DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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Re: Eligibility of Gralise (gabapentin) for orphan-drug exclusivity

Dear Mr. Katz:

Depomed, Inc. (Depomed) has requested that the Food and Drug Administration (FDA or Agency) reconsider its decision that Gralise (gabapentin) is not entitled to seven years of orphan-drug exclusivity for the management of postherpetic neuralgia (PHN). Depomed asserts that it was automatically entitled to such exclusivity because Gralise was the first approved drug for this indication that was also orphan designated, even though Gralise is the same drug as another gabapentin product that had already been approved for the same indication. In the alternative, Depomed asserts that Gralise is entitled to orphan-drug exclusivity because it has demonstrated clinical superiority over the previously approved drug, Neurontin (gabapentin).

We have carefully reviewed the submissions made to the Agency on these issues[1] and additional relevant materials. For the reasons set forth below, we deny Depomed's request and affirm that Gralise is not entitled to orphan-drug exclusivity.

I. Summary

Section 527(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 360cc)[2] generally grants orphan exclusivity to designated drugs upon approval,

[1] These materials include a letter from Hogan Lovells US LLP regarding orphan exclusivity for Depomed, dated September 9, 2011 ("September 2011 letter"), the arguments you advanced during our meeting with you on April 11, 2012 ("April 2012 meeting"), as well as supplemental scientific information you submitted to the Office of Orphan Products Development (OOPD) on May 10 and May 24, 2012 ("May 2012 submissions"), July 3, 2012, July 6, 2012 ("July 2012 submission"), August 6, 2012 ("August 2012 submission"), and September 25, 2012.

[2] In this response, references to statutory "sections" are to the FD&C Act, not the U.S. Code.

but does not address eligibility for exclusivity when the same drug has already been approved for the same orphan indication. FDA interprets this statute to confer exclusivity only to drugs that are designated and *not* the same as an already approved drug. By regulation, FDA requires sponsors of orphan-designated drugs to demonstrate the clinical superiority of their drug to the previously approved drug to show that their drug is not the same as the previously approved drug and is therefore eligible for exclusivity.[3,4]

Gralise obtained orphan designation pursuant to section 526(a) (21 U.S.C. § 360bb) by offering a plausible hypothesis of clinical superiority over the previously approved drug, Neurontin. But, at the time of approval, Depomed was unable to demonstrate actual clinical superiority. Nor have any additional Depomed submissions demonstrated Gralise's clinical superiority over Neurontin. Gralise is therefore the "same drug" as the previously approved drug, Neurontin, and is ineligible for orphan exclusivity.

II. Factual And Procedural Background

A. Neurontin

Pfizer Inc.'s Neurontin was the first gabapentin drug approved on May 24, 2002 for management of PHN in adults.[5] Under section 526, certain drugs for rare diseases may obtain "orphan designation," which provides valuable incentives and is a predicate for orphan-drug exclusivity. Pfizer did not seek or obtain orphan-drug designation for Neurontin, despite being eligible to do so.

There are many generic versions of Neurontin that are approved and currently marketed. Nearly 30 such A-rated generics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("*Orange Book*").[6]

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[3] In this response, references to "exclusivity" are to orphan-drug exclusivity unless otherwise noted.

[4] The phrase "the same drug" in this response refers to the definition of sameness in the orphan drug regulations, which takes into account the chemical and clinical features of drugs and their intended use. 21 CFR 316.3(b)(13). Although this definition covers the drugs having the same intended use, we sometimes refer to "same drug for the same use" to emphasize that the intended use is the same.

[5] Neurontin (gabapentin) was approved for other indications as early as 1993: as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years old with epilepsy, and as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years. Neurontin is currently approved in capsule form (100 mg, 300 mg, and 400 mg of gabapentin), in tablet form (600 mg and 800 mg of gabapentin), and as an oral solution (250 mg/5 mL gabapentin). The FDA-approved Neurontin labeling is available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_Approval History. Because Gralise is approved for its orphan indication, it may be prescribed by physicians (but not promoted by Depomed) for off label uses, including other uses for which only Neurontin is approved even though the two products are not therapeutically equivalent. It is also well known that part of the market for gabapentin drugs represents uses for which no gabapentin product is approved by FDA.

[6] "A" rated generics have been determined to be therapeutically equivalent to the innovator or reference listed drug, and may be fully substituted for that product. *See* generally Orange Book Preface, *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm. At least 20 such generics were approved before the date that Gralise was approved (January 28, 2011); at least nine gabapentin generics have been approved after the date of Gralise's approval.

B. Gralise

Gralise contains the same active moiety as Neurontin but is a slightly different formulation that incorporates different inactive ingredients and gastric-retentive technology, which you describe as a "polymer technology that enables the tablet to expand in the stomach when taken with the evening meal." September letter, p. 18. By virtue of this new formulation, FDA views Gralise as a *different drug product* from Neurontin despite being *chemically the same drug* within the meaning of the orphan drug regulations.[7] This new formulation allows Gralise to be taken once-daily instead of Neurontin's three daily doses. Whereas Neurontin is to be titrated up to a dosage of 1800 mg divided into three daily doses (TID) taken with or without food,[8] Gralise is to be titrated to an 1800 mg dose taken orally, once-daily.[9]

Gralise's former sponsor[10] requested orphan designation to manage PHN on December 21, 2006.[11] FDA ultimately granted designation on November 8, 2010, after several rounds of deficiency letters that are detailed in your September 2011 letter (pp. 3-6). Many of these deficiency letters, and the sponsor's responses, reflected a disagreement as to the regulatory requirements for designation. The crux of this disagreement was whether the designation request for Gralise needed to contain a plausible hypothesis of clinical superiority over Neurontin, the same drug already approved for the same orphan use. Consistent with its long-standing interpretation of the orphan drug regulations, the Office of Orphan Products Development (OOPD) maintained that designation for Gralise could not be obtained absent such a plausible hypothesis of clinical superiority, per 21 CFR 316.20(a) and (b)(5). The sponsor countered that, under 21 CFR 316.24, FDA must grant designation unless any of the reasons specified at 21 CFR 316.25 applies – and the latter regulation does not list "failure to include a plausible hypothesis of clinical superiority where the same drug is already approved for the same use" as a reason for refusing designation. FDA disagreed with this interpretation of its regulations, as described further below in Section IV.B.

The sponsor ultimately provided a hypothesis of greater safety for Gralise over Neurontin, which FDA deemed plausible. "The comparison of the incidence of adverse

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[7] Different drug products (*i.e.*, with different dosage forms or different inactive ingredients) may incorporate the same drug (*i.e.*, have the same active moiety or principal molecular structural features). *Compare* 21 CFR 314.3(b) (defining "drug product") *with* 21 CFR 316.3(b)(13) (defining "same drug").

[8] Neurontin PI, Dosage and Administration, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s050,020882s035,021129s033lbl.pdf (label approved by FDA on 8/10/2011).

[9] Gralise PI, Dosage and Administration, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022544s006lbl.pdf (label approved by FDA on 1/31/2012).

[10] As detailed in the September 2011 letter, ownership of Gralise changed in these intervening years, from Depomed to Solvay Pharmaceuticals (later acquired by Abbott Products, Inc. (Abbott)), and again back to Depomed. September 2011 letter, at pp. 3-6. For ease of reference, we refer to the "sponsor" throughout this response to refer to the entity that owned Gralise at the relevant time, whether Depomed, Abbott, or Solvay.

[11] There is no dispute in this matter that PHN qualifies as a rare disease or condition under section 526.

events of [Gralise] to the reported incidence of adverse events of Neurontin, found in the Neurontin package insert, is adequate for supporting a *plausible hypothesis* that [Gralise] is clinically superior to the currently marketed form of gabapentin, based on better safety[,] for the purpose of orphan[-]drug designation." OOPD designation letter, November 8, 2010 (emphasis added). The designation letter advised, however, that clinical superiority over Neurontin would have to be *demonstrated* in order for Gralise to obtain orphan exclusivity upon approval.

FDA approved Gralise 300 mg and 600 mg tablets for the management of PHN on January 28, 2011 (NDA 22-544). The Gralise NDA relied on the Agency's previous finding of safety and efficacy for Neurontin; Neurontin was the reference listed drug for the Gralise application.[12] As FDA's summary review explained, "[Because] this [Gralise] application is relying on the Agency's previous finding of safety and efficacy for Neurontin, which carries an indication for PHN, during development the division agreed that only a single adequate and well-controlled study would be required to establish the efficacy of the new formulation."[13] To meet this requirement, the Gralise sponsor submitted efficacy data from a randomized, double-blind, placebo-controlled study in 452 PHN patients treated with either Gralise 1800 mg once daily or placebo in an approximately 1:1 ratio for a total of 11 weeks.[14] This efficacy study was considered essential to and supported approval of the new formulation. Accordingly, Gralise received three years of market exclusivity following the date of NDA approval. This three-year exclusivity bars FDA from approving any ANDA or 505(b)(2) application by another party that relies on the information supporting the conditions of approval of Gralise until January 28, 2014. Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act; 21 CFR 314.108(b)(4).[15]

FDA did not grant orphan exclusivity to Gralise upon approval because Gralise was not demonstrated to be clinically superior to Neurontin and, therefore, under FDA's interpretation of the statute, was the "same drug" as Neurontin and not eligible for exclusivity.[16]

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[12] This application was submitted in accordance with section 505(b)(2) (21 U.S.C. § 355(b)(2)) ("505(b)(2) application").

[13] NDA 22-544 Summary Review, p. 3, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022544Orig1s000SumR.pdf. The applicant submitted the results of three efficacy trials, one Phase 2 and two Phase 3 studies. The Phase 2 study and one of the Phase 3 studies failed to demonstrate a statistically significant treatment effect. *Id.*, p. 11.

[14] *See id.* For the successful Phase 3 study, the primary efficacy endpoint was the mean change in average daily pain scores from the baseline week to the final week of the efficacy treatment period for patients treated with Gralise compared to placebo. The analysis of efficacy demonstrated a statistically significant superiority for Gralise compared to placebo.

[15] A three-year exclusivity is granted for a drug product that contains an active moiety that has been previously approved if the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to and supported approval of the application. Changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration, or conditions of use, for example, may be granted exclusivity if clinical investigations are essential to and support approval of the application containing those changes.

[16] We note that FDA approved a prodrug of gabapentin for management of PHN on June 6, 2012. This prodrug, Horizant, is an extended-release formulation of gabapentin enacarbil. It received orphan

C. Challenges To FDA's Exclusivity Decision

Following approval, Depomed challenged FDA's decision that Gralise was not entitled to orphan exclusivity on two separate bases. First, by letter dated September 9, 2011, Depomed asserted that the plain language of the statutory provision in section 527 compelled exclusivity because Gralise was designated and approved, even though Gralise was not demonstrated to be clinically superior to Neurontin. *See* September 2011 letter, pp. 7-15.

Second, Depomed provided additional evidence to support its claim that Gralise was clinically superior to Neurontin. In these submissions, Depomed alleged that Gralise was clinically superior to Neurontin either by providing greater safety or by making a major contribution to patient care.[17]

On September 25, 2012, while FDA and Depomed were still discussing the possibility that Gralise might receive orphan exclusivity predicated on a clinical superiority showing,[18] Depomed sued FDA in the United States District Court for the District of Columbia seeking declaratory, injunctive, and other relief, for FDA's failure to recognize orphan exclusivity for Gralise.[19] This complaint reiterated many of the legal arguments in the September 2011 letter and also included allegations not previously raised before the Agency. *See* Complaint ¶¶ 51-58. FDA has reviewed these new allegations and describes its findings and analysis below, in Section IV.C.

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exclusivity without having to demonstrate clinical superiority over the previously approved versions of gabapentin because it was not considered to be the "same drug" under 21 CFR 316.3(b)(3). It was considered to have a different active moiety owing to the chemical structure of its active ingredient. For a description of Horizant's chemical properties, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022399s003lbl.pdf (Section 11, Description).

[17] For a list of these submissions, see *supra* note 1.

[18] OOPD was in e-mail and phone communication with Depomed on the morning of September 25, 2012, concerning the design of the physician survey that Depomed had submitted in support of its contention that Gralise is clinically superior to Neurontin by providing a major contribution to patient care. For further discussion of this physician survey, see Section V.B of this response.

[19] This lawsuit was filed even though existing three-year exclusivity, to which Depomed is entitled as described on page 4 of this response, would bar approval of any generic copy of its product until early 2014 and even though ongoing patent litigation appears likely to delay such approval even longer. *See* Depomed, Inc. Form 10-Q, 8/3/2012, p. 32, *available at* http://investor.depomedinc.com/phoenix.zhtml?c=97276&p=irol-SECText&TEXT=aHR0cDovL2lyLmludC53ZXN0bGF3YnVzaW5lc3MuY29tL2RvY3VtZW50L3YxLzAwMDExMDQ2NTktMTItMDU0MTU0L3htbA%3d%3d. This document describes patent suits involving seven generic applications for copies of Gralise and states that, with respect to the first three such applications, "We commenced the lawsuit within the 45 days required to automatically stay, or bar, the FDA from approving the ANDAs for 30 months or until a district court decision that is adverse to the asserted patents, whichever may occur earlier. Absent a court order, the 30-month stays are expected to expire in July 2014 and August 2014." For the additional suits the same statement is made with the exception that the expected expiration is stated to occur, respectively, in September, October, and November 2014.

III. Statutory And Regulatory Authorities

In 1983, Congress enacted the Orphan Drug Act (Public Law 97-414) to provide incentives to develop drugs to treat rare diseases and conditions. The Orphan Drug Act included amendments to the FD&C Act (sections 526-528). As defined in section 526(a) (as amended by a 1984 amendment to the statute), a rare disease or condition includes any disease or condition that affects fewer than 200,000 persons in the United States. Drugs for rare diseases or conditions are "commonly referred to as 'orphan drugs,'" Congress explained, because "[t]hey generally lack a sponsor to undertake the necessary research and development activities to attain their approval by the [FDA]." H.R. Rep. 97-840, Pt. 1, at 6 (1982). Rare diseases and conditions "affect such a small number of persons that there is virtually no commercial value to any drug which is useful against them. . . ." *Id.* To mitigate these commercial disincentives and foster the development of drugs that would not otherwise be developed and approved, Congress created a system to reduce the cost and increase the potential reward for developing orphan drugs. "The legislative history is replete with references to the fundamental need to provide treatment for *presently untreated patients*." *Genentech v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987) (emphasis added).

Among the incentives provided by the Orphan Drug Act are tax credits for clinical testing, research grants, and the possibility of seven years of market exclusivity. Orphan-designated drugs are also exempt from application user fees.[20] Following enactment of the Orphan Drug Act in 1983, FDA's program has successfully enabled the development and marketing of more than 400 drugs for rare diseases and conditions.[21] By contrast, fewer than ten such products supported by industry came to market between 1973 and 1983.[22]

A drug must first be designated as an orphan drug to be potentially eligible for orphan exclusivity upon approval. *See* sections 526(a) & 527(a); 21 CFR 316.31 and 316.34. In order to obtain designation, the drug's sponsor must submit to FDA a request for designation that includes, among other things, a description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed. 21 CFR 316.20(b)(3); *see generally* 21 CFR 316.20 and 316.21. When a drug is otherwise the same (*i.e.*, contains the same active moiety or principal molecular structural features[23]) as an already approved orphan drug for the same use, the request for designation must contain "a plausible hypothesis of clinical superiority" over the previously approved drug. 21 CFR 316.20(a) and (b)(5).

Section 527 instructs FDA not to approve "another application . . . for *such drug* for such disease or condition" (emphasis added) for seven years from the date that a

[20] This application user fee exemption was enacted as part of the Prescription Drug User Fee Act of 1992 (PDUFA), since reauthorized.
[21] *See* Developing Products for Rare Diseases & Conditions, *available at* http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.
[22] *See id.*
[23] See 21 CFR 316.3(b)(13).

particular designated drug is approved, with certain exceptions not relevant here.[24] Congress provided no guidance on what "such drug" means in this context. *See* 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992); *Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) ("Given the multiple definitions of the term 'drug,' and the different purposes that various statutory provisions can serve, the Court cannot find that the definition of 'drug' in § 360cc(a) is clear and unambiguous."). After extensive consideration of the Orphan Drug Act's text and purpose, FDA defined "such drug" through implementing regulations defining sameness. *See* 56 Fed. Reg. 3341 (Jan. 29, 1991); 57 Fed. Reg. 62076.

Under these regulations, FDA will not approve the "same drug," as defined in 21 CFR 316.3(b)(13), for a period of seven years. Two drugs that are chemically the same and indicated for the same use may nevertheless not be the "same drug" if the second drug is "clinically superior" to the previously approved drug, as defined in 21 CFR 316.3(b)(3). A sponsor may demonstrate clinical superiority by showing that its drug provides a "significant therapeutic advantage" by providing greater effectiveness or safety or by making a "major contribution to patient care" as compared to the previously approved drug that is chemically the same. 21 CFR 316.3(b)(3). A clinically superior drug may be approved with its own term of orphan exclusivity – and notwithstanding any existing exclusivity for the previously approved drug that is chemically the same – because FDA interprets a clinically superior drug as not being within the meaning of the term "such drug" in section 527. *See* 56 Fed. Reg. 3338 (describing these implementing regulations as fulfilling a main purpose of the Orphan Drug Act, "to stimulate innovation in developing treatments for patients with rare diseases and conditions"). These implementing regulations have been upheld upon judicial review as a reasonable construction of the statute. *Baker,* 132 F. Supp. 2d at 36.

If a sponsor fails to demonstrate clinical superiority of a drug that is chemically the same as a previously approved drug and for the same use, the subsequent drug would be considered the "same drug" and so fall within the meaning of "such drug" in section 527. It could not be approved during the pendency of the first-in-time drug's exclusivity, if any, and when approved would not receive a separate, additional term of orphan exclusivity. This is because FDA interprets section 527 as according orphan exclusivity to a designated drug only the first time that drug is approved for the orphan use. *See* 56 Fed. Reg. 3341 ("FDA interprets the act to accord [orphan] exclusive approval only to the first drug approved.").

We note that the clinical superiority requirements are different at the designation and approval stages, respectively. At the designation stage, the sponsor needs to provide a *plausible hypothesis* of clinical superiority, as described above. At the approval stage,[25] however, the sponsor must *demonstrate* clinical superiority over the previously approved

[24] These exceptions involve the sponsor's inability to assure availability of sufficient quantities of the approved drug and the sponsor's written consent for other applications to be approved during the exclusivity period. Section 527(b).

[25] In this context, the terms "at the approval stage" or "upon approval" do not preclude the possibility of demonstrating clinical superiority in a supplemental submission for the drug, after approval.

drug in order to obtain orphan exclusivity and to be approved despite any existing orphan exclusivity for the previously approved drug. *See* 21 CFR 316.3(b)(3) ("Clinically superior means that a drug *is shown to provide* a significant therapeutic advantage . . . .") (emphasis added); 56 Fed. Reg. 3343 ("the burden of proof (including the burden of production of evidence and the burden of persuasion of FDA) [is] on the sponsor of the subsequent drug who is contending that its drug is different"). This difference in clinical superiority requirements is intended to encourage the development of improved versions of existing drugs while still protecting the value of any orphan exclusivity. The former is achieved through liberally granting designation based on a plausible hypothesis of clinical superiority, allowing drugs to benefit from development incentives that flow from designation, including tax credits and exemption from application user fees. The latter is achieved through reserving exclusivity for a subsequent drug only if the subsequent drug is shown to provide a significant therapeutic advantage compared to the existing product. *See* 56 Fed. Reg. 3338, 3340.

Under this clinical superiority framework, FDA applies the same standard for granting orphan exclusivity whenever the same drug is already approved, whether or not the previously approved drug has orphan exclusivity. In this way, the framework furthers the aim of the Orphan Drug Act, to promote development and innovation of orphan drugs that have not already been developed and approved. *See* H.R. Rep. 97-840, Pt. 1, at 6 (1982); 56 Fed. Reg. 3338; *Genentech*, 676 F. Supp. at 305-06, 312. If a sponsor is able to demonstrate clinical superiority over a drug that is previously approved with or without exclusivity, that sponsor would receive its own orphan exclusivity and would not be blocked by any orphan exclusivity attaching to the previously approved drug. Conversely, even if the previously approved drug does not have exclusivity, the sponsor of the drug seeking exclusivity will not obtain exclusivity if it cannot demonstrate clinical superiority over the previously approved drug. Thus, the exclusivity status of the previously approved drug – whether it has, had, or never had exclusivity – does not affect the clinical superiority requirements. *See* 76 Fed. Reg. 64868, 64870 (Oct. 19, 2011) ("If the same drug has already been approved for the orphan disease or condition, *with or without orphan exclusivity*, designation [absent a plausible hypothesis of clinical superiority] would be inappropriate because it would be inconsistent with the primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions that would not otherwise be developed and approved.") (emphasis added).[26]

[26] This preamble explains, "In the absence of a clinical superiority hypothesis, the Agency does not interpret the orphan-drug regulations to permit orphan designation of a drug that is otherwise the same as a drug that is already approved for the orphan use, either where the approved drug received orphan-drug exclusive approval (even after such drug's exclusivity period has run out) *or where the approved drug was not previously designated as an orphan drug and thus did not receive orphan exclusive approval.*") 76 Fed. Reg. 64870 (emphasis added).

IV. Exclusivity Is Available Only If The Same Drug Has Not Been Previously Approved For The Orphan Indication

A. The Statute Does Not Automatically Accord Orphan Exclusivity To All Designated Drugs Upon Approval

You contend that Gralise is "automatically" entitled to orphan exclusivity under section 527 because it is a drug that received designation and was then approved for marketing, even though Neurontin was the same drug as Gralise and had already been approved for the same orphan indication. *See* September 2011 letter, pp. 13-15. But the statute cannot be logically read to confer exclusivity to every designated drug that gets approved, as your argument would require.

The statute generally confers exclusivity by prohibiting FDA from approving later drugs after a previous drug has been designated and approved. "[I]f the Secretary [] approves an application . . . .for a drug designated under section 526 . . . the Secretary may not approve another application . . . for *such drug* . . . until the expiration of seven years from the date of the approval of the approved application." Section 527(a) (emphasis added). Courts construing this statute have held "such drug" to be ambiguous, and have upheld FDA's regulatory scheme to require a showing of clinical superiority over a previously approved drug in order for the clinically superior drug to not be blocked by another sponsor's exclusivity and to obtain its own period of exclusivity. *See Baker*, 132 F. Supp. at 37.

Section 527(a) is also ambiguous on the question whether a drug may be eligible for exclusivity when *another* drug that is the same has already been approved. *See* section 527(a) (referring to an approved drug and unapproved applications for such drug, but not to any drugs approved previously to the approved drug). Under FDA's interpretation, any such previously approved drug matters and precludes exclusivity absent a showing of clinical superiority because sponsors could otherwise (1) obtain infinite, successive seven-year periods of exclusivity for the same drug for the same use (when the previously approved drug had exclusivity), or (2) obtain an exclusivity period for a drug without providing any benefit to patients over previously approved therapies (when the previously approved drug did not have exclusivity).

You raise the precise issue of whether a drug may be eligible for exclusivity when another same drug has already been approved and did not have exclusivity. Because the statute does not address that issue, FDA may interpret it, and FDA concludes that a designated drug will receive orphan exclusivity upon approval *only if the same drug has not been previously approved for the same orphan use*. *See* 56 Fed. Reg. 3338, 3341 (Jan. 29, 1991) ("FDA interprets the act to accord [orphan] exclusive approval only to the first drug approved."). This construction implements the exclusivity period as written, is consistent with FDA's regulatory framework, and best effectuates Congress' aim in enacting the Orphan Drug Act, to encourage the development and innovation of

drugs that would not otherwise be developed and approved – not to encourage minor modifications to already approved drugs that confer no meaningful benefit to patients.

You concede that if an orphan-designated drug is the same drug, for the same use, as a drug that is already approved and currently enjoying orphan exclusivity, FDA cannot approve the subsequent drug for the remainder of the exclusivity period (except in limited circumstances).[27] *See* September 2011 letter, pp. 8-10. But, you argue, the statute requires that in all circumstances where FDA is in a position to approve an orphan-designated drug, it must simultaneously grant orphan exclusivity. *See id.*

FDA recognizes that the statute could be read to require a grant of exclusivity to *every drug* that is both designated and approved. But ignoring the significance of any same previously approved drug would turn the statute on its head by allowing a windfall of exclusivity to sponsors whose drugs are the same as previously approved drugs and provide no meaningful benefit to patients.[28] Under your argument, the second drug would be entitled to exclusivity even when the previously approved drug had orphan exclusivity and this exclusivity has run, and the second drug was not clinically superior to the previously approved drug. The same drug would thus receive serial awards of orphan exclusivity for the same use ("evergreening"): a second-in-time drug would be approved with its own orphan exclusivity upon expiration of the first-in-time drug's orphan exclusivity, even when it is the same drug as this first-in-time drug and has been approved for the same use. Under this construction, there could be a situation in which there would be only one drug on the market for seven years, only two drugs on the market for 14 years, only three drugs on the market for 21 years, etc.[29]

Such "evergreening" would allow orphan exclusivity to be extended indefinitely for the same drug without any meaningful benefit to patients, a result at odds with the seven-year period provided by the statute. *See Baker*, 132 F. Supp. at 37 (noting with approval that, under FDA's interpretation, "market exclusivity rights are limited in time to seven years, and granted only for a particular drug for a particular use"). Congress would not have prescribed a definite period of exclusivity and at the same time provided for means to indefinitely extend that period, delaying generic competition in perpetuity. Indeed, the legislative history reflects this by stating that even if multiple sponsors get designation for the same drug, "only the first sponsor to be approved is awarded the seven year market exclusivity for that drug for the approved use." H.R. Rep. 100-473, at 6 (1987).

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[27] *See supra* note 24.

[28] A third possible interpretation of section 527 would grant exclusivity to a designated drug upon approval only if it is *the first designated drug* to be approved for that use (*i.e.*, either the first time such a drug is approved or, if not the first time, if the sponsor(s) of the previously approved drug(s) chose not to seek orphan designation or exclusivity). This interpretation would similarly be at odds with the purpose of the statute by granting the benefit of exclusivity to companies like Depomed that do not develop drugs for new orphan indications but simply wait until someone else does and then develop commercially viable but not clinically superior alternative formulations of those same drugs.

[29] It is uncertain how FDA would implement Depomed's interpretation of the statute if multiple designated drugs were potentially eligible for approval upon expiration of the first-in-time drug's exclusivity.

Even when, as here, the first approved drug did not have orphan designation or exclusivity, awarding orphan exclusivity to a second-in-time drug that has not been shown to be clinically superior to the first approved drug would be incompatible with the core objective of the Orphan Drug Act, to encourage development of drugs that would not otherwise be developed and approved. *See* Section III, *supra*. To award Gralise orphan exclusivity in this instance, despite there being at least 20 versions of the same drug approved at the time of Gralise's approval, would not serve this statutory purpose.

Your interpretation of the statute is also inconsistent with the decisions of courts that have had occasion to address orphan exclusivity. Courts have interpreted section 527 as awarding exclusivity to only the first orphan drug approved for the orphan use. *See Genentech*, 676 F. Supp. at 304 (orphan exclusivity "is reserved for the first manufacturer to receive full FDA approval of its drug as safe and effective for commercial sale," even if multiple drugs have orphan designation); *cf. Baker*, 132 F. Supp. 2d at 31 (if two drugs are the same under FDA regulations, "the second drug may not be approved for market exclusivity"). Although courts have not addressed this precise issue at hand – where the sponsor of the first-in-time drug chose not to pursue orphan designation and orphan exclusivity despite being eligible – the statutory interpretation upon which you rely is inconsistent with the understanding of Congress, the courts, and FDA: namely, that orphan exclusivity is not awarded to all designated drugs upon approval, but is reserved for only those drugs that are not the same as previously approved drugs.

Under your theory of exclusivity, Depomed would obtain a seven-year exclusivity period vis-à-vis all drugs that are the "same" as Gralise, including all generic Gralise and generic Neurontin products. *See* 21 CFR 316.3(b)(12),(13). Gralise would obtain such broad exclusivity even though it has not demonstrated that that it provides any clinical benefit over Neurontin.[30] This result could lead to withdrawal of approval of at least nine generic versions of Neurontin that have been approved since Gralise was approved (January 28, 2011).[31] It would also prevent any additional approvals of generic versions of Neurontin until January 28, 2018 (*i.e.*, because Neurontin would be considered the same drug as Gralise), even though there were over 20 generic versions of Neurontin already approved by the time that Gralise was approved.

Your argument that FDA regulations at 21 CFR 316.3(b)(12), 316.31(a), and 316.34(a) apparently mirror the statute in recognizing automatic orphan exclusivity upon

[30] We note that, in order to obtain approval, the Gralise sponsor (Depomed's predecessor) relied on the Agency's previous finding of safety and efficacy for Neurontin and, because of that reliance, was required to produce only one clinical study showing the effectiveness of its product. Ultimately Depomed submitted the results of three studies, but only one (a randomized, double-blind, placebo-controlled study in 452 PHN patients treated with either Gralise or placebo) was found to show effectiveness. This study showed that Gralise is more effective than placebo; it did not compare Gralise to any already approved versions of gabapentin, including Neurontin.

[31] Depomed does not appear to be seeking the benefit of this breadth of exclusivity (*see* Complaint ¶ 11, referring only to pending ANDAs that "would compete directly with Gralise") and could selectively waive any such exclusivity if it were to prevail on this theory.

approval of any designated drug is equally misplaced.[32] *See* Complaint ¶¶ 28-31. You are interpreting these regulatory provisions in isolation from the remainder of the orphan drug regulations, and your interpretation could dismantle the clinical superiority framework. The provisions you cite, when read in context, provide that if designation is predicated on a clinical superiority hypothesis, clinical superiority would need to be demonstrated upon approval for the drug to receive exclusivity. *See also* 21 CFR 316.3(b)(3) & (13); 316.20. Under your proposed interpretation, the requirement for a plausible hypothesis of clinical superiority in 21 CFR 316.20 would make no sense – if clinical superiority must be hypothesized, then by definition it must be proven. Recognizing exclusivity on the basis of clinical superiority that is not proven, or even proven wrong, would be illogical. Moreover, to read the regulations as automatically awarding such exclusivity would lead to results counter to the Orphan Drug Act, described above, including "evergreening" of exclusivity and allowing a windfall of exclusivity to sponsors whose drugs are the same as previously approved drugs and provide no meaningful benefit to patients.

For all of the foregoing reasons, Gralise is not automatically entitled to exclusivity simply because it is a designated drug that is approved for marketing.

B. Under FDA Regulations, The Gralise Designation Request Required A Plausible Hypothesis Of Clinical Superiority Over Neurontin[33]

You argue that section 526(a) requires FDA to designate a product as an orphan drug if the sponsor timely submits a request for designation and demonstrates that the drug (1) "is being or will be investigated for a rare disease or condition" and (2) if approved, would be approved for that disease or condition. If your argument were adopted, any drug that met these statutory criteria would automatically receive orphan designation, regardless of whether the regulatory requirements for designation are met (*e.g.*, regardless of whether the request includes a plausible hypothesis of clinical superiority where the drug is otherwise the same as an already approved drug). Your argument thus disregards the regulatory requirements for designation.

The FD&C Act expressly provides FDA with the authority to promulgate regulations in this very context. Section 526(d) provides that FDA "shall by regulation promulgate procedures for the implementation of subsection (a)."[34] Relying on this expressly delegated rulemaking authority, FDA issued regulations in 1992. 57 Fed. Reg. 62076 (codified at 21 CFR part 316). These regulations define "same drug" and require

[32] It is true that, when a drug is eligible for orphan exclusivity pursuant to FDA's regulatory scheme, it automatically receives such exclusivity upon approval with or without written notice from FDA. 21 CFR 316.31(a), 316.34(a). Here, the issue is whether Gralise is even eligible for exclusivity in the first place.

[33] We note that the Gralise sponsor already received designation and FDA is not proposing to revoke designation, whether or not Gralise receives orphan exclusivity. The question whether the Gralise designation request required a plausible hypothesis of clinical superiority is therefore moot. It has no bearing on whether Gralise is automatically entitled to orphan exclusivity upon approval. We are nonetheless including this discussion for the sake of completeness, to respond to your arguments in the September 2011 letter and related submissions.

that designation requests for drugs that are otherwise the same as already approved drugs include a plausible hypothesis of clinical superiority, as described above. These regulations defining "same drug" have been upheld as a permissible construction of the statute. *Baker*, 132 F. Supp. 2d at 36. Because FDA acted within its expressly delegated authority in issuing these regulations, the regulations are entitled to deference. *See Arent v. Shalala*, 70 F. 3d 610, 615 (D.C. Cir. 1995). We thus find unpersuasive your argument that Gralise was by statute entitled to designation regardless of whether the regulatory requirements for designation were met.

You further maintain that FDA did not have authority under its orphan drug regulations to require that the Gralise designation request include a plausible hypothesis of clinical superiority over Neurontin. September 2011 letter, p. 11. By your reasoning, FDA could not deny Gralise's designation based solely on a failure to include such a hypothesis, because that failure – when the previously approved drug did not have orphan-exclusive approval, as is the case here – is not expressly listed at 21 CFR 316.25 ("Refusal to grant orphan-drug designation"). You maintain that section 316.25 circumscribes FDA's ability not to grant designation to the reasons expressly listed.

FDA disagrees. Nothing in section 316.25 supports the conclusion that the list of reasons for refusing to grant an orphan designation request contained in this section is exclusive. Instead, that regulation states that FDA will refuse to grant a designation request if certain stated reasons apply; it does not state all potential reasons for declining designation. In particular, 21 CFR 316.25 does not reiterate all of the eligibility criteria for designation that are listed elsewhere in the statute and in part 316. These eligibility criteria include that the designation request be submitted before submission of the marketing application, as is required by section 526(a) and 21 CFR 316.23(a), and that the product be a drug, as is required by section 526(a) and 21 CFR 316.20. The statute and regulations thus identify eligibility criteria for designation that are not explicitly reiterated as grounds for refusing designation at section 316.25. Under FDA's long-standing interpretation, a designation request that failed to meet any of these eligibility requirements would be denied on this ground alone without resort to section 316.25. This interpretation is bolstered by section 316.29(a)(3), which allows for revocation of designation if the drug was not in fact eligible for designation at the time of the submission of the request. Thus, particularly when read in context, section 316.25 does not purport to contain an exhaustive list of deficiencies that would require FDA to deny an orphan-drug designation request.

FDA has consistently interpreted 21 CFR 316.20(a) and (b)(5), in particular, as requiring that a designation request include a plausible hypothesis of clinical superiority whenever the same drug is already approved for the same use, regardless of whether this same drug has, had, or never had orphan exclusivity: *i.e.*, where the drug is "otherwise the same drug as an already approved orphan drug." "Orphan drug" is defined at section 316.3(b)(10) as a drug for a rare disease or condition; *it does not include any requirement*

[34] Courts have assumed that the authority to promulgate "procedures" includes the authority to substantively define terms such as "drug." *See Genentech*, 676 F. Supp. at 312.

that the drug receive orphan designation or orphan exclusivity.[35] The text of section 316.20(a) specifies that "a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may *seek and obtain* orphan-drug designation for the subsequent 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" (emphasis added). It follows from this "seek and obtain" language that, absent such a hypothesis, designation can be neither sought nor obtained. Indeed, the Common EMEA/FDA Application Form for Orphan Medicinal Product Designation (Form FDA 3671) states as much. It provides that sponsors may request designation from FDA for "a *potentially clinically superior* medicinal product containing the same active substance as one in an *already authori[s]ed medicinal product* for the same orphan use" (emphasis added), indicating that clinical superiority must be hypothesized whenever the same drug is approved with or without exclusivity.[36] It is FDA's long-held position that a request that fails to meet this threshold eligibility requirement will be denied on this ground alone and will not fall within the ambit of sections 316.24 ("Granting orphan-drug designation") and 316.25 ("Refusal to grant orphan-drug designation"). This has been FDA's consistent position since the regulations took effect on January 28, 1993.[37] FDA's interpretation of its own regulations in this manner is entitled to great deference. *Sigma-Tau Pharms. v. Schwetz*, 288 F. 3d 141, 146 (4th Cir. 2002); *see Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *Udall v. Tallman*, 380 U.S. 1, 16 (1965); *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 413-414 (1945).

In your contrary interpretation of the regulations, Depomed points to section 316.25(a)(3), which addresses a situation in which the sponsor of a previously approved drug sought and obtained orphan-drug designation and exclusivity. The Agency did not, in drafting that provision, focus on the rare instances where the sponsor of the previously approved orphan drug did not seek orphan-drug designation or exclusivity. This situation has presented itself on only a few occasions, though FDA has reviewed thousands of requests for designation under the statute. There is nothing to suggest that FDA, in drafting the regulations, intended the requirement for a plausible hypothesis of clinical superiority not to apply in the latter circumstance – especially in light of the threshold eligibility requirements in section 316.20. (As noted and described further below, when this situation has presented itself in designation requests, FDA has acted consistently with the position it is taking here.)

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[35] It is worth noting that this definition of "orphan drug" is consistent with how Congress used the term "orphan drug" in enacting the Orphan Drug Act, to refer to drugs intended for use by such a small population that they have little to no commercial value and hence generally lack sponsors (*i.e.*, are "orphans"). H.R. Rep. 97-840, Pt. 1, at 6 (1982).

[36] The version of this form approved in 2011 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048361.pdf. The earlier version of this form, approved in 2008 (see 73 Fed. Reg. 2504), contained the same cited excerpt.

[37] To FDA's knowledge, this interpretation of the regulations has been consistent since at least the effective date of the final rule, January 28, 1993. *See* Section IV.C, *infra*. The Kogenate example cited by Depomed in its complaint (see Section IV.C of this response) is not relevant to this point because, at the time that the Kogenate sponsor submitted a request for designation, the same drug had not yet been approved for marketing for the orphan indication in question. The designation request for Kogenate thus did not require a plausible hypothesis of clinical superiority. Note also that this designation request was submitted in 1989, several years before the final rule issued.

Finally, we note that your arguments, by their own terms, fail to advance your claim. If we were to adopt your proposed interpretation of the regulations – in particular, your interpretation of the term "orphan drug" as meaning only drugs with orphan exclusivity (September 2011 letter, p. 12) – then the sponsor of Gralise would not have been eligible even to *request* orphan designation under section 316.20(a), with or without a clinical superiority hypothesis. The text of section 316.20(a) reads:

> A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent 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.

Were we to interpret "orphan drug" as narrowly as you urge, then the sponsor for Gralise would not have fit into any of the above-specified categories: (1) Gralise was not a "previously unapproved drug" because the same drug has already been approved numerous times; (2) management of PHN was not a "new orphan indication for an already marketed drug," as the already-marketed drugs were approved for management of PHN; and (3) if we were to accept your interpretation that the term "approved orphan drug" means only "approved orphan drug with orphan-drug exclusivity," Gralise was not otherwise the same as an already approved orphan drug, because the already approved drug never had orphan exclusivity. Your proposed interpretation thus excludes Gralise from the categories of drugs that are eligible to *submit* a designation request, let alone obtain designation. It is only by virtue of the broad definition of "orphan drug" under section 316.3(b)(10) that the Gralise sponsor was even eligible to seek designation under section 316.20(a). You are thus in the untenable position of arguing that "orphan drug" is both broad and narrow in section 316.20: broad for the purpose of determining which sponsors can submit designation requests, but narrow for the purpose of determining which designation requests require a plausible hypothesis of clinical superiority.

FDA acknowledges that the situation presented here, in which a company does not develop a new drug for a new orphan indication but nevertheless seeks to obtain orphan-drug exclusivity for its version of the already approved drug because the original developer of the drug had not done so, does not arise often. These circumstances have arisen on only a handful of occasions in nearly 30 years and were not publicized owing to confidentiality constraints. This does not, however, erode the deference owed FDA on its interpretation of its regulations or otherwise preclude FDA from maintaining a position that comports with the statute, FDA regulations, and long-standing Agency practice.

C. Allegations In Recent Lawsuit

In its complaint filed in D.C. District Court on September 25, 2012, Depomed seeks declaratory, injunctive, and other relief for FDA's failure to recognize orphan exclusivity for Gralise on the date of Gralise's approval, January 28, 2011. To the extent

the allegations in the complaint reiterate the legal arguments in the September 2011 letter, they are addressed above. Depomed also made new allegations not previously raised before the Agency. *See* Complaint ¶¶ 51-58. These allegations concern FDA's approval of Kogenate on February 25, 1993 and FDA's recognition of orphan exclusivity for Kogenate even though Kogenate was the same drug as a previously approved drug, Recombinate, that did not have orphan designation or exclusivity. FDA did not require a demonstration of clinical superiority in order for Kogenate to be awarded orphan-exclusive approval.

As described below, the 1993 grant of exclusivity for Kogenate was an outlier and erroneous decision reflecting an unusual agreement between the sponsors. Moreover, the Kogenate circumstances are not directly analogous to the circumstances here because the same drug had not been approved at the time of the Kogenate designation request. FDA is aware of at least five counter examples in which FDA *did require a plausible hypothesis of clinical superiority* in order for a drug to receive orphan designation when the drug was the same as one already approved that lacked orphan designation and exclusivity. These examples occurred in 1994, 2001, 2004, 2007, and 2012.[38] The sponsors in these examples ultimately failed to receive designation, but the examples are directly analogous to Gralise because FDA required the sponsors to offer a plausible hypothesis of clinical superiority in exactly the same circumstances that FDA did for Gralise.

Further, if any of these sponsors had ultimately received designation, FDA would not have granted orphan exclusivity unless they had also demonstrated clinical superiority upon approval, just as FDA has required for Gralise. FDA has identified at least nine instances in which drugs that have received orphan designation (based either on a presentation of a plausible hypothesis of clinical superiority or on the fact that the same drug had not yet been approved at the time of the designation request) were denied exclusivity when they have failed to demonstrate upon approval that they were in fact clinically superior to the previously approved drug. Contrary to Depomed's assertion, FDA is treating like products the same in requiring a clinical superiority hypothesis and then demonstration of superiority for Gralise to be eligible for orphan designation and exclusivity. Were FDA to depart from this practice, and not require clinical superiority for Gralise, it would be treating Depomed differently from how it has treated a significant number of similarly-situated sponsors.

The Kogenate example has several distinguishing features. Kogenate and Recombinate are both recombinant antihemophilic factors used to prevent and treat bleeding episodes in patients with hemophilia A; they are considered the same drug under orphan drug regulations. The Kogenate sponsor, Miles (later Bayer), sought and received orphan designation in 1989 before any such recombinant drug had been approved for the orphan indication in question (unlike the scenario here, where the Gralise sponsor sought designation more than four years after Neurontin had already been approved for the orphan indication at issue).[39] The Recombinate sponsor, Baxter, chose not to seek orphan

[38] FDA cannot disclose the details of these prior examples because of confidentiality constraints.
[39] *See supra* note 37.

designation for its drug. Both the Kogenate sponsor and the Recombinate sponsor submitted marketing applications and were uncertain about which product would be approved first. Presumably because of this uncertainty, the two sponsors reached a contractual agreement in which they agreed to share orphan exclusivity.[40] FDA supported this agreement at the time, in mid-1992 (prior to publishing the final rule,[41] which took effect in early 1993) because this agreement to share Bayer's exclusivity encouraged the development and availability of two recombinant products instead of just one. Having two such products available was a particular priority because of concerns about potential viral transmission (*e.g.*, HIV viral transmission) associated with the existing plasma-derived products – concerns not associated with the two recombinant products under review. Further, FDA was anticipating the possibility of a shortage of recombinant products, which could be mitigated by having two recombinant products on the market instead of one (indeed, product shortage was the focus of the 1998 advisory committee meeting cited by Depomed).

To FDA's knowledge, the Kogenate example is an outlier that was influenced by the exigencies of the time and peculiar circumstances. Depomed tries to suggest otherwise – that this decision reflected a fundamentally different understanding of the Orphan Drug Act – by citing an excerpt from the 1998 advisory committee meeting on product shortage, in which a question arose about why Kogenate received orphan-exclusive approval despite being approved after Recombinate and not having demonstrated clinical superiority to Recombinate. *See* Complaint ¶ 57. Depomed cites this transcript excerpt out of context. Almost immediately following Depomed's selected excerpt, the same FDA presenter clarified that "The Baxter product, and [the] Bayer [product], are [both] on the market because of an agreement between the two companies. I believe that is public knowledge." Transcript of December 11, 1998, meeting of FDA Blood Products Advisory Committee, p. 108.[42] At any rate, the statement that Depomed cites – the statement of one FDA official allegedly purporting to interpret the Orphan Drug Act in an advisory committee meeting addressing shortage of blood products – was informal communication that does not bind or otherwise obligate or commit the Agency to the views expressed. 21 CFR 10.85(k).

In short, FDA is treating Depomed in the same fashion that it has treated a number of similarly-situated sponsors in the last decade. Our decision is thus consistent with *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997).

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[40] FDA had previously rejected the idea of "shared" exclusivity under the statute "except where agreed to by the sponsor of the drug with the right to exclusive marketing." 56 Fed. Reg. 3338.

[41] See Orphan Drug Regulations (final rule), 57 Fed. Reg. 62076 (Dec. 29, 1992).

[42] In FDA's version of the public transcript, the excerpt that Depomed cites is on the page immediately prior to this one, page 107. (Depomed appears to be citing a differently paginated version of the transcript when it cites page 101, not page 107.)

V. Scientific Analysis: Gralise Is Not Eligible For Orphan Exclusivity Predicated On A Clinical Superiority Demonstration

Under Depomed's alternative exclusivity theory premised on clinical superiority, Depomed seeks a seven-year exclusivity period of a more limited scope vis-à-vis generic Gralise products (rather than all generic versions of both Neurontin and Gralise). A demonstration of clinical superiority for orphan exclusivity would require that Gralise be "shown to provide a significant therapeutic advantage over and above that provided by" Neurontin, whether in terms of greater effectiveness, greater safety, or a major contribution to patient care. 21 CFR 316.3(b)(3).

Following approval, Depomed contacted OOPD to inquire about exclusivity on the ground of clinical superiority. OOPD consulted with the Center for Drug Evaluation and Research (CDER), Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), as to whether the application for Gralise demonstrated clinical superiority over Neurontin in terms of greater safety. On February 9, 2011, OOPD notified the sponsor by phone that FDA had determined that the Gralise NDA had not included sufficient data and information to demonstrate that Gralise was clinically superior to Neurontin in terms of greater safety. The sponsor continued to make a case for the clinical superiority of Gralise through submissions to the Agency dated from early May 2011 through late September 2012. *See, e.g.*, September 2011 letter, pp. 15-28; April 2012 meeting; May 2012 submissions; July 2012 submission; August 2012 submission; September 25, 2012 submission.[43] FDA has evaluated the data and information submitted in support of the assertion that Gralise is clinically superior to Neurontin in terms of greater safety or, alternatively, by making a major contribution to patient care. For the reasons described below, FDA has determined that Gralise has not been shown to be clinically superior to Neurontin. Accordingly, Gralise is not eligible for orphan exclusivity predicated on clinical superiority.

A. Gralise Has Not Been Shown To Provide "Greater Safety In A Substantial Portion Of The Target Populations"

Clinical superiority in terms of greater safety, for the purpose of orphan exclusivity, is defined as "[g]reater safety in a substantial portion of the target populations." 21 CFR 316.3(b)(3)(ii). The sponsor argued that Gralise is associated with reduced incidence of adverse events (AEs) compared to Neurontin, in particular lower incidence of the three most common AEs for Neurontin – dizziness, somnolence, and peripheral edema – as evidenced by the AEs reported during the separate clinical trials supporting approval of Gralise and Neurontin, respectively. These studies each compared one drug, Neurontin or Gralise, to a placebo; no head-to-head trials were performed directly comparing Gralise to Neurontin. Although the sponsor concedes that "a direct comparison cannot be made" between the separate clinical trials for each drug, the sponsor maintains that the separate studies were "of similar size and nearly identical design." September 2011 letter, p. 15 (quoting an earlier Abbott submission for

[43] *See supra* note 1.

Gralise[44]). Among the cross-study similarities you note in your September 2011 letter are similar patient populations, including age and sex, and similar duration of drug exposure despite higher maximum dosage in the Neurontin studies (1800 to 3600 mg/day versus 1800 mg/day in the Gralise studies). *Id.*, pp. 18-21. You state that: "Given these similarities in the Gralise and Neurontin studies, comparison of the incidence of adverse events in the studies is a valid method for demonstrating clinical superiority of Gralise over Neurontin with regard to safety." *Id.*, p. 22. Using various methodologies described in the September 2011 letter (pp. 22-27), the sponsor compared the AEs across the different studies and estimated various degrees of difference between the Neurontin and Gralise AEs. One comparison methodology, which controlled for dosage of gabapentin at 1800 mg/day, yielded the following differences for the three most common AEs associated with Neurontin: 28.7% of patients experienced dizziness on Neurontin versus 10.9% on Gralise; 17.4% of patients experienced somnolence on Neurontin versus 4.5% on Gralise; and 7.0% experienced diarrhea on Neurontin versus 3.3% on Gralise. *Id.*, p. 27.

FDA disagrees with your methodology for comparing the AEs in this instance. Cross-study comparisons are generally of only limited utility for a variety of reasons, including: differences in clinical practice and clinical conditions in which the studies are conducted (*e.g.*, if the studies are several years or more apart, as occurred here); differences in how AEs are reported and documented (*e.g.*, self-reported or solicited, at what intervals, whether classification by severity was left to the investigator's discretion or delineated in the protocol); differences in methodologies for compiling and analyzing AEs; and the possibility that there will be differences in the incidence of AEs based on chance alone, regardless of study design. In addition to these general infirmities, in this instance the AE profiles for Neurontin and Gralise are quite similar in terms of specific types and seriousness of AEs, differing only in proportions of study subjects experiencing the AEs. Further infirmity in this cross-study comparison stems from the fact that the AEs were for the most part patient-reported outcomes, such as dizziness, nausea, and somnolence, rather than objective outcomes that can be measured by an observer. For all of these reasons, Depomed's cross-study comparison does not provide persuasive evidence to show that Gralise is clinically superior to Neurontin regarding safety.

FDA acknowledges that the pharmacokinetic (PK) profiles of the two products are different, as illustrated in the graph included in your July 2012 submission (p. 5). Depomed attributes the purported reduction in AEs to this difference – to the fact that Gralise's once-daily evening dosing achieves a single, extended peak of the drug throughout the late evening and early morning hours, whereas Neurontin's three-times daily dosing achieves multiple peaks of the drug during the day. July 2012 submission, p. 5. As described above, FDA does not agree that the AEs for Gralise have been shown to be meaningfully lower than the AEs for Neurontin. In addition, although the PK profiles for the two products are different, it is unclear whether and how these PK profiles influence safety. The pharmacokinetic/pharmacodynamic (PK/PD) relationship for the AEs for gabapentin has not been defined. Although it is theoretically possible that the different PK profile for Gralise results in greater safety compared to Neurontin, this

[44] *See supra* note 10.

theory assumes that the AEs resulting from gabapentin administration are related to the peak plasma concentrations of gabapentin, which has not been demonstrated.

For the reasons described above, FDA has determined that the cross-study comparison does not demonstrate that Gralise provides a significant therapeutic advantage over Neurontin in terms of safety. FDA acknowledges that the orphan drug regulations state that direct comparative trials would be required in only "some cases" to support greater safety showings, as compared to in "most cases" for greater effectiveness showings. *Compare id. with* 21 CFR 316.3(b)(3)(i). FDA has nonetheless determined that, in the absence of more convincing data than Depomed has been able to produce to date, this greater safety showing for Gralise would require head-to-head trials given the overall similarity in type and seriousness of AEs, their patient-reported nature, and the undefined PK/PD relationship for AEs for these drug products.

In the past, FDA has accepted diminution in AEs as manifested in cross-study comparisons as evidence of clinical superiority in terms of greater safety for other (non-analgesic) drug products. Two examples of such regulatory decisions, which you cite in your September 2011 letter (p. 17), involved Avonex versus Betaseron (interferon beta-1a) and AmBisome versus Abelcet (amphotericin B). In both prior cases, the AEs were objective endpoints that could be measured by an observer – skin necrosis and injection site reactions for Avonex, and infusion-related reactions for AmBisome – unlike the largely patient-reported outcomes for Gralise and Neurontin. Additional distinguishing features were the seriousness of the AEs for Avonex and Ambisome, as well as the degree of difference in reported AEs between these two drugs and their respective comparators. *See Berlex Labs. v. FDA*, 942 F. Supp. 19, 23-24 (D.D.C. 1996) ("The substantial disparity between Avonex and Betaseron with regard to injection site necrosis was surely a factor relevant to safety, and Berlex [manufacturer of Betaseron] does not challenge the sufficiency of the record evidence on that point. FDA had an adequate basis upon which to consider Avonex 'clinically superior' to Betaseron.").

Other Agency decisions that you cite as "regulatory precedent" are likewise inapposite. FDA has previously found products to be clinically superior in terms of safety, for the purpose of orphan exclusivity, without requiring evidence from direct comparative trials when the drug products at issue eliminated an ingredient or contaminant known to be associated with a relatively frequent adverse event or when the manufacturing process yielded a superior safety margin. Two examples of such regulatory decisions, which you cite in your September 2011 letter (p. 17), were: comparing Mononine versus AlphaNine (coagulation factor IX (human)), based on a difference in the manufacturing process relevant to the risk of Hepatitis C transmission; and comparing BeneFix (coagulation factor IX (recombinant)) versus Mononine and Alphanine (coagulation factor IX (human)), based on the former being recombinant rather than human-derived and hence inherently safer regarding person-to-person transmission of infectious agents.[45] In these examples, an inherent difference between

[45] Plasma-derived products carry a risk of viral transmission due to inclusion of human components. Recombinant products are formulated without the use of any human components, so there is believed to be no risk of passing any pathogen found in human blood.

the products conveyed a significant therapeutic advantage in terms of safety. By contrast, the inherent difference between Gralise and Neurontin – the differing PK profile as a result of Gralise's once-a-day formulation versus Neurontin's three daily doses – has not been shown to convey any such therapeutic advantage. As described above, the PK/PD relationship for the AEs for gabapentin has not been defined; Depomed has not demonstrated that Gralise's PK profile, as compared to Neurontin's, leads to greater safety in a substantial portion of the target population.

B. Gralise Has Not Been Shown To Provide A "Major Contribution to Patient Care"

FDA regulations provide that, "[i]n unusual cases, where neither greater safety nor greater effectiveness has been shown," a drug may be considered "clinically superior" for the purpose of orphan exclusivity through "a demonstration that the drug otherwise makes a major contribution to patient care." 21 CFR 316.3(b)(3)(iii). Major contribution to patient care is intended to capture only significant improvements, not minor conveniences or otherwise insignificant changes. *See* CFR 316.3(b)(3) (defining "clinically superior" as having "shown to provide a *significant therapeutic advantage* over and above that provided by" an already approved drug) (emphasis added). Since first proposing the orphan drug regulations in 1991, FDA has stated that major contribution to patient care represents a "narrow category . . . not intended to open the flood gates . . . for every drug for which a minor convenience over and above that attributed to an already approved drug can be demonstrated." 56 Fed. Reg. 3343. Indeed, the regulation itself makes clear that the category is restrictive, with the phrase "[i]n unusual cases." 21 CFR 316.3(b)(3)(iii). An example that FDA has proffered in the past of a "major contribution to patient care" is an oral dosage form for a drug that was previously available only in a parenteral dosage form. 56 Fed. Reg. 3343. FDA has further stated that any determination of major contribution to patient care is to be made on a case-by-case basis, taking into account the nature of the specific disease or condition, the nature of the specific drug, the nature of the mode of administration, and other factors. 57 Fed. Reg. 62079.

The sponsor presented its case for Gralise making a major contribution to patient care in its submissions to the Agency dated from early May through late September 2012. According to the sponsor, a "global assessment" of the following factors leads to a finding of major contribution to patient care:

1. Greater safety of Gralise, as demonstrated by "significant reductions in the most frequent and material adverse events" when compared to Neurontin;
2. "[A]n enhanced ability to titrate patients to the optimal effective dose" because of this purported reduction in AEs;
3. "[F]ewer patients switching to other therapies or adding therapies (often opioids)," again because of the purported reduction in AEs;
4. Greater convenience in once-a-day dosing, which "leads to better compliance"; and

5. "[E]nhanced relief of nighttime pain" owing to Gralise's evening dosing schedule and PK profile. July 2012 submission, pp. 2-3.

FDA has evaluated these reasons individually and cumulatively and has determined that Gralise has not been shown to provide a major contribution to patient care.

1. Greater Safety

The sponsor maintains that Gralise has fewer AEs than Neurontin, based on a comparison of the safety data in the product labels for each drug. In particular, the sponsor points to a reduction in somnolence and dizziness as leading to fewer falls among the geriatric population. *See* July 2012 submission, p. 7. As described in detail in Section V.A, above, FDA has determined that the sponsor's cross-study comparison of AEs does not demonstrate that the AEs for Gralise are meaningfully lower than the AEs for Neurontin. In particular, the sponsor has not demonstrated that Gralise carries a reduced incidence of dizziness and somnolence that results in a reduced risk of falls among the elderly patients who constitute the majority of PHN patients.[46]

2. Enhanced Ability To Titrate To Optimal Effective Dose

The sponsor also maintains that Gralise provides an enhanced ability to titrate patients to the optimal effective dose of at least 1800 mg/day because there are fewer AEs. As support, the sponsor offers the purported reduction in AEs coupled with claims data and internal script volume data.[47] According to these claims data, less than 15% of patients prescribed gabapentin TID were titrated to the optimal dose of at least 1800 mg/day.[48] Further, the mean maximum dose, which was defined as the highest observed daily dosage for at least 14 consecutive days, was only 970 mg.[49] In contrast, the sponsor points to internal script volume data from the first 8 months following the Gralise launch, which indicates that over 61% of the Gralise prescriptions were for at least 1800 mg/day, with an average daily dose of 1371 mg. July 2012 submission, p. 7.

FDA finds the reduction in AEs unconvincing, as already discussed. These claims data and internal script volume data are likewise unpersuasive. The data collected for gabapentin TID was for a significantly longer period of time than the data collected for Gralise (*i.e.*, greater than four years versus eight months). Based on the limited data collected for Gralise, it is unclear whether the Gralise population would be able to sustain this higher dosage for long periods of time. Even assuming the sponsor could show that

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[46] The sponsor cites articles from Hausdorff *et al.*, Hornbrook *et al.*, and Sterling *et al.* (references 6, 7 and 9 in July 2012 submission) to augment the claim that the elderly population is at an increased risk of falling and suffering injury from falls compared to the general population. Even assuming that the elderly population has this increased risk, the sponsor has not provided data to show that the use of Gralise, as compared to gabapentin TID, decreases the risk of falls and associated injuries in the elderly.

[47] These internal script volume data do not appear to be validated.

[48] The claims data were described in two poster presentations by Johnson *et al.*, one at the May 2012 American Pain Society Annual Meeting and one at the February 2012 Conference of the American Academy of Pain Medicine.

[49] With a reported standard deviation of 738 mg.

the average daily dose of Gralise remains higher than gabapentin TID over a prolonged period, this feature would not rise to the level of providing a "significant therapeutic advantage" over Neurontin, at least not without also showing that this higher dose results in fewer AEs or that it achieves greater pain control. 21 CFR 316.3(b)(3).

3. Fewer Patients Switching Or Adding Therapies

The sponsor contends that fewer patients who are treated with Gralise, as compared to Neurontin, either switch therapies or add therapies (*i.e.*, opioids). As support, the sponsor again relies on the claimed reduction in AEs for Gralise, and notes that dizziness and somnolence AEs were cited as the primary reasons for discontinuing both Neurontin and Gralise. The sponsor also relies on the claims data and internal script volume data described above. The claims data, according to the sponsor, indicate that 57.9% of patients prescribed gabapentin TID switched therapy, while 37% added a therapy (adding opioids more than half of the time) from June 2005 to February 2010.[50] The internal script volume data purportedly show that over 61% of the Gralise prescriptions were for at least 1800 mg/day (*i.e.*, at or above therapeutic levels) eight months after the launch of Gralise. The sponsor presents these internal data presumably to suggest that the Gralise patients did not add other therapies. *See* May 2102 submissions.

FDA does not agree that these data and information demonstrate that fewer patients on Gralise switch or add therapies. As noted, the cross-study comparison of AEs does not demonstrate that Gralise is associated with a reduced incidence of AEs as compared to Neurontin. The claims data do not address why patients discontinued the gabapentin TID or whether the discontinuation was due to AEs. The sponsor also did not provide any data on the number of patients who discontinued Gralise; without this data, it is impossible to compare these two groups for this factor. Lastly, as noted earlier, the claims data evaluating gabapentin TID spanned more than four years, whereas the internal script volume data for Gralise were generated for only eight months. This difference in time periods is likely to result in an increased statistical probability for there to be reports of switching and/or supplementing therapies with gabapentin TID.

4. Increased Convenience And Compliance

The sponsor states that the once-a-day dosing of Gralise provides greater convenience and leads to improved patient compliance when compared to Neurontin. The sponsor cites an article by Saini *et al.* (reference 14 in July 2012 submission) that indicates that, among patients with chronic diseases with long quiescent phases, there is a 22% to 41% increase in adherent days for once-a-day dosed patients as compared to the thrice-a-day dosed patients.

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[50] Data is from a poster presentation by Johnson *et al.* at the May 2012 American Pain Society Annual Meeting.

FDA finds this article unpersuasive. The dosing regimens reviewed in the article were for chronic diseases that, unlike PHN, were quiescent (*i.e.*, maintenance therapy). The sponsor did not provide any data that extrapolates the compliance rate for maintenance therapy to therapy for an active painful condition such as PHN. One could reasonably expect a person with an active painful condition to be more compliant with a medical regimen than a person with an asymptomatic chronic condition. This article therefore does not demonstrate that patients on Gralise, with its once-a-day dosing, will be more compliant than patients on gabapentin TID. To the extent that once-a-day dosing may be more convenient than thrice-daily dosing, FDA has never accepted "minor convenience" as evidence that a drug provides a major contribution to patient care. *See* 56 Fed. Reg. 3343 (describing "major contribution to patient care" as a "narrow category . . . not intended to open the flood gates . . . for every drug for which a minor convenience over and above that attributed to an already approved drug can be demonstrated").

5. Enhanced Nighttime Pain Relief

Lastly, the sponsor states that Gralise's nocturnal dosing enhances nighttime pain relief because of the drug's PK profile, which shows higher nocturnal plasma concentrations of Gralise than gabapentin TID. The sponsor references a study by Odrcich *et al.* that documents increased nocturnal pain in patients suffering from chronic neuropathic pain, including patients with PHN. *See* July 2012 submission, p. 5 and ref. 15. The sponsor also provides results of an Awareness, Trial and Usage (ATU) survey conducted among 275 physicians, in which 49% of physicians agreed that Gralise provides meaningful nocturnal pain relief as compared to 23% for gabapentin TID. *See* August 2012 submission.

FDA finds the sponsor's evidence unpersuasive. First, although the PK profiles for the two products are different, it is unclear whether and how these PK profiles influence pain relief; the sponsor has not provided any data to relate the higher nocturnal blood levels of gabapentin to improved pain control. Although it may appear that higher blood levels of gabapentin could produce improved pain control, no data were provided to identify relevant saturation levels for this treatment. Second, although the survey could have provided association between increased blood levels of Gralise and pain control had it represented patient response to Gralise or physician experience prescribing Gralise, the survey did neither. The survey does not reflect the physicians' actual experience with Gralise: only 2% of the 275 physicians surveyed had ever prescribed Gralise. The survey instead reflects physicians' perception of Gralise after reading the Gralise labeling and comparing it to the Neurontin labeling. Because the survey did not evaluate the product based on actual usage, it is inadequate to demonstrate that Gralise provides a "significant therapeutic advantage" over Neurontin. 21 CFR 316.3(b)(3). Another weakness in the study is that the physician sample is not a random sample but instead appears to be a sample of convenience.[51]

[51] Inferences drawn from a convenience sample (*i.e.*, a sample selected based on easy access/availability rather than chosen in such a way as to be representative of the target population) are rarely generalizable to the target population and may not be valid.

6. Cumulative Assessment

FDA has articulated why each of the factors identified by the sponsor individually fails to demonstrate that Gralise provides a major contribution to patient care. FDA has also assessed these factors cumulatively, as the sponsor requested. In this cumulative assessment, FDA has considered all factors that are sufficiently supported by data or information. As noted above, FDA has evidentiary concerns with each of the factors identified by the sponsor except for the minor convenience of once-daily dosing instead of thrice-daily dosing. Even if FDA also accepted the contention that Gralise has an average higher daily dose compared to gabapentin TID, this factor is likewise not significant absent information showing that this higher dose is due to fewer AEs and/or achieves greater pain control. These two minor features combined do not rise to the level of demonstrating that Gralise provides "a significant therapeutic advantage" over Neurontin through providing a major contribution to patient care. 21 CFR 316.3(b)(3).

What the sponsor has not provided to assist with this cumulative assessment – despite a number of requests from FDA – is information that correlates the PK data (the high plasma levels of gabapentin at night) to clinical effect (*e.g.*, nighttime pain control, fewer AEs leading fewer falls, etc.). This information, if provided, may help bolster many of the theories proffered by the sponsor, including enhanced nighttime pain relief and lower risk of injury. The ATU survey could perhaps have made the connection if it were a random sampling of patients and/or physicians who were surveyed on their actual experiences with Gralise (instead of labeling comprehension). Even now, if the sponsor were able to correlate plasma levels with the occurrence of AEs or the elevated plasma levels with greater pain control, FDA would take such information into consideration in re-assessing major contribution to patient care.

In sum, FDA has determined that, based on the information provided by the sponsor to date, Gralise is not eligible for orphan exclusivity predicated on major contribution to patient care.

VI. CONCLUSION

For the reasons described above, we reaffirm our initial conclusion that Gralise is not entitled to orphan-drug exclusivity under the Orphan Drug Act and FDA regulations absent a demonstration of clinical superiority, because it is the same drug as a drug already approved for the same use, Neurontin (and multiple approved generic versions of Neurontin). We further conclude that Gralise has not been demonstrated to be clinically superior to Neurontin, whether in terms of greater safety or by making a major contribution to patient care. Gralise is thus ineligible for orphan-drug exclusivity. This decision is consistent with the governing statute, implementing regulations, and Agency practice, and best effectuates the important aim of the Orphan Drug Act.

Gralise will continue to enjoy its three years of market exclusivity vis-à-vis potential generic competitors under section 505 (21 U.S.C. § 355), for conducting one

clinical investigation considered essential to and supporting approval of its new formulation of gabapentin. Depomed is not, however, entitled to a seven-year period of exclusivity vis-à-vis all gabapentin products indicated for this orphan indication.

Sincerely,

Gayatri Rao

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