b. The absence of "clinical superiority" in § 360cc(a)

Second, Jazz highlights the express inclusion of "clinical superiority" in new subsection (c) but not in subsection (a). Jazz's Opp'n at 19. According to Jazz, Congress did this intentionally to convey that "clinical superiority" is relevant only under subsection (c) to prevent the problem of serial exclusivity made possible by *Depomed*, but not under subsection (a) to authorize the FDA to overcome, or "break," an already approved drug's existing exclusivity period. Jazz's Mem. at 22; *see also id.* at 23 ("When Congress amended the statute in 2017, FDA had been insisting for 25 years that clinical superiority restricted both (i) eligibility for serial exclusivity and (ii) the scope of initial exclusivity. By codifying that view ***only*** as to serial exclusivity, Congress necessarily rejected the agency's additional theory that clinical superiority can break or overcome unexpired exclusivity.") (emphasis in original) (citation omitted). To read § 360cc otherwise, Jazz says, "is tantamount to rewriting the statute to include a third exception to the prohibition in [§ 360cc(a)]." *Id.* at 22.

But this contention ignores Congress's addition of subsection (e). Congress included that provision to "assist sponsors in demonstrating clinical superiority." 21 U.S.C. § 366cc(e). It states that, "upon granting *exclusive approval . . . under subsection (a)* on the basis of a demonstration of clinical superiority as described in subsection (c)," the FDA "shall publish a summary of the clinical superiority findings." *Id.* § 360cc(e)(2) (emphasis added). Congress thus clearly contemplated that the FDA would make approval *and* exclusivity decisions for new orphan drugs "under subsection (a)" based on "clinical superiority" determinations. Congress therefore did not limit a "clinical superiority" evaluation only to combat the problem of serial exclusivity. It expressly contemplated that "clinical superiority" would be an equally relevant inquiry in "exclusive approval" determinations made under subsection (a).

c. The commonality of "same drug"

Third, Jazz contends that "same drug" is "'too common and context dependent' a phrase to assume that it bears the agency's 'loaded meaning wherever it appears.'" Jazz's Opp'n at 16 (quoting *Yellen v. Confederated Tribes of Chehalis Rsrv.*, 141 S. Ct. 2434, 2445 (2021)). To make this point, Jazz notes that "same drug" appears multiple places in the Food, Drug, and Cosmetic Act ("FDCA"). *See id.* But that argument misses an obvious point. Jazz admits that "[t]he term 'drug' has multiple meanings in the FDCA," Jazz's Mem. at 20, so the definition of "same drug" for purposes of the ODA is necessarily context dependent. That context—including the relevant history—establishes that Congress substituted "same drug" for "such drug," knowing that the FDA had long equated the two. The court's reading thus does not require "same drug" to carry the FDA's regulatory definition "wherever it appears." That definition is applicable only in the context of the ODA.

For those reasons, this case is different from the two decisions on which Jazz relies, *Bruesewitz v. Wyeth LLC*, 562 U.S. 223 (2011) and *Yellen v. Confederated Tribes of Chehalis Reservation*, 141 S. Ct. 2434 (2021). Jazz's Opp'n at 16. In *Bruesewitz*, the term at issue—"unavoidable"—had no "special significance . . . standing alone." 562 U.S. at 235. And, in *Yellen*, the Court concluded that the word "recognized" was too general to support a term-of-art construction because the "context" did not call for it. 141 S. Ct. at 2445. Here, as discussed, the "context" does support Congress's ratification of a longstanding regulatory definition.

To be fair, as Jazz argues, reading the definition of "same drug" into each location that the term appears in § 360cc arguably would create a "hash" of § 360cc(c)(1). Jazz's Opp'n at 16. That provision requires a sponsor of a designated drug "that is otherwise the same, as determined by the Secretary, as an already approved . . . drug" that is seeking exclusivity "to demonstrate 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) (emphasis added). Substituting the regulatory definition for "same drug" into the provision would mean the sponsor would have to show "clinical superiority" over an approved drug, "except that if the subsequent drug can be shown to be clinically superior to the first drug." 21 C.F.R. § 316.3(b)(14)(i). That circularity makes no sense.

But once more context matters. The start of § 360cc(c)(1) provides that a subsequent drug that is "otherwise the same" must make a showing of "clinical superiority" to secure exclusive approval. "[O]therwise the same" in that context means a subsequent drug that contains the same active moiety and is intended for the same use as the approved drug but not yet deemed to be "clinically superior" to the approved drug. The reference to "same drug" at the end of subsection (c)(1) thus refers to the approved drug, without regard to "clinical superiority." That reading makes sense. After all, the whole purpose of subsection (c) is to distinguish between an

approved drug and a subsequent drug based on "clinical superiority." This straightforward reading of § 360cc(c)(1) therefore does not create the "hash" that Jazz fears.

d. The "old soil" canon

Finally, Jazz claims that the FDA's invocation of the "old soil" canon is misplaced because "same drug" lacks the "equivalent longevity" of those terms to which the canon has been applied. Jazz's Opp'n at 17. Although the FDA raises the "oil soil" canon, it has little application here. FDA's Mem. at 15, 17–18; FDA's Reply at 8–11.

Under the "old soil" canon, when a statutory term is "obviously transported from another legal source, it brings the old soil with it," *Taggart v. Lorenzen*, 587 U.S. 554, 560 (2019) (internal quotation marks and citations omitted), meaning that the term brings with it "the state of [a] body of law" at the time of enactment, *George v. McDonough*, 596 U.S. 740, 750 (2022) (internal quotation marks and citation omitted). But this case is not about the "old soil" lying beneath the term "same drug." Defendants are not, for example, asking the court to apply the FDA's past interpretations or applications of the term "same drug" to assess whether the approval of Lumryz was arbitrary or capricious. Rather, the question here simply is whether Congress ratified the agency's definition of that term in the 2017 amendments. That question is resolved by the statutory text, history, and purpose, not by the "old soil" that accompanies the term "same drug."

e. Jazz's theory for the amendment of § 360cc(a)

Jazz claims there is a "far simpler explanation" than ratification for the change from "such drug" to "same drug": Congress amended the text "to resolve a specific ambiguity" identified by the court in *Baker Norton*. Jazz's Opp'n at 18. The court had deemed the meaning of "such drug" to be ambiguous—it could refer either to the "application filed" with the FDA under § 355 (i.e., the finished drug product) or the drug substance "designated under section 360bb" (i.e., the active

moiety). Jazz's Opp'n at 18. Jazz says Congress changed "such drug" to "same drug" to "tether[] the word 'drug' to its immediate antecedent—the 'drug designated,' which for small molecule drugs had always been the active moiety." *Id.*

But that explanation for the amendment makes little sense. If accepted, it would mean that Congress amended the ODA to codify a meaning of § 360cc(a) that is *different* than the agency's decades-long understanding of the term "same drug." Remember, in *Baker Norton*, the court agreed that the FDA's definition of "same drug" was a reasonable one, including the criterion of clinical superiority. Nothing in the ODA, the court wrote, "prevents subsequent applicants from obtaining FDA approval for . . . a clinically superior drug with the same active moiety for the same use." *See Baker Norton*, 132 F. Supp. 2d at 37. Yet, under Jazz's view, Congress's supposed effort to resolve ambiguity *constrained* the FDA's approval authority. It unwound the deference that *Baker Norton* had afforded the longstanding regulatory definition of "such drug." That cannot be right. Again, the purpose of the 2017 amendments was to codify the FDA's authority to make "clinical superiority" determinations in the context of exclusive approvals, which *Depomed* had called into doubt. It makes far more sense that Congress selected the term "same drug" to enshrine into law the Agency's decades-old understanding that § 360cc(a) authorized it to consider "clinical superiority" in deciding whether to approve a subsequent orphan drug during an already approved drug's unexpired exclusivity period.

* * *

In sum, the court holds that when Congress changed "such drug for such disease or condition" to "same drug for the same disease or condition," it intended to ratify and incorporate the FDA's longstanding definition of the term "same drug." That definition permits the Agency to consider whether a subsequent drug is "clinically superior" to an approved drug in determining

whether they are the "same drug." Here, the FDA determined that Lumryz was not the "same drug" as Xywav because its single-dose formula was clinically superior to Xywav. The FDA did not exceed its statutory authority under § 360cc by comparing the clinical benefits of the two drugs in deciding whether to approve Lumryz during Xywav's unexpired exclusivity period.

3. Exclusive Approval Authority under § 360cc(c)

Before moving on, the court wishes to express its view that, even under Jazz's preferred reading of "same drug," the outcome would be no different. If, as Jazz contends, "same drug" under subsection (a) refers solely to active moiety, the FDA nonetheless had authority under subsection (c) to grant "exclusive approval" to Lumryz based on its "clinical superiority," notwithstanding Xywav's unexpired period of exclusivity. Neither the FDA nor Avadel has advanced this interpretation of § 360cc(c). The court therefore has not rested its decision on it. It is, however, an alternative basis—and, in the court's mind, the better way—to reach the same result, even if Jazz's interpretation of "same drug" is the correct one.

By its plain terms, subsection (c)(1) applies when a subsequent drug that is "otherwise the same . . . as an already approved drug is seeking *exclusive approval* . . . described in subsection (a)." 21 U.S.C. § 360cc(c)(1) (emphasis added). That is precisely what occurred here. Lumryz is "otherwise the same" as Xywav—it contains the same active moiety and is intended for the same use. Avadel sought from the FDA "exclusive approval" "described in subsection (a)" for Lumryz. For the Agency to grant such approval, Avadel had to demonstrate that Lumryz was "clinically superior" to Xywav. Because it did so, the Agency had the power to grant "exclusive approval" to Lumryz under subsection (c).

This court is not the first to interpret § 360cc in this way. The Eleventh Circuit did so in *Catalyst*. Recall, under § 360cc(b), the FDA is permitted to approve "a drug that is otherwise the

same" during an approved drug's exclusivity period, if: (1) the FDA determines that the approved drug's sponsor cannot supply the drug in sufficient quantities or (2) if the approved drug's sponsor consents to the subsequent drug's approval. The court in *Catalyst* read subsection (c) to create an additional exemption. It wrote that § 360cc contains "*three* statutory exemptions to market exclusivity." *Catalyst*, 14 F.4th at 1312 (emphasis added). Two can be found in subsection (b) and the third in subsection (c). *See id.* The court said that subsection (c) did not apply in that case, because "there is no record evidence that Jacobus [the subsequent drug's sponsor] filed its NDA based on the representation that Ruzurgi [the subsequent drug] is clinically superior to Firdapse [the approved drug]." *Id.* The converse is true here. Avadel filed its NDA for Lumryz as "clinically superior" to Xywav. Under this and the *Catalyst* court's reading of § 360cc, subsection (c) itself authorized the FDA to grant "exclusive approval" to Lumryz before Xywav's exclusivity expired. 21 U.S.C. § 360cc(c)(1).

This interpretation has implications for the interaction between subsections (a) and (c). Subsection (a) is not, as the FDA contends, limited to determining whether an already approved drug can block approval of a new drug. FDA's Mem. at 6 (stating that subsection (a) concerns the "the *scope* of exclusivity") (emphasis in original); AR529 (explaining that § 360cc(a) of the ODA "prevents [it] from approving or licensing the same drug for the same use or indication . . . until the expiration of seven years from the date of approval or licensure"). And, subsection (c), contra the FDA, is not limited to deciding whether a newly approved drug can receive a period of exclusivity. FDA's Mem. at 5 (describing the subsection (c) inquiry as "a condition of orphan-drug exclusivity for the newly approved drug"); AR529 (stating § 360cc(c) "concerns [the] potential eligibility of a subsequent drug for its own period of [orphan drug exclusivity] and does not address whether a subsequent drug's approval is blocked by another drug's [orphan drug

exclusivity] even where clinical superiority of the subsequent drug has been shown . . . . [T]he blocking effect of [orphan drug exclusivity] of a previously approved drug is instead described in [§ 360cc(a)]").

Instead, subsection (c) is applicable whenever a second drug seeks "exclusive approval" based on "clinical superiority," regardless of whether there is an ongoing period of exclusivity. The statutory text of subsection (c) makes no distinction between a new drug sponsor facing an unexpired period of exclusivity versus one that does not. Because Avadel sought "exclusive approval" based on Lumryz's "clinical superiority," subsection (c) authorized the FDA to grant Avadel's application upon making that showing.

B. FDA's Determination Regarding Lumryz's Clinical Superiority

Having addressed the statutory interpretation question, the court now considers whether the FDA acted arbitrarily and capriciously in finding that Lumryz is "clinically superior" to Xywav. Jazz asserts that the decision was unlawful for three reasons: (1) it departed from the FDA's longstanding comparable safety requirement; (2) the Agency did not comply with its internal dispute resolution policies; and (3) it was inconsistent with prior FDA determinations and scientific literature. The court is not persuaded by any of these arguments.

1. Comparable Safety

Under the FDA's regulations, the sponsor of a subsequent drug that has the same active moiety and treats the same disease or condition as an approved drug can demonstrate clinical superiority in one of three ways: (1) by providing greater effectiveness than an approved drug; (2) by providing greater safety in a substantial portion of the target population; or (3) "[i]n unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care." 21 C.F.R. § 316.3(b)(3). The

FDA approved Lumryz based on the third criterion. It found that Lumryz's once-nightly dose, as compared to Xywav's twice-nightly dose, provided a greater opportunity for normalized sleep and "is inherently more convenient, easier, and less burdensome" insofar as it eliminates a forced awakening to take a second dose of medication. AR552. At the same time, the FDA acknowledged that Lumryz's higher sodium content presented a "safety concern" that "was present for Xyrem" but "is not present with Xywav." AR554. The Agency nevertheless concluded "that Lumryz is clinically superior to Xywav as a [major contribution to patient care]" because "the benefit of Lumryz's once-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients." *Id.*

a. Claimed "comparable safety" policy

Jazz contends that the FDA's major contribution determination was improper because it departed from "longstanding policy" without explanation. Jazz's Mem. at 24–25. Specifically, Jazz says, it has long been the FDA's policy that "the major contribution pathway 'is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug.'" Jazz's Mem. at 24 (quoting *Orphan Drug Regulations*, 76 Fed. Reg. 64868, 64871 (Oct. 19, 2011)). "Thus, to be considered a major contribution, the new product's changes must not 'render[] the drug less safe or less effective than the approved drug.'" *Id.* at 24–25 (quoting 76 Fed. Reg. at 64871). Lumryz admittedly presents greater safety risks than Xywav because of its higher sodium content. But instead of rejecting Lumryz's application for not satisfying the "comparable-safety policy," the FDA "denied that this agency policy exists" and failed to explain its deviation from the policy. *Id.* at 25. That action, Jazz contends, was arbitrary and capricious. *Id.* (citing *FCC v. Fox Television Stations, Inc.,* 556 U.S. 502, 515 (2009) (stating that agency acts in an

arbitrary and capricious manner when it "depart[s] from a prior policy *sub silentio*" or if it "simply disregard[s] rules that are still on the books")).

The court concludes, however, that the FDA has never had a "comparable safety" policy. Its approval of Lumryz without demanding equivalent safety to Xywav therefore was not arbitrary and capricious.

Neither the ODA nor agency regulations require a showing of comparable safety. Section 360cc defines a "clinically superior" drug disjunctively, as one providing "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." 21 U.S.C. § 360cc(c)(2) (emphasis added). So, too, do the agency's regulations, upon which Congress patterned the statutory definition. *See* 21 C.F.R. § 316.3(b)(3). Neither speak of a comparable safety requirement to satisfy the major-contribution pathway. Such a requirement would be no small matter. Drug sponsors seeking approval under the major-contribution pathway surely would need to know that a showing of comparable safety is a condition of approval. The absence of any mention of comparable safety in either the ODA or the implementing regulations strongly suggests there is no such condition.

Jazz locates its strongest textual evidence for a policy by quoting language from the preamble to the FDA's 2011 orphan drug proposed rulemaking. Jazz's Mem. at 25–27. In that preamble, the FDA stated that, in the proposed rule, it wished 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 ([21 C.F.R.] § 316.3(b)(3)(iii))." 76 Fed. Reg. at 64876 (emphasis added). It further wrote that this revision was "consistent with longstanding

policy." *Id.* The proposed rule itself would have amended § 316.3(b)(3)(iii) to require "a demonstration that the drug provides safety and effectiveness comparable to the approved drug" as a condition of major-contribution approval. *Id.* at 64878.

Jazz's reliance on the preamble is misplaced for two reasons. First, it is settled that "language in the preamble of a regulation is not controlling over the language of the regulation itself." *Entergy Servs., Inc. v. FERC*, 375 F.3d 1204, 1209 (D.C. Cir. 2004) (quoting *Wyoming Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 53 (D.C. Cir. 1999)). The FDA's regulations make no mention of a comparable safety showing for major-contribution approvals.

Second, there is a good reason that the regulations are silent: The FDA expressly declined to adopt a comparable safety condition. In the final rulemaking, in June 2013, the FDA said that it "is deleting the 'safety and effectiveness comparable to the approved drug' language from the final rule" due to the confusion it has caused. *Orphan Drug Regulations*, 78 Fed. Reg. 35117, 35124 (June 12, 2013). It explained that it "did not intend to propose a new standard for major contribution to patient care with this language; . . . [and] did not mean to suggest that direct proof of comparability to the already approved drug would be required." *Id*. Instead, the FDA continued, it had "intended to convey that major contribution to patient care determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product." *Id.* Such factors may include convenience of the treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and the potential for self-administration. *Id*. at 35125. Presumably, when the FDA declined to adopt an express comparable safety requirement, it did not intend to silently maintain one.

Jazz nevertheless insists that a showing of comparable safety remains a binding agency policy for major-contribution pathway applicants. It contends that the preamble "acknowledg[ed] a necessary condition for finding a major contribution," and that in the 2013 final rule, although the agency professed not to adopt a "new standard," it did not "repudiate the old one . . . described in the 2011 preamble." Jazz's Opp'n at 27.

But Jazz again places too much weight on the proposed rule's preamble. "[I]t would be antithetical to the purposes of the notice and comment provisions of the [APA] to tax an agency with 'inconsistency' whenever it circulates a proposal that it has not firmly decided to put into effect and that it subsequently reconsiders in response to public comment." *Commodity Futures Trading Comm'n v. Schor*, 478 U.S. 833, 845 (1986). Here, the 2013 final rule unequivocally states that comparable safety is considered as a relevant factor—but not a precondition—in determining whether a new orphan drug makes a major contribution to patient care. The 2013 final rule represents the agency's "definitive position" on that matter, and the preamble to the 2011 proposed rulemaking does not alter that reality. *Am. Hosp. Ass'n v. Azar*, 964 F.3d 1230, 1239 (D.C. Cir. 2020); *id.* at 1239–40 (rejecting the plaintiffs' argument that the agency's interpretation was "inconsistent with earlier agency pronouncements" where the plaintiffs merely pointed to an ambiguous statement made in an earlier rulemaking).[5]

b. Orphan drug "precedents"

Without a valid textual hook, Jazz alternatively relies on the FDA's past decisions as to other orphan drug products. Jazz calls these "precedents" of the Agency's longstanding "comparable safety" policy. Jazz's Opp'n at 29–34. This argument fares no better.

[5] Elsewhere, Jazz contends that the language in the 2011 preamble is an "advisory opinion," which the FDA was obligated to apply unless amended or revoked. Jazz's Mem. at 25–26 (citing 21 C.F.R. § 10.85(d)(1), (e), (g)). Whatever label is given to the preamble's language is not dispositive. What matters is that in the final rule the agency expressly disavowed the need for "direct proof of comparability to the already approved drug." 78 Fed. Reg. at 35124.

For starters, the court is skeptical of Jazz's approach. The FDA has made clear that it believes that major contribution approvals will be "unusual," 78 Fed. Reg. at 35125 (refusing to remove "in unusual cases" from § 316.3(b)(3)(iii)), and will be "evaluated on a case-by-case basis for each drug product," *id.* at 35124. Given the array of factors the FDA considers in making a major contribution determination, *see id.* at 35125, discerning the existence and contours of a policy through "precedents" seems a highly subjective enterprise. At the same time, *disproving* the existence of a policy is an equally fraught task. If there is no policy, then the agency has no reason to address the topic. Even Jazz admits that these prior decisions, at most, "can help to illustrate how a publicly stated, longstanding policy works in practice, but they cannot disprove its existence." Jazz's Opp'n at 29.

In any event, the court has reviewed the eight "precedents" identified by the parties. The court concludes that, individually and collectively, these examples do not establish the existence of a "comparable safety" policy, as Jazz claims.

The court starts with the three decisions that pre-date the 2011 proposed rulemaking. Like the parties, the court identifies them by drug brand name and active moiety. None establish a "longstanding policy."

- BeneFix® (coagulation factor IX) (1997) (AR1433–37): The FDA approved BeneFix because of "its clinical superiority by virtue of its greater safety as compared to the previously licensed orphan products." AR1433. Because Benefix did not involve a major contribution evaluation, it is not a helpful comparator.
- Rebif® (interferon beta-1a) (2002) (AR1438–1442): The FDA approved Rebif because "it is clinically superior in terms of efficacy." AR1440. Because Rebif did not involve a major contribution evaluation, it too is not a helpful comparator.

The Rebif decision nevertheless is informative because it suggests the absence of a "comparable safety" policy. It states: "[T]he very term 'major contribution to patient care' implies a more global assessment. So, for example, an assessment of safety or effectiveness of the new form of the subsequent product *might be considered* in determining whether the drug made a major contribution to patient care. However, even in this instance, there can not [sic] be an infinite number of comparison criteria if this provision of the regulation is to be meaningful." AR1440 (emphasis added). Saying that an assessment of safety "might be considered" in evaluating a major contribution is the very opposite of a strict "comparable safety" policy.

- Raviciti® (glycerol phenylbutyrate) (2005) (AR1466–1471a): The FDA denied Raviciti orphan drug designation because it failed to demonstrate a major contribution to patient care. AR1471. As part of the denial, the FDA indicated to the sponsor it would need to "first demonstrate with reasonable certainty that [Raviciti], at the proposed dosages, would offer at least comparable safety and effectiveness profiles as those of [the approved drug]." *Id*. Understandably, Jazz views this as proof of a policy. But closer inspection shows otherwise. The FDA mentioned comparable safety in the context of a drug sponsor that had "expect[ed] that the safety and effectiveness profiles [of Raviciti] would be similar to those of" the approved drug, yet had no "[d]ata to support that expectation" because "the drug ha[d] not been clinically studied in patients with" the relevant disease. AR1468. The Agency's demand for a safety showing when the sponsor had failed to make one at all is not indicative of a "comparable safety" policy.

The exemplars that post-date 2011 do not establish a policy, either. At most, they show that the FDA evaluates safety as one relevant factor in making a major contribution assessment.

- Orenitram® (oral treprostinil) (2012) (Griffin Decl. I, Ex. 1, ECF No. 36): The FDA denied orphan drug designation to Orenitram in part because it failed to make a sufficient hypothetical showing of "clinical superiority." *Id.* at 3. The Agency wrote that "clinical superiority is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug." *Id.* Though this statement is consistent with Jazz's theory, its weight is diminished by the fact that, due to heavy redactions, the court cannot discern whether the agency rejected a major contribution hypothesis due to the lack of comparable safety, comparable effectiveness, or for some other reason.

  The FDA later approved Orenitram but denied it marketing exclusivity in 2016. *See* Second Decl. of Sean C. Griffin [hereinafter Griffin Decl. II], Ex. 46, ECF No. 62-7. Here, the denial was based on a failure to show "clinical superiority." The sponsor did not prove greater efficacy, greater safety, or an adequate major contribution. *Id.* at 2. As to major contribution, the agency rejected that pathway based on the "inconveniences and complexities to the patient associated with daily dosing." *Id.* It said nothing about the failure to make a showing of comparable safety as a reason for denial.

- Procysbi® (cystemine bitartrate) (2013) (AR1496–1506): The FDA approved Procysbi as "clinically superior" based on a major contribution because it could be used every 12 hours instead of every six. AR1504–05. As part of its review, the agency noted that "a comprehensive safety analysis could not be conducted"

because only "top-line safety data was available." AR1501. The agency's overall conclusion was that the safety profile was "similar to" the approved drug, although "higher incidence" of gastrointestinal adverse events were observed in a key clinical trial. *Id.* The Procysbi approval does not support a comparable safety requirement. To the contrary, the Agency repeated what it had said in the 2013 final rule, which is that it makes major contribution determinations "on a case-by-case basis considering the unique nature of the drug and disease, among other factors." AR1504. The FDA determined that Procysbi's less frequent dosing overcame its documented greater safety risks—the same as it would a decade later as to Lumryz.

- Signifor® LAR (pasireotide) (2018) (Griffin Decl. I, Ex. 10, ECF No. 36-9): The FDA approved Signifor based on a major contribution in large part because the new orphan drug had a once-per-month intermuscular injection dosage administered by a health-care provider versus twice daily, self-administered subcutaneous injections. *Id.* at 3. The agency determined that the "safety and efficacy profiles" of the two drugs were "similar," though it could not evaluate the new drug for greater safety. *Id.* Though it made a "similar" safety-profile finding, the FDA nowhere said it had done so to satisfy a comparable safety condition of approval.
- Valtoco® (diazepam nasal spray) (2020) (AR1522–1528): The FDA approved Valtoco based on a major contribution because, unlike the approved drug that had to be administered rectally, Valtoco is taken as an intranasal spray. AR1524. The agency noted that safety concerns raised by a citizen petition were unsubstantiated.

AR1527. But once more, the FDA did not reference any comparable safety requirement.

After the close of the record, Jazz submitted an eighth exemplar. *See* Third Decl. of Sean C. Griffin [hereinafter Griffin Decl. III] , Ex. 48, ECF No. 99-2. This one was for the drug Mycapssa® (octreotide), which the FDA approved in June 2020 as "clinically superior" based on a major contribution. Mycapssa is taken orally while the approved drug is administered through injections. *Id*. In its approval, the Agency noted that data showed that Mycapssa's safety profile was "consistent" with approved drug products but did not establish greater safety. *Id.* at 5. The Agency also explained the role of safety in assessing a major contribution: "A drug is not required to have comparable effectiveness or safety to the previously approved drugs in order to provide a [major contribution] over those drugs, but relative effectiveness and safety of the drug may be relevant in assessing whether the drug makes a [major contribution to patient care]." *Id.* In a footnote, the FDA acknowledged that in 2010 it had advised the sponsor that it would have to demonstrate "comparable [] efficacy and safety," and that ten years later it had made similar statements in a consult request. *Id.* at 5 n.7. The FDA said, however, that it no longer stood by those statements because it had determined that "agency precedent is devoid of instances in which we refused to find a [major contribution] for a drug based only on a failure to show comparable safety or efficacy." *Id.*

As with the other exemplars, the Mycapssa approval does not prove that the FDA has adopted a policy requiring a comparable safety showing to secure approval through the major-contribution pathway. In fact, the decision on Mycapssa says just the opposite. Jazz tries to make hay of the agency's acknowledgment that it twice advised the sponsor of a comparable safety

requirement. But two such instances ten years apart with respect to a single drug application is weak evidence of a "longstanding" comparable safety condition.

In short, none of the eight "precedents" supports Jazz's position. Among them, there is not a single example of the FDA *rejecting* a new orphan drug approval based on a major contribution because the drug's sponsor failed to establish comparable safety to an approved drug.

* * *

The FDA has never adopted a "comparable safety" policy. It therefore did not deviate from a policy without adequate explanation when it approved Lumryz, and it did not act arbitrarily and capriciously.

2. Compliance with Agency Policies and Procedures

Next, Jazz urges the court to vacate the FDA's approval of Lumryz because the Agency "departed from inter-agency dispute resolution procedures without explanation." Jazz's Opp'n at 34. Specifically, after the Review Division declined to find that Lumryz was "clinically superior" to Xywav, the OOPD sought out a second opinion from Sleep Team experts housed in the Center for Devices and Radiological Health, which regulates medical devices, not drugs. *Id.* at 34–35. After the Sleep Team opined that Lumryz's once-nightly dosing did in fact provide clinical benefits over the twice-nightly Xywav, the Review Division changed its earlier position.

According to Jazz, by seeking a second opinion from the Sleep Team, the Agency failed to comply with OOPD's Standard Operating Procedures and the FDA's Staff Manual Guide. Jazz's Mem. at 28–29. Jazz says that those policies required OOPD to (1) elevate the dispute through its own chain of command, (2) elevate the dispute through the Review Division's chain of command, or (3) refer the dispute to the Orphan Drug Products Policy Council. *Id.* at 29 (citing AR2191-92; Griffin Decl. I, Ex. 4, ECF No. 36-3; Ex. 8, ECF No. 36-7). It instead went to a

review team in a different center "with no experience in regulating drugs, let alone orphan-drug exclusivity." Jazz's Opp'n at 35. This, Jazz argues, was arbitrary and capricious.

The court disagrees. For starters, Jazz's factual premise that OOPD reached an "impasse" with the Review Division, which triggered internal dispute resolution policies, is not supported by the record. Jazz's Mem. at 29. True, the Review Division opined in a single sentence and without elaboration that Lumryz did not provide a major contribution based on once-nightly dosing. AR480. But it also said that its written response was a "preliminary review," "which is ongoing," AR479, and that the response did "not represent the [Review Division's] final or current thinking on the matter," as "the orphan-drug exclusivity issues associated with this application remain under review." AR483–84. That does not sound like a final position that caused an "impasse."

Moreover, nothing in the OOPD's Standard Operating Procedures or the FDA's Staff Manual Guide precluded OOPD from seeking a second consult from a different center within the Agency. The Standard Operating Procedures provide that, in the event an agreement cannot be reached with the consulted review center, the decision "should be discussed" with the OOPD Director, OOPD regulatory counsel, the consulted center (in this case, the Center for Drug Evaluation and Research), or sponsors "as needed." AR2192. The words "should" and "as needed" do not denote a proscriptive rule. They indicate some degree of discretion. And OOPD exercised discretion to gather additional information from a different center within the FDA that had relevant expertise and experience. *See* AR587 (stating that Sleep Team members are "board certified sleep specialists" based on their training and expertise in sleep disorders); AR533 n. 44 (noting that one of the Sleep Team members treats patients with sleep disorders in a clinical setting). Doing so was not arbitrary and capricious.

In any event, as a "general principle" "it is always within the discretion of . . . an administrative agency to relax or modify its procedural rules adopted for the orderly transaction of business before it when in a given case the ends of justice require it." *Am. Farm Lines v. Black Ball Freight Serv.*, 397 U.S. 532, 539 (1970) (cleaned up). Such discretionary actions are "not reviewable except upon a showing of substantial prejudice." *Id.* (internal quotation marks and citation omitted); *see also Associated Press v. FCC*, 448 F.2d 1095, 1104 (D.C. Cir. 1971).

Jazz does not genuinely grapple with the *American Farm Lines* rule. It says only that the Standard Operating Procedure and Staff Manual Guide "help to ensure that the FDA does not break a sponsor's statutory right to orphan-drug exclusivity without input from and alignment with experts who are most directly involved in regulating a given drug." Jazz's Mem. at 30; *see* Jazz's Opp'n at 35. But a rule that "help[s] to ensure" input from persons with expertise is a far cry from a rule that is "intended primarily to confer important procedural benefits upon individuals in the face of otherwise unfettered discretion." *Am. Farm Lines*, 397 U.S. at 538. The former is subject to *American Farm Lines*; the latter is not. *See Lopez v. FAA*, 318 F.3d 242, 247 (D.C. Cir. 2003) (distinguishing between "procedural rules benefitting the agency" and "procedural rules benefitting the party otherwise left unprotected by agency rules").

This case bears no resemblance to *Massachusetts Fair Share v. Law Enforcement Assistance Administration*, 758 F.2d 708 (D.C. Cir. 1985), which Jazz calls "instructive." Jazz's Mem. at 29. In that case, the D.C. Circuit found that one agency's unilateral withdrawal of a conditional grant in a federal crime prevention program that was "jointly developed and administrated" by two agencies was improper. *Mass. Fair Share*, 758 F.2d at 711–12 (internal quotation marks and citations omitted). There, the "highly-refined procedures for treatment" of grant applications were "jointly formulated, publicized and instituted by [both agencies] in a

statutorily-sanctioned cooperative endeavor," and "described a selection methodology assigning equal roles to the two agencies" for selecting grant finalists. *Id*. Per those procedures, the Circuit concluded, "[t]he power to revoke, no less than the power to grant, was subject to the requirement of joint agency action." *Id*. at 712.

Here, in sharp contrast, the Standard Operating Procedures and the Staff Manual Guide are not "self-adopted rules by which the interests of others are to be regulated." *Id.* at 711. They are merely the internal procedures by which the FDA makes decisions about orphan drug exclusivity. AR2186 ("This Standard Operating Procedures and Policies (SOPP) document describes the administrative and review procedures for the Orphan Drug Exclusivity Decisions, which occur in the [OOPD]."). They do not establish individual rights or entitlement to any benefit. Nor does the Agency's authority to act depend on those rules.

Finally, Jazz has made no "showing of substantial prejudice." *Associated Press*, 448 F.2d at 1104. There is no indication OOPD's consultation with the Sleep Team impeded Jazz's ability to protest the exclusive approval of Lumryz. To the contrary, Jazz's challenge to Avadel's application was nothing less than robust. *See e.g.*, AR851–72 (22-page letter from Jazz, dated September 16, 2021); AR1240–49 (10-page letter from Jazz, dated December 6, 2022); AR1291–42 (52-page PowerPoint presentation by Jazz on January 18, 2023).

Accordingly, the court concludes that OOPD's consultation with the Sleep Team regarding the benefits of Lumryz's once-nightly dosing was not arbitrary and capricious.

3. The Agency's Consideration of the Scientific Evidence

OOPD found that Lumryz's once-nightly dosing makes a major contribution to patient care for two primary reasons. First, the once-nightly 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 who must either wake up to take a second dose (disrupting sleep architecture) or allow the drug to wear off after 2.5–4 hours (reverting patients back to their naturally occurring, disrupted sleep architecture.)." AR552 (internal quotation marks and citation omitted). Second, Lumryz's "extended release properties provide for longer periods between doses . . . [and] eliminate[] the need to awaken in the middle of sleep to take a second dose," which the FDA considered to be "significantly more convenient for patients, an advancement in the ease of drug administration, and a reduction in the treatment burden." *Id*.

Jazz challenges only the first of these findings.[6] It does so on three grounds. First, Jazz argues that the FDA "irrationally minimized" the clinical significance of reduced sodium content for all narcolepsy patients. Jazz's Mem. at 31. Second, it maintains that the FDA "overstated the downsides of twice-nightly dosing." *Id*. And third, Jazz insists that the Agency "inflated the upside of one-nightly dosing" by claiming that it allows patients to "achieve 'normal' sleep and sleep architecture." *Id.* All three arguments are belied by the record evidence.

Fundamentally, these are challenges to an "area of special expertise" of the FDA. *Baltimore Gas & Elec. Co. v. Nat. Res. Def. Council, Inc*., 462 U.S. 87, 103 (1983). "When FDA makes scientific judgments, [the court] owes the agency the 'most deferential' review." *Takeda Pharms. U.S.A., Inc. v. Burwell*, 691 F. App'x 634, 637 (D.C. Cir. 2016) (per curiam) (quoting *Baltimore Gas*, 462 U.S. at 103)); *see also Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (stating that "the FDA's contrary determination is a scientific judgment within its 'area of

[6] By contesting only one of the two grounds on which the FDA made a major contribution finding, the court arguably need proceed no further. "[W]hen an agency relies on multiple grounds for its decision, some of which are invalid, [the court] may nonetheless sustain the decision as long as one is valid and the agency would clearly have acted on that ground even if the other were unavailable." *Xcel Energy Servs. Inc. on Behalf of Sw. Pub. Serv. Co. v. FERC*, 77 F.4th 1057, 1068 (D.C. Cir. 2023) (cleaned up). Although Avadel urges the court to take that approach, Avadel's Mem. at 35, the FDA has not, FDA's Mem. at 29–33. It has not affirmatively stated that it would have found Lumryz to provide a major contribution based solely on the lesser burdens of taking the medication once nightly. The court therefore will proceed to consider Jazz's arguments.

expertise,' the kind of judgment to which this court gives a 'high level of deference'") (citation omitted); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (The FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *see also Fox v. Clinton*, 684 F.3d 67, 75 (D.C. Cir. 2012) ("[A]rbitrary and capricious review is fundamentally deferential—especially with respect to matters relating to an agency's areas of technical expertise.") (cleaned up). That deference is not absolute, of course. An agency's decision "must be the product of reasoned decisionmaking." *Fox*, 684 F.3d at 74–75. With these principles in mind, the court turns to Jazz's arguments.

a. Lumryz's sodium content

Like Jazz's earlier-approved drug, Xyrem, Lumryz has a significantly higher sodium content than Xywav. "At the recommended daily dose of 6 g to 9 g, Lumryz contains approximately 1,100 mg to 1,640 mg of sodium whereas Xywav contains 87 to 131 mg." AR553. The Centers for Disease Control and Prevention guidelines recommend less than 2,300 mg of sodium each day, meaning a 9-gram dose of Lumryz is equivalent to 71% of the daily recommended limit. AR537.

Jazz says that the FDA "minimized the importance of Xywav's lower sodium by omitting any discussion of its clinical significance and by claiming that patients can readily achieve an equivalent reduction through dietary changes." Jazz's Mem. at 31. According to Jazz, the agency "never acknowledged the weight of interests at issue on the 'risk' side of the balance—material reductions in patients' blood pressure, material increases in the likelihood that any given patient will develop hypertension and/or cardiovascular disease, and material decreases in cardiovascular morbidities." *Id.* at 32. Pointing to extra-record FDA studies demonstrating the difficulties of

lowering sodium intake, *id.* at 33,[7] Jazz argues that the agency "blithely suggested that narcolepsy patients could achieve equivalent sodium reduction through 'other ways' or 'other means,'" and the "[t]he truth is that the ***only*** way for most narcolepsy patients taking oxybate to eliminate 1,500 mg of daily sodium . . . is to switch to Xywav. It was arbitrary and capricious for OOPD to pretend otherwise." *Id.* at 33–34 (emphasis in original).

Jazz is simply wrong. The FDA explicitly recognized the risks of Lumryz's higher sodium content. Quoting an earlier consult memorandum comparing the sodium contents of Xywav and Xyrem, the Agency wrote:

> The relationship between daily salt intake and cardiovascular morbidity is widely accepted, as is the need for salt intake to be generally restricted and not only in subjects with conditions such as hypertension, cardiac failure, and impaired renal function. The difference in sodium content between Xywav and Xyrem is both substantial and clinically meaningful when daily sodium intake requires restriction in patients who concomitantly have conditions such as cardiac failure, hypertension, and renal impairment.

AR554. The FDA went on to "acknowledge[] that the sodium content of Lumryz raises the same safety concern that was present for Xyrem and that is not present with Xywav[,]" and that "the difference in sodium content between Xywav and Lumryz is 'very likely to be clinically meaningful in all patients with narcolepsy.'" *Id.* It therefore concluded that for this "one specific measure, i.e. reduced sodium," "Xywav is safer than Lumryz in all such patients." *Id*. The FDA did not, as Jazz contends, "obscure[] the clinical superiority of Xywav by implying that the sodium

[7] The court addresses Defendants' challenges to these out-of-record citations in a separate order. *See* Avadel's Mot. to Strike Pl.'s Extra-Record Declaration and Exhibits, ECF No. 42; Federal Defs.' Mot. to Strike the Decl. of Sean C. Griffin and Attachments and Exhibits Thereto, ECF No. 47.

difference between Xywav and Lumryz is something minor[.]" Jazz's Mem. at 32. It said just the opposite.

Nor did the FDA "pretend" that it is easy to reduce sodium intake by 1,500 mg per day or dismiss Xywav as a means of doing so for narcolepsy patients. Jazz's Mem. at 34. To the contrary, quoting from the Xyrem–Xywav consult memorandum, the agency recognized that for sodium-sensitive patients, "Xywav rather than Xyrem will be the medication of choice." AR554. The agency did not say a patient's choice between Xywav and Lumryz would be different.

Admittedly, the FDA did not spell out precisely the "other ways" in which narcolepsy patients can reduce sodium intake in their diets. AR555. But that does not make the agency's decision-making arbitrary and capricious. The APA does not require "a model of analytic precision"—so long as the "the agency's path may be reasonably discerned" and its explanations contain a "rational connection between the facts found and the choice made," the APA is satisfied. *Dickson v. Sec'y of Def.*, 68 F.3d 1396, 1404 (D.C. Cir. 1995) (internal quotation marks omitted). The FDA's "path" as it relates to Lumryz's sodium content is clear and unmistakable.

The Agency made a scientific judgment. For narcolepsy patients who are not sensitive to sodium intake, the FDA acknowledged the risks of a higher sodium content but concluded "that a once-nightly dosed oxybate drug will provide a significant therapeutic advantage." AR555.

> [W]e consider the benefit offered by once-nightly dosing to outweigh the risk of increased sodium intake in such patients because having to wake up to take a second dose is antithetical to oxybate's goal of improving sleep; disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increase risk for accidents and death, and detrimental effects on both psychological and physical health; and there are other ways such patients may reduce sodium in their diet.

Id. As to sodium-sensitive patients, the FDA explained that "healthcare practitioners would need to weigh the benefits of once-nightly dosing against the severity of the patient's sodium sensitivity

and the nature of their comorbidities to determine whether, in the practitioner's judgment, use of Lumryz or Xywav was appropriate." *Id.* For that reason, the FDA required that Lumryz's packaging contain a "label[] with an appropriate warning and precaution for patients sensitive to high sodium intake, as has been done with Xyrem." *Id.* Ultimately, the agency "weighed the benefits and risks of Lumryz and determined that the safety profile is adequate to meet the requirements for marketing approval." *Id.*; *see also id.* at 555 ("Thus, although Lumryz has an increased sodium burden compared to Xywav, the safety risk from such an increase is not significant enough to preclude Lumryz from meeting the requirements for marketing approval."). None of the extra-record sodium studies that Jazz cites even hint that the FDA's "weigh[ing]" was improper.

"Happily, it is not for the judicial branch to undertake comparative evaluations of conflicting scientific evidence. [A court's] review aims only to discern whether the agency's evaluation was rational." *Natural Res. Def. Council v. EPA*, 824 F.2d 1211, 1216 (D.C. Cir. 1987) (citation omitted). The FDA's approval of Lumryz notwithstanding its higher sodium content satisfies that standard.

b. Claimed disadvantages of twice-nightly dosing

Next, Jazz takes issue with the FDA's views on the adverse effects of twice-nightly dosing. Jazz's Mem. at 34–37. It says that it is "demonstrably false" that twice-nightly dosing disrupts sleep and can have adverse health effects, as even normal sleep patterns can involve multiple awakenings without harm to individuals. *Id.* at 34, 35–37. It further argues that the FDA failed to grapple with the "clinical reality of narcolepsy," which is that most narcolepsy patients suffer from disrupted nighttime sleep and no treatment has yet to restore "normal" sleep patterns, but studies do show that twice-nightly dosing is actually "highly effective" at consolidating sleep. *Id.* at 35.

The court is unpersuaded. The very Sleep Team consultation that Jazz criticizes acknowledged that brief nocturnal arousals are "normal and [do not] contribute to sleep fragmentation, sleep loss, or daytime sleepiness." AR506. But ordinary arousals were not the focus of the Sleep Team's concerns. Rather, it was the duration of sleep disruption that occurs when waking to take a second dose of medicine. AR508. The Sleep Team concluded that "[a]wakening to take a second dose necessarily disrupts sleep and causes sleep fragmentation." *Id.* "That duration of time in stage W[8] is prolonged and will adversely impact a clinical measure called Wake After Sleep Onset (WASO)—a metric of how much wakefulness happens in a night of sleep." AR508. The goal is to maximize the time in sleep and minimize WASO. "Even with a single nocturnal arousal, there can be impairment of alertness and decline in cognitive performance the following day." AR511. Awakening to take a second dose increases the period of WASO, resulting in a "disrupted sleep architecture." *Id.* The FDA thus provided a rational explanation of the differences between ordinary brief arousals and a prolonged sleep disruption caused by a second dosing of medication.

Nor did the FDA ignore that "twice-nightly sodium oxybate improves and consolidates sleep." Jazz's Mem. at 41. As Jazz acknowledges, the administrative record contains studies reaching that conclusion. *See id.* at 37 (citing AR1200, 1734, 1736). Also, the FDA recognized Xywav and Xyrem as part of "a class of drugs that improve[] symptoms of [excessive daytime sleepiness] and decrease[] episodes of cataplexy," by "consolidating nighttime sleep." AR536. Thus, it is simply inaccurate to say that the FDA failed to "acknowledge[] [the] overwhelming scientific consensus" that "twice-nightly sodium oxybate improves and consolidates sleep."

[8] "[T]he normal adult has a very brief return to stage Wake (stage W), in the transition of going from cycle to cycle, though this awakening is not typically remembered, is normal and does not contribute to sleep fragmentation, sleep loss, or daytime sleepiness." AR506.

Jazz's Mem. at 41. It well understood those benefits. Jazz's extra-record evidence does not alter that conclusion. *Id.* at 39–41.

c. The benefits of once-nightly dosing

Jazz offers multiple critiques of the FDA's finding that once-nightly dosing "provides an opportunity for narcolepsy patients ***to achieve normal sleep architecture***." Jazz's Mem. at 41 (emphasis in original). None rises to arbitrary and capricious agency decision-making.

First, Jazz argues that "Lumryz is not approved to improve, much less 'normalize,' disrupted nighttime sleep." *Id.* The FDA does not contend otherwise. The Agency never said that once-nightly dosing will in fact normalize sleep architecture. Rather, the FDA determined that the "dosing regimen of Lumryz 'provides *an opportunity* for narcolepsy patients to achieve normal sleep architecture" over Xywav, because it does not require waking up to take a second dose. AR552 (emphasis added). The FDA never said that taking Lumryz was certain to normalize sleep architecture.

Second, Jazz argues that the Agency's claim with respect to normalizing sleep architecture "implies that Lumryz is more effective than Xywav," which is contradicted by the agency's determination that there "'is no evidence suggesting that the efficacy of Lumryz is different from that of [Xywav].'" Jazz's Mem. at 41 (quoting AR1369). But there is no contradiction between those statements. The agency reasonably could conclude that, while Lumryz was not clinically superior on greater effectiveness, it provides a major contribution because of the greater "opportunity" for normal sleep architecture and greater ease of administration, as compared to a medication dosed twice nightly.

Third, Jazz says that the FDA's "claim is implausible on its face," as there is yet no treatment invented that can "restore 'normal' sleep to a patient suffering from [disrupted nighttime

sleep] as a result of narcolepsy." *Id.* at 41. But, of course, the agency never said what Jazz claims. It recognized only that once-nightly dosing offers a better chance at achieving less disrupted sleep.

Fourth, Jazz maintains that an Avadel study that the FDA relied upon does not establish that Lumryz normalized sleep in narcolepsy patients. *Id.* at 42. The cited study merely showed that narcolepsy patients who used Lumryz cut the number of nightly arousals by half (80 versus 40). *Id.* Jazz also cites an extra-record study showing that, in a *Xyrem* pediatric trial, Xyrem users had a similar decline in nighttime arousals. *Id.* According to Jazz, these studies establish that the "dosing schedule does not materially impact oxybate's ability to reduce nocturnal arousals," and that "once-nightly dosing will [not] magically restore narcolepsy patients to 'normal' sleep." *Id.* at 42–43.

But Jazz's citation to these studies is a red herring. Once more, the FDA never said that Lumryz would normalize sleep architecture. It merely said that Lumryz offered a greater *opportunity* to do so. The FDA adequately explained why it came to that conclusion. AR505–12, 516–17, 550–52.

Finally, Jazz contends that the FDA was wrong to find that subjective factors of "convenience" and "preference" outweighed "increased risks of cardiovascular morbidity to everyone." Jazz's Mem. at 44. But that is an overly simplified characterization of what the FDA did here. The FDA consulted with internal sleep specialists who opined that a once-nightly dosing of an oxybate product provided a greater opportunity for improved sleep over a twice-nightly dose. AR504–12. The agency then reasonably explained why that possible benefit outweighed the risks associated with increased sodium intake. That is all the FDA was required to do under the APA.

In sum, the FDA reasonably concluded that because "[s]leep consolidation is the intended purpose of oxybate therapy," a drug with once-nightly dosing makes a major contribution to patient

care over a drug that requires a patient to wake up to take a second dose. AR1381. The FDA's approval of Lumryz was not arbitrary or capricious.

V. CONCLUSION

For the foregoing reasons, the court grants Avadel's and Federal Defendants' cross-motions for summary judgment, ECF Nos. 41-2, 45-2, and denies Jazz's motion for summary judgment, ECF No. 34-2. A final, appealable order entering judgment in favor of Defendants accompanies this Memorandum Opinion.

Dated: October 30, 2024

Amit P. Mehta
United States District Judge