IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

DEPOMED INC.,
1360 O'Brien Drive
Menlo Park, California 94025,

Plaintiff,

v.

Case No. _____

UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201,

UNITED STATES FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, MD 20993,

KATHLEEN SEBELIUS, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201,

and

MARGARET HAMBURG, in her official capacity as COMMISSIONER OF FOOD AND DRUGS, UNITED STATES FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, MD 20993,

Defendants.

COMPLAINT FOR DECLARATORY, INJUNCTIVE AND OTHER RELIEF

Plaintiff Depomed Inc. ("Depomed"), for its complaint against defendants the United States Department of Health and Human Services ("HHS"), the United States Food and Drug

Administration ("FDA"), Kathleen Sebelius, in her official capacity as Secretary of HHS, and Margaret Hamburg, in her official capacity as Commissioner of Food and Drugs (together, "Defendants"), asserts as follows:

INTRODUCTION

1. Depomed seeks declaratory and injunctive relief under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701-706, to prevent Defendants from violating the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq.*, and FDA's implementing regulations, 21 C.F.R. Part 316.

2. The Orphan Drug Act, 21 U.S.C. §§ 360aa – 360ee, amended the FDCA to provide incentives for the development and marketing of drugs that treat rare diseases or conditions, which include those that affect less than 200,000 patients per year in the United States.

3. A sponsor seeking the benefits of the Orphan Drug Act for a drug proceeds through two steps. First, the sponsor applies for "orphan-drug designation," which FDA grants if the sponsor has demonstrated that the disease or condition the drug will treat qualifies (*e.g.*, affects fewer than 200,000 people) and that there is reason to believe the drug will be effective in treating the disease or condition. The second step is for the product to receive "orphan-drug exclusivity," which occurs automatically if the sponsor obtains FDA approval of the drug to treat the rare disease or condition for which the product received orphan-drug designation.

4. The incentives of the Orphan Drug Act include a number of benefits that become available to the sponsor upon FDA's grant of orphan-drug designation, including tax credits and research grants. The Act's primary incentive, however, is found in orphan-drug exclusivity. With certain exceptions, this exclusivity precludes FDA approving an application from another

sponsor for a product that is the same drug intended to treat the same rare disease or condition, for a period of seven years. Under the statute, after a drug that received orphan-drug designation for the treatment of a rare disease or condition is approved for that use, the drug automatically is awarded the seven-year orphan-drug exclusivity.

5. At issue here is FDA's denial of orphan-drug exclusivity to Depomed's product, Gralise (gabapentin) tablets. Gralise received orphan-drug designation for the management of postherpetic neuralgia ("PHN"), a condition that causes pain in individuals who have had shingles. Gralise was later approved for that same orphan-designated condition, at which point FDA should have automatically awarded Gralise orphan-drug exclusivity. Despite the clear statutory and regulatory command, that is not what happened.

6. Ignoring the plain language of the statute and its own regulations, FDA refused to grant Gralise the orphan-drug exclusivity to which it is entitled. Instead, the agency placed additional hurdles between Gralise and orphan-drug exclusivity, by attempting to impose requirements that are found nowhere in the statute and that exist in regulation only for circumstances not present here.

7. FDA's regulations impose additional requirements only where a product is the "same drug" as another product "that already has orphan-drug exclusive approval" for the same use, *i.e.*, another product that already obtained orphan-drug exclusivity for treating the same rare disease or condition. By regulation, two products are the "same drug" if, in relevant part, they have the same active moiety (the molecule responsible for the product's therapeutic effect) and are intended for the same use.

8. Another gabapentin product, Neurontin, is the "same drug" as Gralise under the regulations and was approved for the management of PHN before Gralise. Neurontin is not a

drug that already has orphan-drug exclusivity, however. Neurontin never had orphan-drug exclusivity; the product's sponsor never sought or received orphan-drug designation for the product for managing PHN, and accordingly, the product did not receive orphan-drug exclusivity when it was approved for that use. Because it is not a previously approved product "that already has orphan-drug exclusive approval" for the management of PHN, Neurontin provides no basis for FDA to impose additional requirements on Depomed as conditions to be satisfied before Gralise receives the benefits of orphan-drug exclusivity.

9. Gralise is the only product with gabapentin as the active ingredient to receive orphan-drug designation for the management of PHN, and it was approved by FDA for that orphan-designated condition.

10. The denial of orphan-drug exclusivity to Gralise is contrary to the plain language of the Orphan Drug Act and the agency's implementing regulations. Accordingly, Defendants' actions are unlawful, arbitrary, capricious, an abuse of discretion, and contrary to law.

11. Unless overturned, Defendants' conduct will undermine the congressionally enacted incentives for companies to develop products to treat rare diseases and conditions, and will cause significant economic harm to Depomed. Depomed is already aware of six applications pending at FDA for gabapentin products intended to treat PHN, which would compete directly with Gralise. With orphan-drug exclusivity for Gralise, those products cannot be approved before January 2018. Without orphan-drug exclusivity (the current state of affairs), some of these products could be approved and come to market as much as four years earlier, in January 2014. It is protection from competing products such as these that orphan-drug exclusivity is intended to provide, as an economic incentive for companies to expend the effort and money to bring to market products like Gralise that serve a small number of patients.

12. Depomed seeks declaratory and injunctive relief to overturn Defendants' illegal acts and to obtain for Gralise the orphan-drug exclusivity to which the product is entitled under the Orphan Drug Act.

PARTIES

13. Plaintiff Depomed is a specialty pharmaceutical company with its headquarters and principal place of business at 1360 O'Brien Drive, Menlo Park, California 94025. Founded in 1995, Depomed develops, manufactures, and markets drug products with the goal of allowing patients to experience therapeutic efficacy with fewer side effects and more convenient dosing.

14. Defendant HHS is a Department of the United States. Its headquarters and principal place of business are at 200 Independence Avenue, S.W., Washington, District of Columbia 20201. Its governmental activities occur in this District and nationwide.

15. Defendant FDA is an agency of the United States and a division of Defendant HHS. FDA has the delegated responsibility to approve and regulate drugs sold within the United States, including through application of the Orphan Drug Act. FDA's headquarters and principal place of business are at 10903 New Hampshire Avenue, Silver Spring, Maryland 20903. Its governmental activities occur in this District and nationwide.

16. Defendant Kathleen Sebelius is the Secretary of HHS and is ultimately responsible for implementation and execution of the FDCA and associated regulations. The Secretary administers the Orphan Drug Act through FDA. Defendant Sebelius is sued in her official capacity only. Her governmental activities occur in this District and nationwide.

17. Defendant Margaret Hamburg is the Commissioner of Food and Drugs and is directly responsible for FDA's implementation and execution of the FDCA (including the

Orphan Drug Act) and associated regulations. Defendant Hamburg is sued in her official capacity only. Her governmental activities occur in this District and nationwide.

JURISDICTION AND VENUE

18. Subject matter jurisdiction is founded on 28 U.S.C. §§ 1331, 1346, and 1361, as well as 5 U.S.C. § 702. This Court has authority to grant declaratory relief pursuant to 28 U.S.C. §§ 2201 and 2202.

19. There exists an actual and justiciable controversy between Depomed and Defendants requiring resolution by this Court.

20. Venue is proper in this Court under 28 U.S.C. § 1391(b) and (e).

STATEMENT OF CLAIM

The Orphan Drug Act

21. Enacted in 1983, the Orphan Drug Act (Pub. L. 97-414) amended the FDCA for the stated purpose of promoting and encouraging the development of drugs for the treatment of rare diseases or conditions. The Orphan Drug Act is codified at 21 U.S.C. §§ 360aa - 360ee, and the regulations issued under it are found at 21 C.F.R. Part 316.

22. In passing the Orphan Drug Act, Congress sought to benefit the public health by providing economic incentives for companies to develop drug products for diseases or conditions that affect small numbers of patients. Congress recognized that "there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs." Pub. L. No. 97-414, 96 Stat. 2049, § 1(b)(5) (Jan. 4, 1983).

23. The most important of the economic incentives provided by the Orphan Drug Act is the seven-year exclusivity awarded with approval of a drug for a rare disease or condition.

During the exclusivity period, FDA is prohibited from approving an application for another product that is the same drug intended to treat the same disease or condition. To obtain this benefit, a drug must first obtain orphan-drug designation from FDA and then be approved for the rare disease or condition that is the subject of the designation.

24. FDA is required to designate the product as an orphan drug if the sponsor timely submits a request for orphan-drug designation and demonstrates to FDA 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. 21 U.S.C. § 360bb(a)(1). The Orphan Drug Act defines a "rare disease or condition" in relevant part as a disease or condition that "affects less than 200,000 persons in the United States." 21 U.S.C. § 360bb(a)(2).

25. An orphan-drug designation therefore has two components: the drug and its intended use, *i.e.*, the disease or condition for which the drug is being studied and for which the sponsor hopes to receive marketing approval. If the drug ultimately is approved, the intended use is often referred to as the drug's "indication."

26. Orphan-drug exclusivity is triggered by FDA approving a drug for its orphan-designated use. The plain language of the statute makes clear that orphan-drug exclusivity automatically arises when a drug is approved for a use for which the drug has received orphan-drug designation:

> [I]f [FDA] approves an application . . . for a drug designated . . . for a rare disease or condition, [FDA] may not approve another application . . . for such drug for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved application . . . .

21 U.S.C. § 360cc(a).

27. The statute provides two exceptions to the preclusive effect of orphan-drug exclusivity. During the seven-year exclusivity period, FDA may approve another application

"for such drug for such disease or condition" with the consent of the exclusivity holder or if the agency determines that the exclusivity holder "cannot assure the availability of sufficient quantities of the drug" to meet the needs of the patient population with the rare disease or condition. 21 U.S.C. § 360cc(b).

FDA Regulations Implementing the Orphan Drug Act

28. FDA regulations implementing the Orphan Drug Act mirror the statute in stating that orphan-drug exclusivity automatically arises when a product is approved for its orphan-designated indication:

> After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan-drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA[.]

21 C.F.R. § 316.31(a).

29. That orphan-drug exclusivity arises automatically from the approval of a drug for an orphan-designated indication is also made clear in the definition of "orphan-drug exclusive approval," which – by regulation – "means that, effective on the date of FDA approval . . . of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years[.]" 21 C.F.R. § 316.3(b)(12).

30. As FDA explained in proposing the regulation, the Orphan Drug Act "automatically vests a 7-year period of orphan-drug exclusive approval on the date that the agency issues a marketing approval for a designated orphan drug. For this reason, no further action by FDA to bring about exclusive approval is necessary." 56 Fed. Reg. 3338, 3341 (Jan. 29, 1991).

31. Once a product has been approved for an orphan-designated indication, FDA's only responsibilities under the regulations are to give the sponsor "timely written notice recognizing exclusive approval once the marketing application for a designated orphan-drug product has been approved," and publish information providing public notice of the exclusivity. 21 C.F.R. § 316.34.

32. Nothing in the Orphan Drug Act or implementing regulations permits FDA to approve a product for an orphan-designated indication and withhold orphan-drug exclusivity.

33. The regulations also define the preclusive effect of orphan-drug exclusivity and expand on the statutory exceptions to it. In the words of the statute, orphan-drug exclusivity prohibits FDA's approving for seven years another application "for such drug for such disease or condition." FDA's regulations implement this by stating that FDA will not approve another application for the "same drug," 21 C.F.R. § 316.31(a), which is defined in relevant part as a product "that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug." 21 C.F.R. § 316.3(b)(13).

34. As in the statute, the regulations permit approval of another application if the exclusivity holder consents or cannot produce sufficient quantities. *See* 21 C.F.R. § 316.31(a)(3), (4). However, the regulations also create a third exception to the preclusive effect of orphan-drug exclusivity. The regulations also allow FDA to approve another application during the exclusivity period if the subsequent product is "clinically superior" to the drug with orphan-drug exclusivity. The regulations create this third exception by defining "same drug" to exclude a product that, although containing the same active moiety and intended for the same rare disease or condition, "can be shown to be clinically superior to the first drug." 21 C.F.R. § 316.3(b)(13).

35. A product is considered "clinically superior" if it "is shown to provide a significant therapeutic advantage over and above that provided by" the already-approved product. 21 C.F.R. § 316.3(b)(3). Clinical superiority can be based on greater effectiveness, greater safety "in a substantial portion of the target populations," or "where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care." *Id.*

36. Accordingly, clinical superiority, which appears nowhere in the Orphan Drug Act, is established by the regulations as a basis for FDA to approve a product that otherwise could not be approved because it contains the same active moiety, and is intended to treat the same rare disease or condition, as an already-approved product that has orphan-drug exclusivity. The fact that clinical superiority is relevant only when there is an already-approved product with orphan-drug exclusivity is demonstrated by the intersection of the scope of "orphan-drug exclusive approval" (*i.e.*, FDA will not approve another application for the "same drug") and the definition of "same drug" (*i.e.*, a clinically superior product is not a "same drug").

37. The regulations setting standards for orphan-drug designation also reflect this purpose. One of the enumerated bases for denying a request for orphan-drug designation is that the proposed product "is otherwise the same drug as one that 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." 21 C.F.R. § 316.25(a)(3). Further, FDA regulations provide that, unless one of the enumerated bases for denying orphan-drug designation applies, FDA must grant the request for orphan-drug designation. 21 C.F.R. § 316.24(a).

FDA Approved Gralise and Withheld Orphan-Drug Exclusivity

38. By letter dated November 8, 2010, FDA granted orphan-drug designation to Gralise for the management of PHN.

39. On January 28, 2011, FDA approved NDA 022544 for Gralise for the management of PHN.

40. Gralise is the subject of an approved "marketing application for a designated orphan-drug product." 21 C.F.R. § 316.34(a).

41. FDA did not send Depomed written notice recognizing orphan-drug exclusivity for Gralise.

42. FDA did not publish information giving public notice that Gralise has orphan-drug exclusive approval. In fact, the listing for Gralise in FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the *Orange Book*) indicates (by the absence of an affirmative notice) that Gralise does not have orphan-drug exclusivity.

43. Solvay Pharmaceuticals (which was later acquired by Abbott Laboratories) acquired the rights to Gralise from Depomed in January 2009 and Depomed reacquired those rights in March 2011. In a February 2011 telephone call with Abbott Laboratories, a representative of FDA confirmed that, although Gralise had been approved for its orphan-designated indication (PHN), the agency was withholding orphan-drug exclusivity. The FDA representative explained that, in order to qualify for orphan-drug exclusivity, Gralise had to be shown to be clinically superior to Neurontin, another gabapentin product that had been approved for the management of PHN in 2002.

44. Upon information and belief, Neurontin never received orphan-drug designation for the management of PHN.

45. Upon information and belief, Neurontin was never the subject of orphan-drug exclusive approval for the management of PHN, *i.e.*, the product never received orphan-drug exclusivity for the management of PHN.

FDA Required a Plausible Hypothesis of Clinical Superiority For a Grant of Orphan-Drug Designation for Gralise

46. Depomed submitted the initial request for orphan-drug designation for Gralise in December 2006. FDA denied that request because, *inter alia*, Depomed had not provided a plausible hypothesis of clinical superiority over Neurontin.

47. In a March 26, 2010, amendment to the initial request for orphan-drug designation and a subsequent submission on September 1, 2010, Abbott asserted that no showing of clinical superiority was required, because Neurontin had never received orphan-drug exclusive approval.

48. Although Neurontin did not have, and has never had, orphan-drug exclusivity, FDA insisted that orphan-drug designation for Gralise required a plausible hypothesis of clinical superiority to Neurontin.

49. On November 8, 2010, FDA granted orphan-drug designation to Gralise for the treatment of PHN, having concluded that a plausible hypothesis of clinical superiority to Neurontin, by way of greater safety, had been presented. This conclusion was based on a comparison of the incidence of adverse events in Gralise clinical trials with the incidence of adverse events in Neurontin clinical trials, as reported in the approved package insert for Neurontin.

50. Contrary to the plain language of the Orphan Drug Act and FDA's regulations, the letter communicating the grant of orphan-drug designation asserted that approval of Gralise to manage PHN would not automatically lead to orphan-drug exclusivity. The letter stated that,

"should [Depomed] obtain marketing approval for this product, [Depomed] will have to prove clinical superiority . . . in order to obtain seven years of marketing exclusivity."

FDA Did Not Require Clinical Superiority for a Similarly Situated Product

51. Upon information and belief, FDA in 1992 approved Recombinate [antihemophilic factor (recombinant)] for the prevention and control of hemorrhagic episodes in patients with hemophilia A and for the perioperative management of patients with hemophilia A.

52. Upon information and belief, Recombinate had never been granted orphan-drug designation for those indications, nor did the product receive orphan-drug exclusivity upon approval.

53. Upon information and belief, Kogenate [antihemophilic factor (recombinant)] received orphan-drug designation in 1989 for what is essentially the same intended use as Recombinate: "prophylaxis and treatment of bleeding in individuals with hemophilia A or for prophylaxis when surgery is required in individuals with hemophilia A."

54. Upon information and belief, FDA approved Kogenate on February 25, 1993, for the "treatment and prophylaxis of bleeding in patients with hemophilia A (not von Willebrand's disease)." Having been approved for its orphan-designated indication, Kogenate automatically received seven years of orphan-drug exclusivity.

55. Upon information and belief, Recombinate and Kogenate are the "same drug," as that term is defined in 21 C.F.R. § 316.3(b)(13). Upon information and belief, FDA did not require proof of clinical superiority as a prerequisite to awarding Kogenate orphan-drug exclusivity.

56. At the time of Kogenate's approval and grant of orphan-drug exclusivity, FDA's regulations establishing clinical superiority as a basis for avoiding another product's orphan-drug exclusivity were in effect, in the same form as they currently exist.

57. At a public meeting, FDA's Office of Orphan Products Development explained that, because Recombinate had not sought or received orphan-drug designation or exclusivity, its approval prior to Kogenate had no effect on the ability of Kogenate to receive orphan-drug exclusivity upon approval for the orphan-designated indication:

> 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.

Transcript of December 11, 1998, meeting of FDA Blood Products Advisory Committee, at 101.

58. For purposes of orphan-drug designation and orphan-drug exclusivity, Gralise and Kogenate are similarly situated products. Each is the "same drug" as a previously approved product that is approved for the same indication, but that never had orphan-drug designation or orphan-drug exclusivity. Nonetheless, FDA has improperly held the two products to fundamentally different standards as to the grant of orphan-drug designation and the award of orphan-drug exclusivity. *See Bracco Diagnostics, Inc, v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997).

COUNT I

VIOLATION OF ADMINISTRATIVE PROCEDURE ACT

59. Depomed reasserts and incorporates by reference all of the above allegations.

60. The APA prohibits Defendants' implementing the FDCA, as amended by the Orphan Drug Act, in a way that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. 5 U.S.C. § 706(2)(A).

61. Defendants' actions are arbitrary, capricious, an abuse of discretion, and not in accordance with law because they have denied Depomed the orphan-drug exclusivity for Gralise to which Depomed is entitled under the FDCA, as amended by the Orphan Drug Act, and FDA's regulations.

62. Defendants' approval of Gralise for the management of PHN, while withholding the orphan-drug exclusivity that such approval automatically triggered, constitutes final agency action. 5 U.S.C. § 704.

63. Depomed has exhausted its administrative remedies, or, to the extent that it has not, is excused from exhausting its administrative remedies because further pursuit of administrative remedies would not further the goals that exhaustion is designed to further.

64. Depomed has no other adequate remedy at law. 5 U.S.C. § 704.

65. This Court should set aside FDA's unlawful denial of orphan-drug exclusivity to Gralise and declare that Gralise is entitled to seven years of orphan-drug exclusivity.

PRAYER FOR RELIEF

WHEREFORE, Depomed respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that Defendants' refusal to grant Depomed orphan-drug exclusivity for Gralise is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

B. A declaration pursuant to 28 U.S.C. § 2201 that Depomed is entitled to seven years of orphan-drug exclusivity for Gralise;

C. An order directing FDA to recognize that Gralise is entitled to all benefits of orphan-drug exclusive approval, including publication of that status in the *Orange Book* and

other agency public databases, as well as issuance of written notice per 21 C.F.R. § 316.34(a);

D. Injunctive relief enjoining Defendants from approving another gabapentin product for the management or treatment of PHN until January 28, 2018;

E. An order awarding Depomed its costs and attorneys' fees pursuant to 28 U.S.C. § 2412; and

F. Such other and further relief as the Court deems just and proper.

Dated: September 25, 2012

Respectfully submitted,

/s/

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