IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

DEPOMED INC., Plaintiff, v. UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES, *et al.*, Defendants.	Case No. 1:12-CV-01592-RLW

DEPOMED'S COMBINED OPPOSITION TO FDA'S MOTION TO DISMISS OR IN THE ALTERNATIVE FOR SUMMARY JUDGMENT AND REPLY IN SUPPORT OF DEPOMED'S MOTION FOR SUMMARY JUDGMENT

TABLE OF CONTENTS

TABLE OF CONTENTS—Continued

Page

TABLE OF AUTHORITIES

Page(s)

CASES:

TABLE OF AUTHORITIES—Continued

Page(s)

TABLE OF AUTHORITIES—Continued

Page(s)

STATUTES:

REGULATIONS:

OTHER AUTHORITIES:

TABLE OF AUTHORITIES—Continued

Page(s)

INTRODUCTION

Gralise® is the first—and only—gabapentin tablet to be approved for post-herpetic neuralgia ("PHN") after being designated as an orphan drug for that use. Under the plain language of both the Orphan Drug Act and FDA's implementing regulations, this fact straightforwardly entitles Depomed to seven years of orphan-drug exclusivity for Gralise. *See* 21 U.S.C. § 360cc(a)(1); 21 C.F.R. §§ 316.24, 316.25. In its cross-motion and opposition brief ("Opp."), FDA assiduously avoids confronting the plain language of the statute and regulations, instead invoking a litany of policy-laden arguments about whether Gralise is sufficiently "deserving" (Opp. 3) or offers enough of a "material benefit" to patients (Opp. 1). FDA's policy arguments miss the mark, as discussed below, and, more importantly, FDA does not get to re-write the terms of the Orphan Drug Act or to disregard the agency's own duly promulgated regulations in order to prevent Gralise from obtaining exclusivity.

Just the opposite: FDA is bound by the plain language Congress chooses. When, as here, Congress has enacted a broad statutory incentive using plain and unambiguous language, an agency may not narrow the reach of the incentive by creating additional hurdles that prevent some parties from obtaining the incentive, simply because the agency believes doing so would reflect a better policy. Similarly, when an agency has promulgated regulations through notice-and-comment rulemaking, it must follow them unless and until it changes them to say something else. The agency is not free to impose a standard other than the one stated in its regulations. The law is clear on these points. An agency cannot just assert that Congress—and the agency itself—should have set up the incentive scheme differently to deal with a particular fact scenario. Yet, that is exactly what FDA has done here—and why its decision cannot stand.

FDA's Opposition essentially asks the Court to ignore the regulation clearly stating that the agency "will grant" an orphan-drug designation request "if none of the reasons [for denying orphan designation] . . . in [21 C.F.R.] § 316.25 applies." 21 C.F.R. § 316.24. FDA makes this request because the parties *agree* that none of the reasons for denying designation enumerated in § 316.25 applies here. *See* Opp. 26-27. FDA's position, however, is wholly inconsistent with the plain language of the regulations and thus a textbook example of a "'plainly erroneous'" reading of agency regulations. *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (citation omitted). If FDA wants to add to the reasons for denying orphan-drug designation listed in § 316.25, the agency certainly may do so, but only through the same notice-and-comment procedures used to promulgate the regulation in the first instance.[1]

FDA's statutory argument is just as weak. Ignoring the fundamental principle of administrative law that "'an agency may not avoid the Congressional intent clearly expressed in the text simply by asserting that its preferred approach would be better policy," *Southern Cal. Edison Co. v. FERC*, 195 F.3d 17, 24 (D.C. Cir. 1999) (citation omitted), FDA seeks to elevate its preferred policy outcome over the statute's plain language. FDA does not (because it cannot) identify a gap in the Orphan Drug Act that allows the agency to wedge a clinical-superiority requirement between the approval of Gralise for its orphan-designated use and the award of marketing exclusivity for that use. Apparently unhappy with the standard that Congress actually

[1] FDA is aware of its notice-and-comment obligations: In the midst of considering orphan-designation and exclusivity for Gralise, the agency published a proposed rule that would revise its regulations to authorize the approach the agency has taken here. Although FDA characterized the revisions in the proposed rule as merely "clarifying" the current regulations, the revisions are undeniably substantive and material. Therefore, even if the proposed rule is eventually finalized, FDA may not enforce these revisions retroactively. *See Northeast Hospital Corp. v. Sebelius*, 657 F.3d 1, 13-14 (D.C. Cir. 2011) ("[T]he rule against retroactive rulemaking applies just as much to amendments to rules as to original rules themselves.").

established, FDA basically argues that it gets past the first step of *Chevron*[2] because Congress did not expressly negate the agency's authority to carve out exceptions or impose additional requirements if the agency sees fit to do so. But the fact that the statute makes orphan exclusivity broadly available does not equate to Congressional silence as to whether limitations are appropriate. This agency has made similar attempts to add limitations to the availability of statutorily mandated exclusivity incentives, and the D.C. Circuit has rejected those efforts each time at the first step of *Chevron* review. *See Teva Pharms. USA Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120 (D.C Cir. 2006); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998).

Even assuming the Court reaches *Chevron* Step Two, FDA's assertions about the "reasonableness" of its policy choice are not enough to uphold it. The agency first must show that its construction of the statute is "permissible," *Chevron*, 467 U.S. at 843, which means the agency must demonstrate that its interpretation "fits" the statutory text and "conform[s] to" statutory purposes. *See Abbott Labs. v. Young*, 920 F.2d 984, 988 (D.C. Cir. 1990). So eager is FDA to make this case be about policy choices that the agency does not even argue that its treatment of Gralise rested upon a "permissible construction" of any particular provision of the Orphan Drug Act—even though that is the defining basis of deference at *Chevron* Step Two. 467 U.S. at 843. Moreover, because the agency's decision violated its own regulations and departed from what the agency concedes is the sole precedent directly on point (*see* Opp. 40), FDA's action was arbitrary and capricious. *See Teva Pharms. USA. Inc. v. FDA*, 182 F.3d 1003, 1012 (D.C. Cir. 1999).

Finally, although the outcome in this case will be determined by the requirements of the Orphan Drug Act and its implementing regulations—and not the agency's policy preferences—

[2] *Chevron, U.S.A., Inc. v. Natural Res. Defense Council*, 467 U.S. 837 (1984).

the agency's policy arguments are inaccurate and misleading in a number of respects, both as to orphan exclusivity generally and as to Gralise. FDA repeatedly suggests that Gralise does not "deserve" orphan-drug exclusivity because the product is not different in any meaningful way from Neurontin, another gabapentin product already approved for PHN. FDA even suggests that Gralise merely "duplicate[s]" Neurontin and should be treated equivalently with the generic versions of Neurontin the agency has approved—exact copies of Neurontin intended to be freely substituted for that product. Opp. 1. The overstatement—and blatant error—in this self-serving characterization of Gralise is readily apparent: The *FDA-approved* labeling for Gralise states in bold print: "**Important Limitation: GRALISE is *not interchangeable* with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration**."[3]

Similarly, FDA's allegation that Gralise offers "no benefit to patients over existing drugs," Opp. 1, is wrong. Gralise was the first—and is the only—gabapentin tablet a patient takes just once a day; Neurontin and its myriad generics require dosing three times a day. *See* Opp. 10 (acknowledging this difference). The difference in dosing is a material benefit in terms of patient convenience, and one that studies show enhances patient compliance and, therefore, benefit. FDA's reference to Gralise as merely a "tweak[ ]" of Neurontin (Opp. 38) without "meaningful innovation" (Opp. 32) is likewise inaccurate. Gralise incorporates eight patented innovations and required tens of millions of dollars to develop over more than a decade.

FDA's myopic focus on its policy arguments here is misleading in another way, too. In every other context, the agency implements exclusivity broadly, in accordance with the terms of

[3] *See* Gralise Label, Highlights of Prescribing Information, Indications and Usage, http://www.gralise.com/lib/PDFS/GRALISE_PI.pdf (emphasis added). The fact that Gralise is not interchangeable with other gabapentin products is repeated *eight* times on the label and also appears on the approved packaging for the product. *See* FDA Approved Label and Packaging, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022544Orig1s000Lbl.pdf.

the Orphan Drug Act's broad directive regarding exclusivity. For example, FDA grants exclusivity to multiple products designated for the same orphan indication without considering whether the second (or third) product is a material advance in treating that disease or condition.[4] FDA also 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.[5] FDA has never cast exclusivity as a "windfall" or a "loophole" (Opp. 2) in either of these contexts, even though in both cases a drug receiving exclusivity may not offer a benefit "beyond what is already widely available" (Opp. 1) to treat the condition. Accordingly, to the extent the Court looks beyond the plain language of the relevant statutory and regulatory provisions, the agency's policy arguments do not win the day. There is a serious disconnect between FDA's narrow view of exclusivity in this case and the broad statutory directive that the agency has frequently invoked over the years.

Because the Orphan Drug Act and its implementing regulations required FDA to grant Depomed marketing exclusivity for Gralise upon the product's approval for its orphan-designated indication, PHN, Depomed is entitled to summary judgment in its favor.

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[4] For example, both Horizant (gabapentin enacarbil) and Qutenza (capsaicin) have been awarded orphan-drug exclusivity to treat PHN, in 2012 and 2009 respectively. AR 4 n.16 (discussing Horizant); *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as "the *Orange Book*") (32d ed. 2012), Prescription and OTC Drug Product Patent and Exclusivity List, at 27 (listing Qutenza). These drugs received orphan exclusivity because they met the standard in the Orphan Drug Act, not because FDA analyzed whether they provided a "benefit to the patient population beyond what is already widely available." Opp. 1.

[5] Horizant, for example, was FDA-approved to treat restless leg syndrome in 2011. *See* FDA Approval Letter, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022399s000ltr.pdf. Restless leg syndrome is a common disorder affecting between 4 and 29 percent of adults. *See Prevalence of Restless Legs Syndrome in North American and Western European Populations: A Systematic Review*, Sleep Med. 2011 Aug. 12(7):623-34.

THE DECISION UNDER REVIEW

Depomed filed this suit to challenge FDA's final agency action in approving Gralise for marketing while denying it orphan-drug exclusivity. That decision occurred in January 2011. Insofar as the agency's 2007 and 2010 letter rulings on designation are part of the record for that decision—and led irrevocably to it—those rulings are also reviewable. *See infra* p.11. What is not properly part of the administrative record for the January 2011 decision is the agency's November 2012 letter. The reason for this is simple: An agency must defend its actions "on the basis on which they were originally taken." *Grossmont Hosp. Corp. v. Sebelius*, __ F. Supp. 2d __, 2012 WL 5463350, at *15 n.10 (D.D.C. Nov. 9, 2012) (explaining that a court can consider "a more detailed explanation" the agency offers after litigation begins but cannot review reasoning that reflects "a new basis for the agency's action").

With respect to the orphan designation of Gralise, the reasons for FDA's actions appear in the agency's contemporaneous 2007 and 2010 letter rulings. AR 195, AR 265. The November 2012 letter is not a new FDA decision on the designation of Gralise, and FDA does not propose that it is. *See* AR 12 n.33 (stating that the November 2012 letter discusses the agency's earlier designation decision only "for the sake of completeness"); *see also* Opp. 19 (stating that the November 2012 letter responds to Depomed's "exclusivity arguments"). Accordingly, judicial review of the lawfulness of FDA's decision to condition designation of Gralise on a plausible hypothesis of clinical superiority to Neurontin begins and ends with the reasons FDA identified in its 2007 and 2010 letter rulings.

With respect to marketing exclusivity, Depomed challenges the agency's decision to make marketing exclusivity contingent upon proof of clinical superiority to Neurontin. FDA announced that decision for the first time on November 28, 2010, when FDA made that

condition known in granting Depomed's designation request (AR 306), and FDA invoked that decision again on January 28, 2011, when it approved Gralise without orphan-drug exclusivity (AR 43). FDA gave its reasons for imposing a clinical-superiority requirement in its designation letter (AR 306) and confirmed that reasoning in its February 9, 2011 follow-up phone call (AR 1003). Accordingly, judicial review of FDA's decision to make exclusivity contingent upon proof of clinical superiority to Neurontin properly focuses on those contemporaneous statements.

FDA's attempt to shift the Court's focus to the reasons and precedent identified in its November 2012 letter (AR 1) and internal agency memorandum (AR 846) should be rejected—at least to the extent these documents offer "new reasons" for requiring proof of clinical superiority which the agency never previously identified. *Grossmont*, 2012 WL 5463350, at *15 n.10. For example, in the letter, FDA for the first time refers to nine previous instances in which the agency withheld marketing exclusivity in (purportedly) similar circumstances. *See* AR 849-852. But there is no evidence in the record showing the agency looked at (or even looked *for*) relevant precedents at any point before this lawsuit was filed. The November 2012 letter also claims that, regardless of FDA's decisions under its designation-related regulations, the agency could independently require proof of clinical superiority according to a new, previously unannounced interpretation of 21 U.S.C. § 360cc(a)(1). *See* AR 10. But there is no indication in the record that the agency imposed its clinical-superiority requirement here based on this statutory provision. FDA therefore may not defend its decision in court on the basis of this new argument, either.

FDA's contention that, for purposes of judicial review, its November 2012 letter supplants the agency's prior decisions (Opp. 17-18) is without merit, for at least three reasons.

First, although the letter informs Depomed that the additional evidence the company submitted did not establish clinical superiority to Neurontin, FDA's decision to require proof of clinical superiority was final on January 28, 2011, if not earlier. *See Collagenex Pharms., Inc. v. Thompson*, 2003 WL 21697344, at *5-*6 (D.D.C. July 22, 2003) (agency's decision to classify drug as an antibiotic, such that it would not receive marketing exclusivity, was final at time of classification). Depomed's September 2011 letter was not a formal "request for administrative reconsideration" (Opp. 18 n.13), for the same reasons the letter to FDA was not a request for reconsideration in *Collagenex*. There, the company submitted a letter in an effort "to approach the Agency prior to suit, lay out its theories of litigation, and potentially achieve a settlement." 2003 WL 21697344, at *5. Although FDA sought to portray the letter in *Collagenex* as a request for reconsideration, the court rejected that argument in concluding that the letter "was intended to speak frankly with FDA in an effort to avoid litigation and was not intended to be a request for reconsideration." *Id.* So too here. Depomed's letter was not submitted as a citizen petition or through any other formal administrative review mechanism and was submitted in support of a request for a meeting with the agency to discuss Depomed's view of the law and its evidence of clinical superiority. *See* AR 95 (explaining that letter would allow for efficient discussion of issues in subsequent meeting with agency); *see also* AR 5 (on date lawsuit was filed, "FDA and Depomed were still discussing the possibility that Gralise might receive orphan exclusivity predicated on a clinical superiority showing").

Second, no case cited by FDA supports its view that the November 2012 letter (or anything else postdating Gralise's January 2011 approval) should be considered part of the administrative record underlying the agency's decision to approve Gralise without orphan-drug exclusivity. None 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. *See* Opp. 19-20.[6] Moreover, none of these cases suggests that, as FDA asserts, a court can consider post-decisional material so long as the plaintiff "will not be prejudiced." Opp. 19. Nor is the relevant factor the amount of time that has elapsed since the filing of a complaint, as FDA contends. *See* Opp. 19-20. The relevant question is 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.[7]

Third, the Administrative Procedure Act ("APA") requires that agency action be justified at the time it was taken, not just potentially justifiable at some later date on the basis of reasons the agency may be able to articulate in response to a filed complaint. It would elevate form over substance to treat the agency's November 2012 letter as the final decision simply by virtue of its being the most recent—and most expansive—attempt by the agency to rationalize its course of action on Gralise.

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[6] Among other differences, none of the decisions involved a challenge as to what constituted the decision under review. *See Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d 174, 176 (D.D.C. 2010) (after filing of lawsuit, FDA decided to address plaintiff's concerns "administratively" and solicited public comment before issuing final ruling); *Stat-Trade, Inc. v. FDA*, 869 F. Supp. 2d 95, 101 (D.D.C. 2012) (as part of negotiation to avoid preliminary injunction briefing, plaintiff consented to FDA's belated issuance of letter rulings); *Hi-Tech Pharmacal v. FDA*, 587 F. Supp. 2d 1, 6 (D.D.C. 2008) (FDA announced prior to lawsuit that final decision would issue on a date certain). In *Genentech v. Bowen*, the question was whether the *plaintiff* could rely on a rationale other than the one identified in its original complaint. 676 F. Supp. 301, 308 (D.D.C. 1987).

[7] FDA seems to criticize Depomed for not amending its complaint after FDA issued its November 2012 letter. Opp. 20. But the cases FDA cites in support of its criticism involved parties that amended their complaints in very different procedural circumstances. *See Actavis-Elizabeth*, 689 F. Supp. 2d at 176 (complaint amended after FDA opened case administratively, solicited public comment, and issued formal ruling); *Stat-Trade, Inc.*, 869 F. Supp. 2d at 101 (complaint amended after FDA issued letter rulings with plaintiff's prior consent); *Hi-Tech Pharmacal v. FDA*, 587 F. Supp. 2d 13 (D.D.C. 2008) (complaint amended after court denied motion for preliminary injunction).

Depomed's objection to FDA's injection of new reasons via the November 2012 letter has nothing to do with "shield[ing] the court from the agency's rationale" or "tactical gamesmanship." Opp. 20-21. It has to do with blackletter APA law about how courts review agency action. Under FDA's "shielding the court" theory, an agency could always develop, supplement, or expand its justification for taking action at some point down the road once the affected party files suit. That is not how the APA works. Parties 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. But in any event, as Depomed shows below, Depomed is entitled to summary judgment in its favor even if the Court considers the arguments FDA made for the first time in the November 2012 letter.[8]

[8] FDA wrongly suggests that if its pre-November 2012 communications with Depomed "inadequa[tely]" describe FDA's reasoning, the Court would have to remand to FDA for it to provide the explanation that it later provided in the November 2012 letter. Opp. 21. That is simply untrue. Unlike a situation where a court cannot discern an agency's rationale for a decision, here the agency offered a rationale—just one that is legally infirm. Therefore, because "the agency's path may reasonably be discerned" from its May 2007, June 2010, and November 2010 letters as well as its February 2011 phone call confirming that it denied Gralise orphan-drug exclusivity in January 2011, there is no reason to remand for further explanation in this case. *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 286 (1974); *cf. Florida Power & Light Co. v. FERC*, 85 F.3d 684, 689 (D.C. Cir. 1996) (courts consider whether agency action was justified by the reasons the agency articulated at the time, not "post hoc salvage operations" raising new arguments not mentioned or implied in the decision on review). The proper remedy here is to order FDA to provide Gralise with orphan-drug exclusivity from the date of its marketing approval.

ARGUMENT

I. THE GOVERNING REGULATIONS DID NOT PERMIT FDA TO CONDITION ORPHAN-DRUG DESIGNATION FOR GRALISE UPON DEPOMED PRESENTING A PLAUSIBLE HYPOTHESIS THAT GRALISE IS CLINICALLY SUPERIOR TO NEURONTIN.

A. Depomed's Challenge To FDA's Unlawful Action At The Designation Stage Is Not Moot.

Depomed's opening brief explained why FDA's actions at the designation stage are not moot: FDA's arbitrary and capricious action in applying the clinical-superiority framework to Gralise at the designation stage led to the agency's decision to withhold exclusivity from Gralise. Depomed Mem. in Supp. of Mot. for S.J. ("Depomed Mem.") 21. The agency's designation-stage decision accordingly presents a live controversy that has a "continuing, present adverse effect[ ]" for Depomed. *Chem. Mfrs. Ass'n v. EPA*, 859 F.2d 977, 982 (D.C. Cir. 1988) (quoting *O'Shea v. Littleton*, 414 U.S. 488, 496 (1974)). *See also Caiola v. Carroll*, 851 F.2d 395, 401 (D.C. Cir. 1988) (holding that expiration of debarment orders against plaintiffs did not moot lawsuit because debarment carried "prospect of lingering stigma or other adverse impact").

FDA nevertheless contends that Depomed's challenge is mooted by the fact that the agency "decided in Depomed's favor" when it granted Gralise designation. Opp. 24. Not so. To meet its "heavy" burden of demonstrating mootness, FDA must show that its subsequent designation decision "completely and irrevocably eradicated the effects of the alleged [legal] violation." *City of Los Angeles v. Davis*, 440 U.S. 625, 631 (1979). FDA has not made such a showing, nor can it: The designation of Gralise did not "eradicate[ ]" the effects of FDA's unlawful decision to apply the clinical-superiority framework at the designation stage. Gralise remained subject to the conditions and requirements of that framework at the time of approval, and its orphan-drug exclusivity has been withheld on the basis of that framework. Depomed therefore may properly seek relief against the initial decision to invoke the framework in the first

place. *See Chem. Mfrs. Ass'n*, 859 F.2d at 983 (manufacturer's submission of required chemical-testing data did not moot lawsuit challenging EPA's decision to require such testing, which triggered other regulatory burdens).

The Tenth Circuit recently applied these principles to FDA's approval process in *Cody Labs, Inc. v. Sebelius*, 446 F. App'x 964 (10th Cir. 2011). In *Cody*, FDA had approved the manufacturer's drug as a "new" drug, but the manufacturer argued that its drug should have been considered a "grandfathered" drug exempt from the approval process from the start. *Id.* at 967. The court of appeals held that the approval of the drug did not moot the manufacturer's claims because "new" drugs are subject to greater regulatory burdens than grandfathered drugs, and a decision reversing the grandfathering determination would afford the plaintiff "meaningful relief in the form of freedom from these burdens." *Id.* That is the case here. 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. Therefore, Depomed's claim, like the claim in *Cody*, is not moot.

FDA also contends that it would have required proof of clinical superiority as a prerequisite to exclusivity regardless of its decisions at the designation stage. Opp. 24. But 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. FDA's designation letter made clear that Depomed would not be able to obtain marketing exclusivity for Gralise until it proved that Gralise was clinically superior to Neurontin "based on better safety." AR 306. That condition laid the foundation for FDA's subsequent denial of marketing exclusivity in 2011. *See* AR 1003 (because designation of Gralise for PHN "was based on the hypothesis that [Gralise] was clinically superior due to better safety," Depomed "would have to prove this hypothesis" to

receive exclusivity). As a result, FDA's contention that the designation challenge "would make no difference to the exclusivity outcome that Depomed seeks" (Opp. 25) is flatly contradicted by the record. *See Performance Coal Co. v. MSHRC*, 642 F.3d 234, 238 (D.C. Cir. 2011) ("we understand why [agency] counsel would cling to an anemic claim of mootness because [its] [APA] argument . . . is even weaker").

B. Depomed Was Entitled To Orphan Designation Under 21 C.F.R. § 316.24 Once It Cleared The Hurdles In 21 C.F.R. § 316.25.

FDA's regulations implementing the Orphan Drug Act state that FDA "will grant" a request for designation "if none of the reasons described in [21 C.F.R §] 316.25 for requiring or permitting refusal . . . applies." 21 C.F.R. § 316.24. FDA's brief never grapples with this unambiguous language in its regulation, and it concedes that "none of the reasons" listed in § 316.25 applied to Depomed's request. *See* Opp. 26-27. Accordingly, under the plain language of § 316.24, FDA was obligated to grant Depomed's request for designation, without qualification. Its decision not do so flatly violates that governing regulation.

FDA argues for the first time in its November 2012 letter and brief to this Court that "§ 316.25 cannot reasonably be read as setting forth the exclusive grounds for denying designation." Opp. 26. But nowhere in the contemporaneous record did the agency ever discuss, let alone decide or assert, that § 316.25 is not an exclusive list of the circumstances under which a request for orphan designation may or must be denied. The June 2010 letter mentions § 316.25 only to note that Depomed cited it. AR 265; *see also* AR 202-207. The same approach is reflected in the agency's internal review documents. *See* AR 33-38. As a general rule, an agency "must defend its actions on the basis on which they were originally taken." *Grossmont Hosp.*, 2012 WL 5463350, at *15 n.10. FDA offers no reason for the Court to disregard this well-established standard.

A court should be skeptical when an agency relies upon new regulatory interpretations not reflected in the contemporaneous record of its decision. *See Am. Bar Ass'n v. FTC*, 430 F.3d 457, 471 (D.C. Cir. 2005) (doubting that agency could rely upon interpretive "stretch" advanced in brief that was "conspicuously lacking from the letter determination [under] review"). Yet that is precisely what FDA is doing here. Although FDA claims to have "explained" its "non-exclusive" interpretation of § 316.25 before (Opp. 26-27), the only thing FDA cites is the November 2012 letter, which it sent after this lawsuit was filed and long after the decision at issue. *See* Opp. 26 (citing AR 13). Indeed, the relevant paragraphs of FDA's brief (Opp. 26-27) do not cite any interpretive document showing the agency brought its expertise to bear on this question before it addressed Depomed's request for designation. And as for the agency's citizen petition response that characterized § 316.25 as an exclusive list, FDA claims now that it was "merely restat[ing]" and not "interpret[ing]" its regulations in that instance. Opp. 27 n.17. That makes Depomed's point exactly: If "restat[ing] the language" of the regulation indicates that the list is exclusive, then any "interpretation" of it to mean something else must be erroneous.

As a result, even if FDA's new interpretation of § 316.25 could be retroactively inserted into the reasoning of the June 2010 letter, the fact that it is plainly erroneous means that the interpretation would not be entitled to deference, contrary to the agency's suggestion (Opp. 27). *See Auer*, 519 U.S. at 461; *see also* Depomed Mem. 16-17 (and cases cited therein). Section 316.24 clearly states that § 316.25 lists the only reasons for FDA to deny a designation request. FDA's "non-exclusive" construction violates the plain language of the regulations.

FDA tries to salvage its "non-exclusive" interpretation by asserting that the agency could deny a request to designate "a product other than a drug (e.g., a device)." Opp. 27. But a device is not a "*drug* . . . intended for a rare disease or condition," which means that FDA could (and

would) have to deny a designation request for a device pursuant to 21 C.F.R. § 316.25(a)(1) (emphasis added). The agency's second attempt to bolster its "non-exclusive" argument fares no better. The agency claims that it can deny a designation request that fails to comply with the Orphan Drug Act's requirement that a designation request be made before a marketing application is submitted. Opp. 27; *see* 21 U.S.C. § 360bb(a)(1) ("A request for designation of a drug shall be made before the submission of [a marketing application]"); 21 C.F.R. § 316.23(a) (implementing this requirement). But the statutorily imposed timing requirement is a threshold requirement for submitting a designation request; if a request does not comply with it, FDA has no authority to consider, let alone grant, the request.

In contrast to these other provisions, § 316.25 enumerates the only criteria for FDA to evaluate in determining the merits of a designation request. FDA limited those reasons to four: (1) whether the sponsor provided sufficient evidence documenting the rarity of the condition; (2) whether there is sufficient information to establish a medically plausible basis for expecting the drug to be effective in treating the rare condition; (3) whether the same drug "already has orphan-drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug"; and (4) whether the designation request contains untrue statements of fact or omissions of material facts. FDA could have included any number of other reasons for denying exclusivity, but having decided not to, the agency could not lawfully graft another reason onto § 316.25 by fiat, and then rely on it in ruling on Depomed's designation request.

C. FDA's Reliance On 21 C.F.R. § 316.20(b)(5) Is Misplaced.

FDA's Opposition claims that, notwithstanding § 316.24 and § 316.25, FDA could deny designation to Gralise for lack of a plausible hypothesis of clinical superiority to Neurontin under 21 C.F.R. § 316.20(b)(5). Opp. 25-27. That regulation requires the "sponsor of a drug that is

otherwise the same drug as an already-approved orphan drug" to submit with its request "an explanation of why the proposed variation may be clinically superior to the first drug." 21 C.F.R. § 316.20(b)(5). FDA contends that this regulation provides a reason for denying designation separate from the reason articulated in § 316.25(a)(3). The gist of the agency's argument is that the slight difference in the wording of § 316.20(b)(5) (which refers to an "already-approved orphan drug") gives that regulation much broader reach than § 316.25(a)(3) (which refers to a drug "that already has orphan-drug exclusive approval").

Depomed has already shown that this reading is flatly contradicted by the agency's own explanation of how these two provisions fit together. Depomed Mem. 16-18. In the preambles accompanying the proposed and final regulations, the agency clearly referred to the requirements in § 316.20(b)(5) and § 316.25(a)(3) as interchangeable and co-extensive. *See, e.g.*, 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991), AR 704. Elsewhere, FDA has called these two regulations "parallel requirements." AR 305g. The agency cannot now contend that these "parallel" requirements, which its own rulemaking indicates are co-extensive, in fact require different things.

FDA's new interpretation of § 316.20(b)(5) also departs sharply from the agency's original intent in promulgating that regulation and the definition of "same drug" in § 316.3(b)(13). *See Exportal Ltd. v. United States*, 902 F.2d 45, 50 (D.C. Cir. 1990) (agency may not rely upon "unforeseen interpretations" of its regulations). As FDA explained in its contemporaneous Federal Register preambles, the agency proposed and adopted these provisions—and the clinical-superiority standard they require in some circumstances—to permit the agency to approve an innovation over an existing drug that has orphan-drug exclusive approval notwithstanding that exclusivity.[9] *See, e.g.*, 56 Fed. Reg. at 3340, AR 704 ("FDA [will]

[9] In its November 2012 letter, FDA states that it also applies the clinical-superiority framework when a prior version of the same drug received orphan exclusivity that has since

grant orphan-drug designation even for a drug that is otherwise the same drug as one already given *exclusive marketing approval* . . . when the second sponsor can make a plausible showing that it may be able to produce a clinically superior drug") (emphasis added); 57 Fed. Reg. 62,076, 62,081 (Dec. 29, 1992), AR 721 ("[o]rphan-drug designation can be granted to new sponsors of drugs currently protected by *orphan-drug exclusive marketing*") (emphasis added). A sponsor that shows the "clinical superiority" of its drug to a predecessor product may thus "break" the exclusivity that would otherwise keep it from the market. *See* Depomed Mem. 17 n.10 (quoting FDA Memorandum in Support of Motion for Summary Judgment, *Baker-Norton Pharms., Inc. v. FDA*, No. 98-927 (D.D.C.), 1998 WL 35242732, at *14 (July 27, 1998)). Because Neurontin never had orphan-drug designation or exclusivity, FDA regulations supply no basis whatsoever for the agency's decision to apply the clinical-superiority framework here.

FDA now claims that the agency "applies the same [clinical-superiority] standard for determining eligibility for orphan drug exclusivity w*hether or not there is existing exclusivity to 'break'*." Opp. 7 (emphasis added). The agency's brief, however, does not cite a single interpretive document predating FDA's denial of exclusivity for Gralise that adopts this construction of § 316.20(b)(5). *See* Opp. 7-9. In fact, the agency even provides a chart of its never-before-announced designation and exclusivity "scheme" that contains *no citations* showing where the agency previously adopted the interpretations in the second column ("Same

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expired. In FDA's view, where one drug has "used up" the seven-year orphan exclusivity period, exclusivity should not be available to a subsequent drug unless it is clinically superior to the predecessor. *See* AR 969. FDA tries to characterize Depomed as admitting that FDA's requiring clinical superiority in such instances reflects an appropriate agency interpretation of an ambiguous statute. *See* Opp. 30-31. That misrepresents Depomed's position. Because FDA had previously said the expired-exclusivity situation was relevant, *see* AR 10, Depomed simply wanted to note that the issue is not before the Court in this case, *see* Depomed Mem. 4 n.4 ("this case does not involve a prior, expired exclusivity period"). Any ambiguity—if it exists—regarding that factual scenario has no bearing on the issue here, and whether a court would uphold the agency's position in a case involving expired exclusivity is not relevant.

Drug Previously Approved Without Designation or Exclusivity"). *See* Opp. 9. Given the agency's prior interpretation of § 316.20(b)(5) as a "parallel" provision to § 316.25(a)(3), FDA's new interpretations in this table must be rejected. *See Teva*, 182 F.3d at 1010 (vacating FDA action where agency departed from definition adopted in guidance document).

Although FDA contends that its approach to sponsors like Depomed, who seek designation after the sponsor of a prior product did not, is "long-standing," Opp. 41, the agency admits that the situation has arisen only a "handful" of times. Opp. 26 n.16. Moreover, the five instances the agency says are relevant are not mentioned at all in the administrative record at the time FDA was making its decision on Gralise. Two of these "precedents" could not possibly have been considered by the agency in its decision about Gralise, because they occurred *after* the agency's action with respect to Gralise. *See* Depomed Mem. 20. In any case, no matter how many past precedents FDA can find in its non-public files, none can rehabilitate the agency's plainly erroneous reading of its own regulations, which conflicts with the interpretation the agency has given them publicly.

"Deference to agency interpretations is not in order if a rule's meaning is clear on its face." *Pfizer v. Heckler*, 735 F.2d 1502, 1509 (D.C. Cir. 1984). The clear meaning of FDA's regulations is the one the agency adopted previously: § 316.20(b)(5) and § 316.25(a)(3) are "parallel" requirements. AR 305g. Section 316.20(b)(5) therefore does not give the agency an independent basis to deny a request for orphan designation.[10] If FDA had intended

[10] FDA makes the curious—and incorrect—assertion that Depomed's reading of 21 C.F.R. § 316.20 would somehow "exclude" or "foreclose" Gralise from eligibility for orphan designation. Opp. 26-27. That assertion is premised on Depomed's (supposed) argument that "designation [is] only available to sponsors of drugs that [are] the same as previously approved drugs *with orphan exclusivity*." Opp. 26 (emphasis in original). But Depomed has never made such an argument. Section 316.20 states that a sponsor "may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already-marketed drug." 21 C.F.R. § 316.20(a). In the context of this regulation, the term "drug" clearly refers to the

§ 316.20(b)(5) to have the independent meaning the agency gives it here, and to serve as a fifth permissible ground for denying a designation request, the agency should have included the same language in § 316.25. But FDA did not do so, and it is bound by that choice.

The plain language of FDA's regulations confirms that Depomed's request for designation should not have been denied for lack of a clinical-superiority hypothesis. Accordingly, FDA's decision to hold Depomed to that requirement and deny Depomed marketing exclusivity for failure to prove clinical superiority was arbitrary and capricious.

II. FDA VIOLATED THE ORPHAN DRUG ACT WHEN IT DENIED DEPOMED MARKETING EXCLUSIVITY.

A. FDA's Argument Fails At *Chevron* Step One Because The Orphan Drug Act Is Not Ambiguous As To Which Drugs Receive Exclusivity.

FDA does not dispute that Gralise was the first gabapentin drug to be designated as an orphan drug for the treatment of PHN and approved for that indication, and FDA agrees that the Orphan Drug Act "generally grants seven-year orphan exclusivity to designated drugs upon approval[.]" Opp. 28. Yet, in the very next sentence, FDA claims that the statute "does not address which drugs are eligible for exclusivity in the first instance." *Id.* Actually, the statute does address that question. The drugs eligible for exclusivity are, to use FDA's words, "designated drugs upon approval." The text of the statute makes this explicitly clear:

> if the Secretary—(1) approves an application filed pursuant to section 355 of this title . . . for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title . . . for such drug for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved application.

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sponsor's own drug product, because a sponsor requests and receives designation for a particular drug product—like Gralise. There is no question that at the time Depomed requested designation, Gralise was a "previously unapproved" drug product. *Id.*; *see also* 21 C.F.R. § 316.23(b) (referring to designation of a "drug product").

21 U.S.C. § 360cc(a)(1). This congressional command is unambiguous. When FDA (as the Secretary's designee) approves an orphan-designated drug for the use for which its orphan-drug designation was based, that drug receives seven years of marketing exclusivity. Therefore, when FDA approved Gralise for the treatment of PHN on January 28, 2011, the statute unambiguously required that Gralise be given seven years of marketing exclusivity. FDA's denial of exclusivity violates the statute.

FDA tries to suggest that the statute could be read "a number of ways" because Congress could have (or should have) intended narrower standards to apply in certain scenarios, rather than for the statute to be applied universally and consistent with its terms. Opp. 29. But "[s]uch an approach confuses generality for ambiguity." *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 37 (D.D.C. 2000). "[I]t is axiomatic that the use of broad language in a statute 'undercuts a narrow construction.' " *Id.* (citing *United States v. James*, 478 U.S. 597, 605 (1986)).[11] Congress chose to use broad language in the Orphan Drug Act. The Act includes no exceptions, and there is no suggestion that Congress intended the agency to design any of its own.

Under *Chevron* Step One, that is dispositive. *Chevron* review begins from the well-established tenet that "congressional intent is best divined from the statutory language itself." *Performance Coal*, 642 F.3d at 238. "Thus, to defeat application of a statute's plain meaning, [an agency] must 'show either that, as a matter of historical fact, Congress did not mean what it appears to have said, or that, as a matter of logic and statutory structure, it almost surely could not have meant it.' " *Id.* (quoting *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1089 (D.C. Cir.

[11] In *Mylan*, the statute at issue stated that certain drug exclusivity began on "a date of a decision of a court" holding a patent invalid or not infringed. FDA argued that the statute was ambiguous, because it did not address what to do if the court decision was appealed. The court rejected FDA's interpretation at *Chevron* Step One, concluding that the "unless appealed" exception created by FDA for policy reasons conflicted with the statute's plain language.

1996)). FDA does not try to meet this standard, and its interpretation accordingly fails at *Chevron* Step One.

B. This Case Is No Different From *Mova, Ranbaxy,* And *Teva.*

Depomed's opening brief pointed to three cases in which the D.C. Circuit applied these basic administrative-law principles to reject similar attempts by FDA to add requirements or exceptions to unambiguous statutory language about drug exclusivity. Depomed Mem. 28-31 (discussing *Mova* 140 F.3d 1060; *Ranbaxy*, 469 F.3d 120; and *Teva*, 595 F.3d 1303). Each of these cases holds that where Congress has designed a statutory incentive scheme, FDA may not impose roadblocks of its own design on the basis of the agency's policy preferences. FDA offers no substantive basis to distinguish these cases, simply calling them "inapt" and "not at all like" this case. Opp. 34-35. The agency instead blithely asserts that its clinical-superiority requirement is not "an additional extra-statutory requirement for orphan exclusivity," Opp. 35, but that is exactly what it is. It is not in the statute, and the agency is relying on it to deny exclusivity to Depomed, notwithstanding the fact that Depomed undeniably meets the statutory requirements.

As the D.C. Circuit emphasized in *Ranbaxy*, "FDA may not . . . change the incentive structure adopted by the Congress, for the agency is bound 'not only by the ultimate purposes Congress has selected, but by the means it has deemed appropriate, and prescribed, for the pursuit of those purposes.'" 469 F.3d at 126 (quoting *MCI Telecommc'ns Corp. v. AT & T Co.*, 512 U.S. 218, 231 n.4 (1994)). In other words, when a statute "makes [an] applicant eligible for exclusivity," FDA may not adopt a policy that "makes [the applicant] ineligible." *Id.* at 125-126. That is what the agency has done here, and why the Court should reject its decision.

C. There Is No Gap In The Orphan Drug Act That Would Allow FDA To Create An Exception To The Broad Statutory Directive For Sponsors Like Depomed.

FDA argues that its decision to deny Gralise exclusivity was reasonable, even if it was not statutorily compelled. To withstand scrutiny, however, FDA must "point to [a] particular ambiguity" in the Orphan Drug Act "that permits it to interpolate [its clinical-superiority] requirement." *Mova*, 140 F.3d at 1068. That is because agencies may not add requirements when Congress left "no gap for the agency to fill." *Nat'l Mining Ass'n v. U.S. Dep't of the Interior*, 105 F.3d 691, 694 (D.C. Cir. 1997). *See, e.g.*, *Stat-Trade*, 869 F. Supp. 2d at 104-105 (holding that FDA could not deny fee waiver based on factor not mentioned in statute).

FDA has not identified any relevant gap in 21 U.S.C. § 360cc. Although *Baker-Norton Pharms., Inc. v. FDA*, 132 F. Supp. 2d 30, 34, 36 (D.D.C. 2001), held that the ambiguity of the statutory term "such drug" created a gap with respect to the *scope* of orphan-drug exclusivity (*i.e.*, which products are blocked from approval by virtue of another product's exclusivity), the statute contains no similar gap with regard to *eligibility* for orphan-drug exclusivity. FDA (wrongly) argues that the statute "does not address which drugs are eligible for exclusivity in the first instance," Opp. 28, but it does, and in a straightforward way. Section 360cc(a)(1) specifically states that the products eligible for exclusivity are those "designated under section 360bb of this title for a rare disease or condition." 21 U.S.C. § 360cc(a)(1). Each such eligible drug receives exclusivity when it is approved "for such disease or condition," *i.e.*, the disease or condition for which it received orphan-drug designation. *Id*.

FDA also appears to argue that because imposing a clinical-superiority requirement on Depomed seems reasonable to the agency, there must be a gap in the statute. This approach is backwards, as the D.C. Circuit confirmed in *Mova*, *Ranbaxy*, and *Teva*. When Congress has prescribed a list of requirements for a regulated party to satisfy, an agency may not freely add

requirements, however "reasonable" they may seem to the agency. Statutes do not have gaps just because an agency may believe Congress *should have* included other requirements. *See Ethyl Corp. v. EPA*, 51 F.3d 1053, 1060 (D.C. Cir. 1995) (holding that such an argument "misconstrues the *Chevron* analysis").

Finally, FDA cites three decisions reviewing FDA exclusivity decisions at *Chevron* Step Two that are not remotely akin to the situation here. Opp. 33-34. In each case, the court found specific statutory terms were ambiguous. *See ViroPharma, Inc. v. Hamburg*, __ F. Supp. 2d __, 2012 WL 1388183, at *2 (D.D.C. Apr. 23, 2012) (finding "condition of use" to be ambiguous); *Astra-Zeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 81 (D.D.C. 2012), *appeal docketed* No. 12-5227 (finding "supplement," "new clinical investigation," and "essential to approval" to be ambiguous); *Baker-Norton*, 132 F. Supp. 2d at 36 (finding "such drug" to be ambiguous). These decisions are inapposite to a case like this one, in which FDA fails to peg its interpretation to an ambiguous statutory term.[12]

D. The General Delegation Of Rulemaking Authority In The FDCA Does Not Entitle Every Decision FDA Makes To Deference.

In its brief, FDA claims it does not need to point to a clear statutory hook for its clinical-superiority requirement because Congress gave FDA "general authority to promulgate substantive, binding regulations for the FDCA," of which the Orphan Drug Act is a part. Opp.

[12] Even if, as *Baker-Norton* held, the term "such drug" in § 360cc(a)(1) is ambiguous, FDA does not (and cannot logically) contend that its decision to require Depomed to prove clinical superiority flows directly from that term. *See* Depomed Mem. 27 (explaining that "such drug" defines the scope of a manufacturer's exclusivity and does not bear upon a manufacturer's *eligibility* for exclusivity). The agency appears to rely upon its "regulations" as a whole, *see* Opp. 7, but that approach is impermissible. *See infra* p.27; *see also Stat-Trade, Inc.*, 869 F. Supp. 2d at 104 (rejecting FDA's attempt to limit eligibility for fee waiver by reference to potential ambiguity in an inapplicable term used elsewhere in the relevant statutory provision).

27.[13] The D.C. Circuit has "categorically reject[ed]" this argument. *Ry. Labor Executives' Ass'n v. Nat'l Mediation Bd.*, 29 F.3d 655, 670 (D.C. Cir. 1994) (en banc) ("Unable to link its assertion of authority to any statutory provision, the Board's position in this case amounts to the bare suggestion that it possesses *plenary* authority to act within a given area simply because Congress has endowed it with *some* authority to act in that area. We categorically reject that suggestion.") (emphases in original).

Nor should the court give heed to FDA's claim that it is entitled to special deference in this case because the Food, Drug, and Cosmetic Act is "cumbersome and complex" and "highly technical." Opp. 23; *see also* Opp. 36 (claiming this case "fundamentally resembles the vast majority of instances in which courts . . . have deferred to the agency's expertise in administering a highly technical and complex regulatory scheme"). Under the APA, however, an agency "cannot simply declare its 'expertise'; it must exercise that expertise and demonstrate sufficiently that it has done so." *Village of Bensenville v. FAA*, 376 F.3d 1114, 1122 (D.C. Cir. 2004). Deference is warranted only when the challenged agency action is in fact "the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). The issues presented in this agency challenge are not ones that require scientific and technical expertise; they are straightforward legal arguments.

The real issue in this case is that FDA thinks the circumstances surrounding Depomed's claim to marketing exclusivity for Gralise should disqualify the product from that exclusivity, even though Congress structured the exclusivity provision broadly, in a way that encompasses

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[13] Contrary to FDA's assertion, Depomed did not "argue[ ] that FDA *only* has authority to promulgate non-substantive procedures for designation" under 21 U.S.C. § 360bb. Opp. 27 n.18 (emphasis added). At the cited page, Depomed says: "Unlike the designation section of the Orphan Drug Act, which authorizes FDA to 'promulgate procedures,' *see* 21 U.S.C. § 360bb(d), the exclusivity section of the statute does not direct FDA to engage in rulemaking, *see id.*§ 360cc." Depomed Mem. 6.

those very circumstances. Congress made seeking designation a voluntary undertaking. As a result, drug products may be intended to treat rare diseases and conditions but never "designated" as such under the Act. That is the case with Neurontin: Pfizer never requested orphan designation. Congress gave special statutory status to drugs for which orphan-drug designation was sought and received; drugs like Neurontin that may be intended to treat a rare disease or condition, but that never received designation as such, are afforded no such special status under the statute. Accordingly, 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.

III. FDA'S APPLICATION OF A CLINICAL-SUPERIORITY REQUIREMENT TO DENY DEPOMED EXCLUSIVITY WAS UNREASONABLE.

Even if there was a basis to call the Orphan Drug Act "ambiguous," that conclusion alone would not make all FDA decisions about the statute "reasonable." A court may affirm agency action at *Chevron*'s second step only if the agency's interpretation of the law rests on a "permissible construction of the statute." 467 U.S. at 843. A permissible construction is one that "fit[s] with the statutory language" and "conform[s] to statutory purposes." *Abbott*, 920 F.2d at 988. As discussed above, however, FDA does not even identify a provision of the statute that it is purporting to "construe"; thus, the agency's policy here cannot be said to rest on any "construction of the statute" at all. *See* Depomed Mem. 32.

FDA also fails to respond to Depomed's arguments about reasonableness (and cannot belatedly do so in a reply brief). As Depomed explained, FDA's action here does not "fit" the statute. *See* Depomed Mem. at 32-33. FDA has no response in its brief. Similarly, Depomed showed that it was unreasonable for FDA to rely upon an "anomalous category of 'orphan drugs' that are not 'designated' as such." *Id.* at 33. The Orphan Drug Act does not recognize such a

category of "orphan drugs," and indeed that statute does not use the term "orphan drug" to mean anything other than a drug designated by FDA pursuant to 21 U.S.C. § 360bb(a)(1). FDA has no response to this argument either. And FDA's limited argument about statutory purpose is woefully underwhelming. Opp. 37. It consists of nothing more than a few statements about the general statutory purpose to encourage companies to develop and market drugs for patients suffering from rare conditions—which is what Depomed did—and a conclusory assertion that denying exclusivity to Gralise "furthers" that purpose. If the only drugs that were eligible for exclusivity were "new treatment[s] for patients who would otherwise have no effective or inferior therapy" (Opp. 38), many of the drugs FDA has granted orphan exclusivity would not qualify. *See supra* 4-5 & nn. 4-5. *Chevron* and the APA require more than what FDA has told the Court here. FDA's action, if not unlawful, was at least unreasonable and must be set aside.[14]

IV. DENYING ORPHAN EXCLUSIVITY TO A FIRST-DESIGNATED DRUG BECAUSE OF A NON-DESIGNATED DRUG WAS ARBITRARY AND CAPRICIOUS.

A. FDA Violated Its Own Regulations

Putting aside the plain language of the statute, FDA's own regulations do not allow the agency to require proof of clinical superiority as prerequisite for orphan exclusivity unless there is a prior "same drug" that received orphan-drug exclusive approval. *See* 21 C.F.R. §§ 316.31, 316.3(b)(13); *see also* Depomed Mem. 35-38. The agency never directly responds to Depomed's point that imposing a clinical-superiority requirement in this case violates the agency's exclusivity-related regulations. Instead, in a footnote, FDA contends its role in recognizing

[14] Contrary to FDA's the-sky-is-falling argument, granting summary judgment to Depomed would not force FDA to pull any Neurontin generic products from the shelves. Opp. 38. Each of the generic versions of Neurontin approved after the date Gralise should have been awarded orphan-drug exclusivity is approved for other indications in addition to PHN. Enforcing Gralise's exclusivity against these generics would simply require the generics to strike the PHN indication from their labels, not to withdraw the products from the market.

exclusivity involves a "non-ministerial" exercise of discretion, Opp. 31 n.19, and implies that there is support for requiring proof of clinical superiority in Depomed's circumstances "[u]nder these regulations." Opp. 7. But FDA does not specify which regulations and does not point to any use of the terms "such drug" or "same drug" in the exclusivity regulations that would permit the agency to impose a clinical-superiority requirement on Depomed in this instance. In FDA's exclusivity regulations, it is clear that "same drug" and "such drug" are relevant only to define the scope of exclusivity and not a sponsor's eligibility for it.

Because FDA's regulations regarding exclusivity are unambiguous, *see* 21 C.F.R. Part 316, Subpart D, and the agency has failed to show how its action comports with its regulations, Depomed is entitled to summary judgment on this basis as well. *See Teva*, 182 F.3d at 1010.

B. FDA Concedes It Has No Past Precedent On All Fours With Its Decision Other Than Kogenate, Where The Agency Granted Exclusivity.

Depomed's opening brief pointed out that there is only one instance in which FDA approved an orphan-designated drug that was the same drug as a previously approved, non-designated drug. Depomed Mem. 38-41. Kogenate was the same drug as a prior, approved, non-designated drug (Recombinate), but FDA did not require Kogenate's sponsor to demonstrate clinical superiority to Recombinate because Recombinate had not been designated an orphan drug and never received orphan exclusivity. FDA does not dispute that it has treated Gralise differently from Kogenate, even though it is a bedrock principle of administrative law that "'an agency may not treat like cases differently.'" *Eagle Broad. Group v. FCC*, 563 F.3d 543, 551 (D.C. Cir. 2009) (citation omitted). Rather than offer a legitimate reason for doing so, FDA seeks instead to discount Kogenate as "an incorrect, outlier decision." Opp. 42. This characterization of Kogenate, first announced in the agency's November 2012 letter, is a markedly different view of Kogenate from what the agency has expressed previously. Even well

after the approval of Kogenate, the agency continued to take the position that it had handled the matter correctly, affirmatively enforcing Kogenate's exclusivity against a subsequent sponsor's "same drug." AR 667-668.[15]

The agency also refers to five examples of other cases in which it says that it required a demonstration of clinical superiority as a prerequisite for an award of orphan exclusivity. These examples, which appear for the first time in the November 2012 letter, are so heavily redacted that neither the Court nor Depomed can independently evaluate the relevance of these allegedly similar prior precedents. One thing that can be discerned, however, is that the examples are not particularly relevant: none of them involved denying orphan exclusivity to a drug that was approved for an orphan-designated indication.

The other examples to which the agency points, which involve designated, approved drugs denied exclusivity because they were not clinically superior to an earlier "same drug" with exclusivity, are fundamentally unlike Gralise's factual circumstances. Depomed Mem. 41 (also noting that two of these examples date from 2012); *see also, e.g.*, AR 969 (referring to exclusivity as "used up" or "spent" after it has already been awarded to the same drug that was designated and approved for the same orphan indication). Situations in which the agency decided it would not award a *second* exclusivity period to the same drug go nowhere toward

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[15] At a public meeting in 1998, FDA's Office of Orphan Products Development explained that the earlier approval of Recombinate had no bearing on Kogenate's eligibility for orphan-drug exclusivity because Recombinate's sponsor had not sought or received orphan-drug designation or exclusivity:

> The exclusivity for a product is determined by whether or not somebody applies for an orphan designation. Recombinate did not apply or did not pursue the exclusivity. Therefore Kogenate was the only product which was designated and approved and, therefore, the only product which received the exclusivity.

AR 585.

establishing a 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.

CONCLUSION

The agency's action must be set aside and Depomed granted the exclusivity to which it is entitled. As the D.C. Circuit has explained:

> When a statute commands an agency without qualification to carry out a particular program in a particular way, the agency's duty is clear; if it believes the statute untoward in some respect, then 'it should take its concerns to Congress,' for '[i]n the meantime it must obey [the statute] as written.

Oceana v. Locke, 670 F.3d 1238, 1243 (D.C. Cir. 2011) (quoting *Natural Res. Def. Council v. EPA*, 643 F.3d 311, 323 (D.C. Cir. 2011)). The command of the Orphan Drug Act in this case is clear. If FDA thinks the statute *should* require proof of clinical superiority in cases like Depomed's, the agency's recourse is to take that argument to Congress—not to enforce it against Depomed in violation of the statute.

For the foregoing reasons and those in Depomed's opening memorandum, the Court should grant Depomed's motion for summary judgment and deny the FDA's motion for summary judgment.

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Respectfully submitted,

/s/ Jessica L. Ellsworth
Philip Katz (D.C. Bar No. 440123)
Jessica L. Ellsworth (D.C. Bar No. 484170)
Judith Coleman (D.C. Bar No. 980382)
HOGAN LOVELLS US LLP
555 Thirteenth Street NW
Washington, DC 20004
(202) 637-5886

Counsel for Depomed Inc.