IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

DEPOMED INC., Plaintiff,	)	
v.	)	Case No. 12-1592 (RLW)
UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES, *et al.*, Defendants.	)	

DEFENDANTS' REPLY IN SUPPORT OF MOTION TO DISMISS OR, IN THE ALTERNATIVE, FOR SUMMARY JUDGMENT

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INTRODUCTION

The Food and Drug Administration ("FDA") has appropriately construed silence in the orphan exclusivity statute in accordance with clear Congressional intent. Depomed disparages the government's "policy-laden" defense of FDA's exclusivity decision, but Depomed does not even try to suggest what conceivable legislative interest would be served by interpreting the Orphan Drug Act in the manner Depomed advances, which would reward Gralise with an undeserved seven-year exclusive marketing period of unprecedented breadth.

Instead, Depomed's brief focuses on arguments that make little sense. It contends, for example, that this Court should disregard FDA's comprehensive decisional memorandum setting forth the basis of its decision to deny exclusivity to Gralise even as it criticizes the adequacy of the agency's prior explications of its actions. As demonstrated below, Depomed's arguments on this point are unconvincing but, even if accepted, they would necessarily lead the Court to remand this matter back to FDA to produce exactly the comprehensive explanation that Depomed seeks to avoid. Depomed also urges the Court to address whether FDA should have granted Gralise "designation" under the orphan drug provisions. But Depomed's claim is moot because FDA has already designated Gralise. Even if this claim were properly before the Court, FDA has reasonably construed its own regulations to require that Gralise's designation include a plausible hypothesis of clinical superiority over the previously approved "same" drug, Neurontin, and that interpretation is entitled to substantial deference.

Finally, Depomed argues that the assertedly unambiguous command of the statutory language requires that it be interpreted in a manner that is quite literally the opposite of what Congress intended. Instead of helping patients with a rare disease by incentivizing the development of new and innovative drugs that may not otherwise have been produced,

Depomed's cramped and self-serving construction of the orphan drug exclusivity provisions would *penalize* patients with higher prices by awarding lucrative marketing exclusivity periods to companies (like Depomed) that have done nothing meaningful to benefit those patients. Depomed does not even challenge FDA's conclusion that its product, Gralise, has not been shown to be clinically superior to other versions of the same drug that are already on the market.

In support of its narrow "plain language" reading of the statute, Depomed urges this Court to abandon bedrock principles of administrative law, which accord substantial deference to an administrative agency's interpretation of a statute it administers (and even greater deference to its interpretation of its own regulations), particularly where, as here, the statute does not address the precise question at issue – whether exclusivity attaches when the same drug has previously been approved for the same orphan indication.

For all of these reasons, Depomed's complaint should be dismissed, or, in the alternative, summary judgment should be granted in favor of the federal defendants.

A. This Court Should Review FDA's November 13, 2012, Decision

Depomed continues to insist that the Court should ignore FDA's detailed November 13, 2012, final decision responding to Depomed's September 9, 2011, request for exclusivity, and instead focus its attention on the agency's early communications to Depomed.

First, Depomed argues that its September 2011 letter was not a formal "request for reconsideration," relying on *Collagenex Pharms., Inc. v. Thompson*, No. 03-1405, 2003 WL 21697344 (D.D.C. Jul. 22, 2003). Pl. Opp. at 8. In that case, the court declined to construe a plaintiff's letter to FDA as a request for reconsideration because it was submitted in an effort to avoid litigation. *Id.* at *15. After FDA issued its decision, however, the court reviewed that decision and upheld FDA's interpretation of the statute at issue:

> The 2003 Decision thus represents the very current and new articulation of the agency's interpretation of the statute. * * * The Court defers to FDA in its interpretation of the statutory definition of an "antibiotic." The 2003 Decision provides a reasonable interpretation of ambiguous language which is certainly permissible. The 2003 Decision "claims the merit of its writer's thoroughness, logic, and expertness," and, as such, is entitled to deference.

Collagenex Pharms. v. Thompson, No. 03-1405, 2005 WL 256561, at *12-13 (Jan. 19, 2005).

Thus, even though the court did not initially view the letter as a request for reconsideration sufficient to undermine the ripeness of that case, the court ultimately reviewed the agency's decision, which, as here, was issued after the litigation commenced in response to the plaintiff's letter. This Court should similarly review FDA's response to Depomed's September 2011 administrative submission, whether viewed as an initial request for exclusivity, a request for reconsideration, or (as Depomed now attempts to characterize it) an offer to enter into settlement discussions. Regardless of Depomed's intentions when it submitted that letter to the agency, Depomed brought new arguments and evidence before the agency in support of its claims for exclusivity and clinical superiority, which the agency thoroughly considered. The agency's final decision resolving those issues is properly before this Court.

Second, Depomed attempts to distinguish the cases cited in FDA's opening memorandum based on their procedural posture and their failure to address what Depomed identifies as the "relevant question . . . whether the agency's belated statement of reasons can fairly be characterized as reflecting the original decision-making process, which occurred here in January 2011, at the latest." Pl. Opp. at 8-9. But Depomed's framing of the "relevant" question wrongly presupposes that the agency's letter is only reviewable if it somehow reflects the "original" decision-making process in January 2011, as if the November 2012 letter does not itself reflect FDA's decision-making – indeed its *final* decision – on the very issues that Depomed asked it to

decide. Moreover, each of the cited cases stands for the irrefutable proposition that FDA can and does receive deference for decisions issued after litigation has commenced.[1] Depomed complains that "[n]one of these cases involved a court's accepting an agency request to review a letter the agency issued two years after the challenged decision or presents a remotely similar procedural posture." Pl. Opp. at 8-9.[2] In *Collagenex*, however, upon which Depomed itself relies, FDA's final decision was issued *five years* after the initial challenged decision and was nevertheless accorded deference and upheld. *Collagenex*, 2005 WL 256561, at *2, 12-13.[3]

Third, Depomed argues that FDA's action must be justified at the time it was taken, not at some later date. Pl. Opp. at 9. In support, Depomed cites *Grossmont Hosp. Corp. v. Sebelius*, __ F. Supp. 2d ___, No. 10-cv-1201 (RLW), 2012 WL 5463350, at *15 n.10 (D.D.C. Nov. 9, 2012), in which this Court distinguished an agency's "detailed explanation" of an earlier decision, from a *post hoc* rationalization. Pl. Opp. at 6. The distinction is immaterial here, however, because FDA did not make a final exclusivity decision until November 13, 2012. The

[1] *See e.g.*, *Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d 174, 176 (D.D.C. 2010), *aff'd*, 625 F.3d 760 (D.C. Cir.); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1325 (D.C. Cir. 1998); *Stat-Trade, Inc. v. FDA*, 869 F. Supp. 2d 95, 101 (D.D.C. 2012); *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13 (D.D.C. 2008); *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 308 (D.D.C. 1987).

[2] Depomed also incorrectly asserts that "none of the decisions involved a challenge as to what constituted the decision under review." Pl. Opp. at 9 n.6. In fact, the plaintiff in *Serono* argued (to no avail) that the court should ignore the agency's final decision: "Dr. Woodcock's letter represents the considered views of the agency decisionmaker herself, announced at the usual point in the agency's decision-making process (the end), rather than the views of litigation counsel trying to come up with an explanation after the fact." *Serono*, 158 F.3d at 1325. Depomed's claim that none of the cited cases discuss prejudice is similarly unfounded. Pl. Opp. at 9. In *Genentech*, for instance, the court specifically considered whether the party opposed to reviewing "the facts as they are revealed in the [later-filed] record" would be prejudiced by such review. *Genentech*, 676 F. Supp. at 308.

[3] Depomed contends that the relevant factor is not the amount of time that has elapsed since the filing of the complaint, but rather the time following FDA's preliminary communications. Pl. Opp. at 9. But it was Depomed itself who argued that FDA's decision should not be considered (in part) because it was issued six weeks after the complaint. *See* Pl. MSJ at 18. That the agency's decision ultimately issued some 22 months after Gralise's approval is not unreasonable in any event because Depomed waited nine months to formally raise the exclusivity issue to the agency, and because Depomed does not face any generic competition until January 2014 at the very earliest, and likely not until well after that date. AR 5 n.19.

November 2012 letter does not introduce a "new basis" for the agency's decision, but is *the actual decision* in response to new arguments and evidence raised administratively by Depomed itself. Depomed posits that "the APA works" because the "[p]arties challenging agency action are limited to arguments they presented to the agency, and an agency defending its decision is limited to arguments it articulated in taking that action." Pl. Opp. at 10. Precisely. When parties present arguments and evidence to the agency, as here, the agency's resolution of the issues presented is the proper focus of judicial review.[4]

B. FDA's Designation Decision Is Moot and, in the Alternative, Permissible and Supported by Agency Precedent

1. Depomed's Designation Claim Is Moot

Depomed contends that FDA erred by requiring it to provide a plausible hypothesis of clinical superiority over Neurontin before Gralise could be designated. Pl. Opp. at 11.[5] This claim is moot, however, because FDA *granted* designation after Depomed provided such a hypothesis. Because Depomed already has designation, there is no live controversy about this issue and thus no Article III jurisdiction for the Court to consider it. *See Am. Bar Ass'n v. FTC*, 636 F.3d 641, 645 (D.C. Cir. 2011).

[4] As noted previously, if this Court were to review FDA's initial communications in lieu of its final decision and find those communications wanting, the appropriate action would be to remand to FDA for further consideration and explication which, of course, is exactly what the agency has already done. *See* FDA MSJ at 21; *see also N. Air. Cargo v. U.S. Postal Serv.*, 674 F.3d 852, 861 (D.C. Cir. 2012) ("When a district court reverses agency action and determines that the agency acted unlawfully, ordinarily the appropriate course is simply to identify a legal error and then remand to the agency, because the role of the district court in such situations is to act as an appellate tribunal."). Depomed argues that such a remand would be unnecessary because the agency's rationale is discernable but legally infirm. Pl. Opp. at 10 n.8. Yet Depomed continues to point out alleged shortcomings in FDA's early communications and relies on those in attempting to make its case. *See, e.g.*, Pl. Opp. at 13 (noting that FDA did not discuss the regulation governing designation denial in any detail until the November 13, 2012 letter).

[5] Abbott, not Depomed, was Gralise's sponsor at the time that FDA required the plausible hypothesis of clinical superiority. For convenience, this brief refers to Depomed as Gralise's sponsor throughout.

Depomed seeks to evade this conclusion by insisting that "the designation of Gralise did not 'eradicate[]' the effects of FDA's unlawful decision to apply the clinical-superiority framework at the designation stage." Pl. Opp. at 11. As FDA explained, however, once there is a previously approved same drug for the same orphan indication, FDA applies the clinical superiority framework at both the designation and approval stage. FDA MSJ at 24-25. Thus, Depomed would have been required to demonstrate Gralise's clinical superiority over Neurontin to obtain exclusivity upon approval even if Depomed had not initially offered a plausible hypothesis of clinical superiority (if, for example, Gralise had been designated before Neurontin had been approved).[6] This case would be in the exact same procedural posture either way – with Gralise having been denied exclusivity due to Depomed's failure to demonstrate its clinical superiority over Neurontin.

Nor is this simply a hypothetical prospect, as Depomed seems to suggest. Pl. Opp. at 12 (what "FDA *would* have done is irrelevant, because what FDA *did* do was carry the clinical-superiority framework forward from the designation stage to the approval stage.") (emphasis in original). FDA did not "carry forward" a framework that only existed at the designation stage. The clinical superiority requirement exists, and always has existed, whenever there is a previously approved same drug for the same orphan indication, whether at the designation stage, the approval stage, or both.[7] Thus, FDA correctly determined that the designation challenge

[6] Moreover, Depomed was not required to prove the particular hypothesis that was originally made, but could have demonstrated clinical superiority on a basis other than the original hypothesis. FDA MSJ at 25.

[7] For example, Infasurf was designated in 1985, when there was no previously approved drug; FDA therefore did not require the sponsor to provide a plausible hypothesis of clinical superiority. AR 917. FDA approved Survanta in 1991 and determined that it was the "same drug" as Infasurf. AR 918. Accordingly, FDA required Infasurf's sponsor to demonstrate clinical superiority upon approval, even though it had not previously been required to provide a hypothesis. *Id.* Because Infasurf's sponsor could not make such a demonstration, it was not approved until after expiration of Survanta's exclusivity and, when approved, did not earn its own period of exclusivity. AR 850.

"would make no difference to the exclusivity outcome that Depomed seeks," and Depomed's claim is moot. *Id*. at 13.

Depomed's reliance on *Cody Labs, Inc. v. Sebelius*, 446 F. App'x 964 (10th Cir. 2011) (unpublished) is unavailing. *Cody* concerned FDA's approval of a new drug application where the manufacturer contended that its drug was "grandfathered" and did not require FDA approval in the first place. 446 F. App'x at 967. The court found the plaintiff's grandfather claim was not moot (a conclusion FDA did not contest) because a determination that the drug was not "new" would have relieved the plaintiff of the greater, ongoing regulatory burdens applicable to new drugs. *Id.* Depomed's attempt to analogize *Cody* to this case fails because it is simply not true that "[a] declaration reversing FDA's decision to apply its clinical-superiority framework to Gralise would free Depomed from the burden of having to prove clinical superiority in order to obtain marketing exclusivity." Pl. Opp. at 12.

As noted above, FDA requires a showing of clinical superiority to obtain exclusivity when there is a previously approved same drug, regardless whether the sponsor was previously required to provide a plausible hypothesis at the designation stage. While Depomed is free to challenge FDA's clinical superiority requirement in the context of the agency's denial of orphan exclusivity, its effort to avoid the mootness of its designation claim is unavailing because it depends on the false premise that the clinical superiority requirement would not have applied at the exclusivity stage if it had not applied at the designation stage. Unlike the plaintiff in *Cody*, Depomed faces the *same* regulatory burden to demonstrate clinical superiority to obtain exclusivity, without regard to FDA's designation decision. Thus, *Cody* does not lend support to Depomed's claim.

2. FDA Properly Interpreted its Designation Regulations to Require a Plausible Hypothesis of Clinical Superiority Over Neurontin

Alternatively, if this Court decides to reach the merits of Depomed's designation claim, it should uphold FDA's interpretation and application of its own regulations.

Simply put, if FDA were to adopt Depomed's reading of the regulations, Depomed would not have been eligible to request designation under 21 C.F.R. § 316.20 in the first place, and this case would be over. That regulation provides only three circumstances in which a sponsor may seek designation: (1) for a previously unapproved drug; (2) for a new orphan indication for an already marketed drug; or (3) for a subsequent version of "*an already approved orphan drug*" for the same rare disease or condition "if it can present a plausible hypothesis that its drug may be clinically superior to the first drug." 21 C.F.R. § 316.20(a) (emphasis added). Depomed contends that a sponsor seeking approval of a drug that is the same as an "already approved orphan drug" need only provide a plausible hypothesis of clinical superiority when the previously approved drug had orphan exclusivity. Pl. Opp. at 16-17. But under this reading, Depomed could not even *seek* designation for Gralise, because Neurontin is a previously approved orphan drug *without* exclusivity. Gralise, in other words, would not have fallen into any of the three categories above because it is not: (1) a previously unapproved drug (the same drug Neurontin is already approved); (2) for a new indication of an already marketed drug (it shares the same indication as Neurontin); or (3) a subsequent version of an already approved drug *with orphan exclusivity* (applying Depomed's interpretation of "already approved orphan drug").

In a belated attempt to cure this deficiency, Depomed weakly suggests that it may request designation under 21 C.F.R. § 316.20(a) as a "previously unapproved drug" because the term

"drug" in the regulation should refer to the specific *drug product* Gralise, and Gralise was not approved at the time that Depomed sought designation. Pl. Opp. at 18-19 n.10. But *every* drug product is unapproved at the time designation requests are made. Because a sponsor must request designation even before submitting a marketing application for the orphan indication, designation requests must necessarily be made before a specific drug product has been approved for the indication. *See* 21 U.S.C. § 360bb(a)(1); 21 C.F.R. § 316.23(a), (b). Depomed's reading would thus sweep so broadly it would eviscerate the eligibility criteria for requesting designation in § 316.20(a) altogether by making the criteria just a restatement of when a request can be submitted under § 316.23.

Aside from this fundamental flaw in Depomed's proposed construction of FDA's orphan regulations, Depomed improperly reads the regulations in isolation, focusing solely on the regulatory grounds for denying designation requests, and ignoring precursor requirements that must be satisfied before designation can be sought in the first instance. Thus Depomed argues that the regulations governing *denial* of designation, 21 C.F.R. §§ 316.24 and 316.25, should be read to require FDA to automatically *grant* designation when there is a previously approved same drug that never had orphan exclusivity. Pl. Opp. at 13-15. But this argument ignores 21 C.F.R. § 316.20's threshold requirement that sponsors submitting a request for orphan-drug designation must provide a plausible hypothesis of clinical superiority over an already approved orphan drug. FDA has reconciled these regulations to give effect to this threshold requirement, such that a sponsor must have a basis to request designation in the first instance before FDA assesses whether designation can be granted under § 316.24.

FDA does not read 21 C.F.R. §§ 316.24 and 316.25 as setting forth an exclusive list of reasons for denying designation, and has specifically identified two other instances in which

designation may be denied for reasons that are not enumerated in § 316.25. Depomed's primary response is to criticize FDA for failing to cite these examples prior to its November 13, 2012 final decision. Pl. Opp. at 13-14. But even if that decision were not appropriately before this Court (which it is), the cited examples speak for themselves and plainly illustrate the point: that the grounds enumerated in § 316.25 for denying designation are neither exhaustive nor exclusive. FDA properly denies designation if other eligibility criteria are not met: for example, if the sponsor seeks designation of a product that is not a drug, if the request for designation is untimely, or, as relevant here, if the sponsor submitting a request for orphan-drug designation does not provide a plausible hypothesis of clinical superiority over an already approved orphan drug. AR 13.[8]

Depomed further complains that FDA's brief fails to cite "a single interpretive document predating FDA's denial of exclusivity for Gralise that adopts this construction of 316.20(b)(5)." Pl. Opp. at 17. What FDA *did* cite were the only five examples of which it is aware when a sponsor sought designation of a previously approved orphan drug that never had exclusivity. In each of these examples, FDA applied its clinical superiority framework at the designation stage. Each of these examples predated the agency's relevant November 13, 2012, decisional document. FDA did not promise that these were "interpretive document[s]," or use these examples in an attempt to "rehabilitate" the agency's reading of its regulations. Pl. Opp. at 18.

[8] Depomed attempts to distinguish the timeliness example on the ground that the *statute* does not allow for designation in this circumstance, and so the regulation must also be read to deny designation for this reason, even though it is not enumerated within 21 C.F.R. § 316.25. Pl. Opp. at 15-16. Depomed thus itself acknowledges that 21 C.F.R. § 316.25 is not exhaustive, and that precursor eligibility criteria must additionally be satisfied in order to obtain orphan designation, as further confirmed by 21 C.F.R. § 316.29(a)(3), which provides that "FDA may revoke orphan-drug designation for any drug if . . . FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor." *See also* AR 13. If FDA may later revoke a designation request for failing to meet eligibility criteria, it likewise may deny that request in the first instance for such failure.

Rather, in its thorough consideration of this issue and in response to Depomed's own arguments, FDA identified its only known examples of like circumstances, and determined that it would apply the same approach to Depomed that it has applied to other sponsors.[9]

In sum, FDA has fully considered 21 C.F.R. §§ 316.24 and 316.25 in view of the eligibility requirements for requesting designation in 21 C.F.R. § 316.20, *see* AR 13-14, and resolved the potentially conflicting language between those regulations by giving effect to the eligibility criteria in 21 C.F.R. § 316.20, recognizing that 21 C.F.R. §§ 316.24 and 316.25 do not mandate designation if the sponsor's request for designation is ineligible in the first instance. Rather than "graft[ing] another reason onto § 316.25 by fiat," Pl. Opp. at 15, FDA has rationally determined that the reasons for denying designation in §§ 316.24 and 316.25 apply only to requests that are eligible under § 316.20 in the first instance, such that the former provisions do not trump the latter.

FDA's interpretation of its regulations to require a plausible hypothesis of clinical superiority at the designation stage in this instance is reasonable, consistent with agency precedent, and entitled to "substantial" deference, particularly when, as here, "the regulation concerns 'a complex and highly technical regulatory program,' in which the identification and classification of relevant 'criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.'" *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) (citation omitted); *see also Auer v. Robbins*, 519 U.S. 452, 461 (1997) (agency's interpretation of own regulations is "controlling" unless plainly erroneous or inconsistent with regulation).

[9] Moreover, many of these examples describe FDA's position rather than just apply it. *See, e.g.*, AR 884 ("To make a case for clinical[] superiority in an orphan drug designation application, a sponsor must submit a medically plausible hypothesis showing that the drug has significantly greater effectiveness[,] is significantly safer or provides a major contribution to patient care over the existing same product.").

C. FDA Reasonably Interpreted the Orphan Drug Act to Deny Exclusivity to Gralise

1. The Statute Does Not Address Eligibility for Exclusivity When the Same Drug Has Been Previously Approved

Depomed contends that the statutory text unambiguously mandates exclusivity in this case, and that "FDA has not identified any relevant gap in 21 U.S.C. § 360cc." Pl. Opp. at 19-20, 22. To the contrary, FDA explained in great detail that the statute does not address eligibility for exclusivity when the same drug has already been approved for the orphan indication. FDA MSJ at 28-31; *see also* AR 9-11. The statute is indisputably ambiguous on this point when the previously approved drug has an existing exclusivity period, and Depomed does not challenge the propriety of FDA's clinical superiority framework to address that ambiguity. *See Baker Norton Pharms., Inc. v. FDA*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) (determining that "such drug" is ambiguous and upholding FDA's framework); *see also* Pl. Opp. at 22.

Indeed, Depomed has itself admitted that the statute does not address exclusivity in the context of a previously approved same drug with *expired* exclusivity. *See* Pl. MSJ at 4 n.4 ("The statute does not address whether, or under what circumstances, a second exclusivity period should be awarded if, after the expiration of a drug's orphan-drug exclusivity, FDA later designates and approves a subsequent product that the agency considers to be the 'same drug' as the one with expired marketing exclusivity."). Depomed now seeks to retract that admission, insisting that it only meant to imply that that issue is not presented in this case. Pl. Opp. at 16-17 n.9. Depomed's backtracking notwithstanding, the statute refers to exclusivity solely in terms of

the drug that has just been approved and a subsequent application.[10] It does not refer to a previously approved drug at all, let alone whether that drug may have had exclusivity or whether any such exclusivity has expired.

In the face of such silence, "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 665 (2007); *see Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843-44 (1984) ("If Congress has explicitly left a gap for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation. Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute."). To address this gap, FDA applies its clinical superiority framework to ensure that exclusivity is only granted to drugs that demonstrate significant improvement over existing drugs.

FDA explained that the statutory gap could be addressed several different ways. FDA MSJ at 29. First, the existence of the previously approved drug could be irrelevant, and FDA could grant exclusivity to every drug that was designated and approved (allowing for delays in approval if there is an exclusivity bar). AR 10. This would result in exclusivity for Gralise as well as the likelihood of serial seven-year exclusivity periods for the same drug, which would create an indefinite bottleneck on approvals of orphan drugs. *Id.* FDA has already rejected this

[10] Except as provided in subsection (b), if the Secretary--
(1) approves an application filed pursuant to section 505 [21 U.S.C. § 355], or
(2) issues a license under section 351 of the Public Health Service Act [42 U.S.C. § 262]
for a drug designated under section 526 [21 U.S.C. § 360bb] for a rare disease or condition, the Secretary may not approve another application under section 505 [21 U.S.C. § 355] or issue another license under section 351 of the Public Health Service Act [42 U.S.C. § 262] for such drug for such disease or condition for a person who is not the holder of such approved application or of such license 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).

approach both in the context of this case (when the previously approved same drug never had exclusivity) and when the previously approved same drug's exclusivity has expired. *See* AR 976-991 (rescinding exclusivity to sponsor who failed to demonstrate clinical superiority over a previously approved drug with expired exclusivity).

Second, FDA could grant exclusivity only to the first *designated* drug that is approved, which would result in exclusivity for Gralise and other drugs like Gralise – drugs not shown to be clinically superior to previously approved drugs – but preclude serial seven-year exclusivity periods for the same drug. AR 10 n.28.

Third, FDA could grant exclusivity only to the first *approved* orphan drug (assuming it has been designated) – but not to any subsequently designated same drug approved for the same orphan indication. FDA's decision to select the third of these equally permissible alternatives reflects the agency's best policy judgment in the face of a statute that is silent on this point, and is fully entitled to deference under *Chevron* step two.

Rather than address any of these scenarios, Depomed argues that FDA has confused "generality for ambiguity," and that the statute must instead "be applied universally and consistent with its terms." Pl. Opp. at 20. To the contrary, these scenarios illustrate that the statute can be read in a number of ways. Unlike *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30 (D.D.C. 2000), on which Depomed relies, this is not a case where Congress has addressed the issue at hand using broad and general language, but rather a case where Congress has not addressed the issue at all. FDA has reasonably interpreted this Congressional silence to limit exclusivity to the first drug that is approved, if it is designated. Depomed's own policy preference for the first interpretation above – requiring exclusivity for every designated drug upon approval – is not mandated by the statute and is contrary to both legislative intent and

agency precedent. Indeed, if this Court were to adopt Depomed's proffered approach, it would immediately open the door to serial bottlenecks of exclusivity for the same drug, and run directly contrary not only to Congressional intent, but also to the manner in which exclusivity is determined in the case of expired exclusivity – an anomalous and irrational result that would serve only to sow confusion and inconsistency. *See* AR 976-991.

2. *Mova, Ranbaxy,* and *Teva* Do Not Compel Orphan Exclusivity for Gralise

Depomed continues to cling to the talismans of *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120 (D.C Cir. 2006), and *Teva Pharms. USA Inc. v. Sebelius*, 595 F. 3d 1303 (D.C. Cir. 2010), as if merely reciting instances in which courts construed the 180-day generic drug exclusivity provision at *Chevron* step one would somehow make the orphan drug provision here at issue equally unambiguous. But this case presents an entirely different exclusivity regime with a statutory gap that Depomed has itself previously acknowledged and that FDA has appropriately filled by applying its clinical superiority framework. The agency has exercised its delegated regulatory authority in a manner that preserves and strengthens the incentive for drug manufacturers to engage in the type of innovative product development that Congress sought to encourage. AR 6.

It is well established that agencies routinely receive deference when interpreting statutory gaps, and this case is no different. *See Regions Hosp. v. Shalala*, 522 U.S. 448, 457–65 (1998) (deferring to HHS reaudit rule because relevant provisions of statute were silent, and therefore ambiguous, on the relevant issue, and because rule reflected a reasonable interpretation of law); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629 (1973) (upholding FDA interpretation of "new drug" definition to contain requirement – not found in statutory language

– for adequate and well controlled clinical trials because "the statutory scheme and overriding purpose of the 1962 amendments compel the conclusion that the hurdle of 'general recognition' of effectiveness requires at least 'substantial evidence' of effectiveness for approval of a [new drug]"); *Mount Royal Joint Venture v. Kempthorne*, 477 F.3d 745, 754-55 (D.C. Cir. 2007) (conferring *Chevron* step two deference on Interior Board of Land Appeals' interpretation of relevant provisions of Federal Land Policy and Management Act because they were silent regarding consecutive segregations); *City of Waukesha v. EPA*, 320 F.3d 228, 239 (D.C. Cir. 2003) ("[T]he agency is justified in describing this as an instance where 'the statute is silent . . . with respect to the specific issue,' and hence where judicial deference to the agency's interpretation is warranted . . . "); *Mylan Labs., Inc. v. Thompson*, 332 F. Supp. 2d 106, 118 (D.D.C. 2004) ("However, these statutory provisions are silent as to the FDA's responsibilities in the situation, such as the one here, where final effective approval had been received but a patent court delayed the effective approval date designated by the FDA for a generic drug to be introduced into the market. Thus, the FDA's decisions should be given *Chevron* deference so long as they represent a 'permissible construction' of these statutory provisions.").

An analogous example in the FDA context is *Apotex Inc. v. FDA*, 414 F. Supp. 2d 61, 68-70, 74 (D.D.C. 2006), in which the court upheld FDA's patent-based approach to awarding 180-day generic drug exclusivity in light of the statute's failure to address the particular issue at stake. As the court explained, the relevant provision "is silent regarding the issue of how many exclusivity periods may arise in connection with a single drug product. Moreover, because of that silence, the provision lends itself to multiple interpretations, and hence is ambiguous under *Chevron* step one." 414 F. Supp. 2d at 68-69. So too here, the orphan drug exclusivity statute does not address exclusivity in the context of a previously approved drug. In light of this silence,

FDA has properly filled the statutory gap by applying a clinical superiority framework to address exclusivity issues whenever there is a previously approved same drug.

3. FDA's Interpretation is Entitled to Deference

Depomed does not dispute FDA's general rulemaking authority or the specific rulemaking authority relating to designation under 21 U.S.C. § 360bb(d), nor can it. Depomed instead mischaracterizes FDA's position: "FDA claims it does not need to point to a clear statutory hook for its clinical-superiority requirement" under this general rulemaking authority. Pl. Opp. at 23 (citing FDA Opp. at 27). FDA's interpretation of the statute in both its regulations and in the individual adjudication at issue here is based on the statute's *silence* on the exclusivity question when there is a previously approved same drug. As described in section C.4 below, FDA has reasonably interpreted this statutory silence to conform to the statute's purpose.

Depomed also asserts that the issues presented in this case do not merit special deference to the agency because they "are not ones that require scientific and technical expertise; they are straightforward legal arguments." Pl. Opp. at 24. But FDA routinely receives *Chevron* deference for its construction of the complex, often interrelated FDCA regime, even when scientific issues are not at stake. *See Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1280 (D.C. Cir. 2004) (granting deference to FDA's resolution of difficult statutory questions, noting that "[t]here is no denying the complexity of the statutory regime under which the FDA operates"). Indeed, FDA is *required* to apply its expertise and understanding of the statutory goals when construing its organic statute: "It is up to the agency to 'bring its experience and expertise to bear in light of competing interests at stake' and make a reasonable policy choice." *Teva Pharms. USA. Inc. v. FDA*, 441 F.3d 1, 5 (D.C. Cir. 2006). And when it does so, even when its scientific expertise is not at issue, FDA is entitled to deference. *Apotex, Inc. v. FDA*, No. 06-

0627, 2006 WL 1030151 at *16 (Apr. 19, 2006), *aff'd*, 449 F.3d 1249 (D.C. Cir. 2006) (upholding FDA's ultimate interpretation of the statutory exclusivity issues in *Teva*).

Depomed further faults FDA for not according "special statutory status to drugs for which orphan-drug designation was sought and received," arguing that "FDA cannot treat a non-designated drug as if it were designated, and seek to use such a drug as a predicate for imposing a clinical-superiority requirement on other sponsors whose products qualify under the statutory scheme as enacted." Pl. Opp. at 25. Contrary to Depomed's suggestion, however, FDA has not treated Neurontin as if it were designated; it has never afforded Pfizer (Neurontin's sponsor) any of the special designation benefits (including such financial incentives as clinical trial tax credits and application user fee waivers) that sponsors of designated drugs enjoy. AR 849-851. FDA has merely recognized that Neurontin, though never orphan designated, is the same drug as Gralise. In these circumstances, the statute should not be construed to award marketing exclusivity to a second or third or fourth drug that is the same as a previously approved drug (whether or not that previous drug itself had orphan exclusivity) unless the subsequent drug is somehow *better* than the previous drug and thus offers some significant benefit to the patient population beyond what the previous drug already provides.[11] FDA's position is simply that a previously approved drug is a necessary part of the exclusivity analysis, and that Gralise should not obtain a windfall of exclusivity over a previously approved drug unless it can demonstrate clinical superiority over that drug. This position permissibly interprets the statutory silence and is entitled to deference.

[11] Moreover, if Pfizer had received designation, any exclusivity would have expired on May 24, 2009, before Gralise was even approved. *See* AR 2 (noting that Neurontin was approved for PHN on May 24, 2002). Depomed would thus be in the different posture of seeking a second seven-year exclusivity period for the same drug.

4. FDA's Position is Reasonable

Depomed claims that FDA "fail[ed] to respond to Depomed's arguments about reasonableness (and cannot belatedly do so in a reply brief)." Pl. Opp. at 25. To the contrary, FDA explained at length why its decision was reasonable and furthered the goals of the Orphan Drug Act. *See* FDA MSJ at 28-37 (heading entitled "FDA's Interpretation of the Exclusivity Statute and Regulations Is Reasonable"). Depomed had argued that FDA's interpretation did not "fit" the statute because, for example, FDA's role was allegedly ministerial, and Depomed should have automatically been awarded exclusivity. Pl. MSJ at 32-33. In response, FDA explained why exclusivity is not automatic when there is a previously approved same drug and that FDA has an important, non-ministerial role in determining whether a drug is clinically superior to any previously approved same drug in such circumstances. FDA MSJ at 31 n.19.

Depomed further argued that Neurontin is not an "orphan drug" because it was never designated. Pl. Opp. at 33. But this argument is premised on ignoring FDA's regulatory definition of "orphan drug" as "a drug intended for use in a rare disease or condition," 21 C.F.R. § 316.3(b)(10). *See* FDA MSJ at 25-26. Moreover, as FDA explained, this definition of "orphan drug" is what allowed Depomed to seek designation for Gralise under 21 C.F.R. § 316.20(a). *Id.*; *see also* AR 15. Otherwise, if Neurontin were not considered to be an "orphan drug," Depomed would have had no basis for even seeking designation under that regulation. *See* section B.2., *supra*. Rather than being "far afield of anything Congress contemplated in the statute," Pl. MSJ at 33, FDA's regulatory definition of "orphan drug" and its application in this case provides the very construct by which Depomed was able to seek and obtain designation for Gralise.

Depomed also characterizes FDA's argument about statutory purpose as "woefully underwhelming" and complains that FDA offered no more than a "conclusory assertion that denying exclusivity to Gralise 'furthers' that purpose." Pl. Opp. at 26. As FDA explained, however, the agency's implementation of the Orphan Drug Act directly furthers the statutory goals to both encourage and reward the development of innovative new treatments that provide benefits to patients over existing therapies. FDA MSJ at 37. Depomed was encouraged to develop Gralise by obtaining designation after providing a clinical hypothesis of clinical superiority over Neurontin. But Gralise did not ultimately qualify for exclusivity because Depomed was unable to demonstrate clinical superiority – *i.e*. that Gralise provided a meaningful benefit to patients over the already approved same drug. *Id*. at 38. FDA has reasonably interpreted the Orphan Drug Act to deny the exclusivity reward in these circumstances.

Moreover, as FDA pointed out, Depomed's claim for exclusivity would upend the statute by rewarding Depomed with a broader scope of exclusivity extending to all previously approved same drugs, including Neurontin, than if it had successfully demonstrated clinical superiority. *Id*. Depomed responds that exclusivity for Gralise would not require that the generic versions of Neurontin approved after Gralise be pulled entirely from the shelves, but Depomed does not deny that the other products could no longer be approved by FDA to treat the orphan indication, post-herpetic neuralgia (PHN). Pl. Opp. at 26 n.14. Nor does Depomed explain how this unprecedented breadth of exclusivity – blocking approvals of other versions of a previously approved same drug, despite showing no superiority over that drug – fits within any reasonable construct of the Orphan Drug Act or advances any conceivable legislative purpose. That is because it does not. *See* 56 Fed. Reg. 3338, AR 702 ("Congress sought to promote the development of drugs . . . that are needed by, but not available to, people in the United States

with 'rare diseases or conditions.'"). By contrast, FDA's interpretation furthers the overall purpose of the Orphan Drug Act.

Finally, Depomed argues that FDA has granted orphan exclusivity to many drugs that are not "new treatment[s] for patients who would otherwise have no effective or inferior therapy," citing FDA's approval of Horizant and Qutenza to treat PHN. Pl. Opp. at 26 & 5 n.4. Depomed correctly observes that "[t]hese drugs received orphan exclusivity because they met the standard in the Orphan Drug Act," and FDA did not separately evaluate whether they were clinically superior to Neurontin. Pl. Opp. at 5 n.4. Depomed fails to note, however, that these drugs contained different active moieties than Neurontin, unlike Gralise, which has the same active moiety (albeit in a different formulation).[12] As such, Horizant and Qutenza are by definition not the "same drug" as Neurontin, and the sponsors were not required to demonstrate clinical superiority. 21 C.F.R. § 316.3(b)(13). FDA's regulations reasonably draw this line because different active moieties are generally expected to have different activity and require a significant amount of additional testing. *See* 56 Fed. Reg. at 3341 (AR 705) (distinguishing among drugs with different active moieties for purposes of the Orphan Drug Act because "such differences are highly likely to lead to pharmacologic differences," and because "the development of an agent with a novel active moiety is not a financially or intellectual trivial matter; it represents a considerable effort and a substantial risk").[13]

[12] *See* AR 4-5 n.16 (discussing Horizant); Electronic Orange Book, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (search for Qutenza showing that it has a different active ingredient (capsaicin 8% patch) than gabapentin, and was granted "new chemical entity" exclusivity, meaning that its active moiety has never previously been approved (*see* 21 C.F.R. § 314.108)).

[13] Depomed further asserts that "FDA . . . grants exclusivity to products approved for orphan indications even if those products are already approved and marketed for diseases and conditions affecting millions of people," suggesting that this practice undercuts FDA's arguments against granting exclusivity to Gralise. Pl. Opp. at 5. It is settled law, however, that orphan exclusivity applies only to protected uses of a drug, not to a drug for any and all

5. FDA Did Not Violate Its Own Regulations

Depomed claims that FDA's regulations do not allow the agency to require a demonstration of clinical superiority unless a prior "same drug" has received orphan-drug exclusive approval, and wrongly asserts that FDA "never directly responds to Depomed's point that imposing a clinical-superiority requirement in this case violates the agency's exclusivity-related regulations." Pl. Opp. at 26 (citing 21 C.F.R. §§ 316.31, 316.3(b)(13)). To the contrary, FDA's brief explained the agency's non-ministerial role in determining whether a drug qualifies for exclusivity under the clinical superiority framework (FDA MSJ at 31 n.19) and both the agency's brief and letter decision explained at length how FDA interpreted its regulations to support the approach it took for Gralise. FDA MSJ at 7-9; AR 12 (explaining that its regulations must be read in context, particularly with 21 C.F.R. § 316.20, which requires a plausible hypothesis of clinical superiority to obtain designation).

The agency's regulations, like the statute itself, do not directly address the question of exclusivity when there is a previously approved same drug that does not have exclusivity or whose exclusivity period has expired. In the absence of an explicit regulatory provision, FDA's application of the clinical superiority framework in this context is fully consistent with the overall regulatory scheme and purpose, just as it is consistent with Congressional intent – unlike Depomed's preferred approach, which would automatically (and non-sensically) award exclusivity upon approval of a designated drug even when, as here, the sponsor fails to substantiate a hypothesis of clinical superiority, or otherwise demonstrate such superiority. AR 12. FDA's decision to apply the clinical superiority framework and "same drug" definition

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uses. *Sigma-Tau Pharms. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002). It follows that FDA grants exclusivity to a drug for an orphan use even if the drug is already approved for other non-orphan uses.

across the board to all "same drug" exclusivity decisions regardless whether there is existing exclusivity to "break" (*i.e.*, whether the previously approved drug has exclusivity remaining, had exclusivity that expired, or never had exclusivity) is eminently reasonable and does not contravene the regulations. AR 8.

6. FDA's Decision is Consistent With Precedent

FDA's decision is consistent with all of its known precedent on the applicability of the clinical superiority framework when there is a previously approved but not designated orphan drug, except for one example that FDA has considered and now believes to be erroneous. Depomed's continued reliance on this one discredited example is misplaced.

Contrary to Depomed's claim, FDA offered a fully "legitimate" explanation of Kogenate's history and why it was an "outlier" from how the agency has treated other sponsors. AR 17. Although Depomed asserts that the agency had previously stood behind its exclusivity decision for Kogenate and enforced it against another sponsor, Pl. Opp. at 28, the subsequent sponsor did not challenge Kogenate's exclusivity on the ground that there was a previously approved same drug and that Kogenate should not have received exclusivity without a demonstration of clinical superiority over that drug. AR 476.[14] Moreover, as FDA pointed out in its letter decision, statements made by an individual at a public meeting erroneously describing the agency's exclusivity regime do not bind the agency. AR 17 (citing 21 C.F.R. § 10.85(k)); *see also Holistic Candlers & Consumers Ass'n v. FDA*, 664 F.3d 940, 945 (D.C. Cir. 2012) (a "statement or advice given by an FDA employee orally…is an informal communication

[14] Rather, a subsequent sponsor sought to challenge Kogenate's exclusivity on the ground that it was in short supply. *Id.*

that… does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed").[15]

FDA described five examples in which it had denied designation to sponsors because there was a previously approved same drug that never had exclusivity and the sponsors did not provide a plausible hypothesis of clinical superiority. AR 847-849. Depomed dismisses these examples as "not particularly relevant" because "none of them involved denying orphan exclusivity to a drug that was approved for an orphan-designated indication." Pl. Opp. at 28. But Depomed does not and cannot deny that these examples support the proposition for which they were cited: that "absent a plausible hypothesis of clinical superiority, FDA has repeatedly denied designation requests for drugs that have been previously approved but not designated." FDA MSJ at 39-40.

FDA separately cited nine additional examples of situations in which the agency has required sponsors to demonstrate clinical superiority upon approval to obtain exclusivity. AR 849-851. Taken together, these examples demonstrate FDA's consistent and long-standing practice to require a plausible hypothesis of clinical superiority over a previously approved same drug as a basis for designation (as FDA did for Gralise), as well as FDA's general practice to require sponsors to demonstrate clinical superiority over previously approved same drugs upon approval to obtain exclusivity. AR 849. Moreover, in three of these examples, FDA required

[15] Depomed wrongly suggests that FDA has conceded that Kogenate is "the sole precedent directly on point." Pl. Opp. at 3 (citing FDA MSJ at 40). In fact, FDA noted numerous differences between Gralise and Kogenate, such as the fact Kogenate's sponsor had an agreement with the sponsor of the previously approved drug before FDA's final rule was published. AR 16-17. Indeed, the cited page of FDA's brief describes numerous relevant examples that are fully on point, and does not discuss Kogenate at all.

such a showing of clinical superiority to obtain exclusivity when the previously approved drug's original exclusivity period had expired.[16]

Depomed's continued effort to distinguish this precedent is unconvincing. Pl. Opp. at 28-29 ("[s]ituations in which the agency decided it would not award a *second* exclusivity period to the same drug go nowhere toward establishing a[n] FDA practice of denying exclusivity to the *first* sponsor to obtain orphan-drug designation for a particular condition followed by marketing approval for that condition.") (emphasis in original). Contrary to Depomed's suggestion, these situations illustrate the agency's consistent interpretation of the statute and regulations to require a showing of clinical superiority whenever there has been a previously approved same drug, even when there is no existing exclusivity period to break.

CONCLUSION

For the foregoing reasons and those set forth in defendants' opening memorandum, this Court should dismiss Depomed's complaint for failure to state a claim upon which relief can be granted or, in the alternative, enter summary judgment in favor of defendants, and deny Depomed's motion for summary judgment.

[16] Example 6, AR 969, 972; Example 7, AR 979; Example 8, AR 995-998; *see also* FDA MSJ at 41 n.28.

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