IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

EAGLE PHARMACEUTICALS, INC.

Plaintiffs,

v.

SYLVIA BURWELL, in her official capacity as Secretary of Health and Human Services;

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES;

ROBERT CALIFF, in his official capacity as Commissioner of the U.S. Food and Drug Administration;

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Defendants,

Case No. _____

Judge _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Eagle Pharmaceuticals, Inc. ("Eagle") brings this complaint for declaratory and injunctive relief, and states the following in support thereof:

PRELIMINARY STATEMENT

1. Congress enacted the Orphan Drug Act in 1983 to provide statutory incentives to pharmaceutical companies developing so-called "orphan drugs"—drugs that treat rare conditions and diseases that would ordinarily be unprofitable due to the limited market for those drugs. *See* Orphan Drug Act, Pub. L. No. 97-414, § 1(b)(4), 96 Stat. 2049, 2049 (1983) (making statutory findings); *see also* H.R. Rep. No. 97-840, at 1 (1982). The most important of these incentives is a seven year period of market exclusivity, known as "orphan drug exclusivity." Under the Orphan Drug Act, a pharmaceutical company may request that the U.S. Food and Drug Administration ("FDA") designate its drug as an "orphan drug." 21 U.S.C. § 360bb. To receive

such a designation, the pharmaceutical company must show that its drug is being investigated for a rare disease or condition and, if approved, would be approved for use in that disease or condition. *Id.* § 360bb(a). Once FDA grants the ***designation***, the pharmaceutical company can complete development *knowing that it will be more likely to recover its costs because it will receive a seven year period of exclusivity upon approval during which FDA may not approve another application for the same drug for the same disease or condition*. *Id.* § 360cc; Pub. L. No. 97-414, § 1(b)(4), (6), 96 Stat. at 2049 (containing findings that "because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to … incur a financial loss" and that "it is in the public interest to provide … incentives for the development of orphan drugs"). If a previously ***designated*** orphan drug ultimately receives FDA approval finding that the drug is safe and effective for the designated orphan disease, the drug is then ***automatically*** entitled by statute to a seven year period of exclusivity. 21 U.S.C. §§ 360cc(a), 355. Here, Plaintiff's drug Bendeka for treatment of two rare lymphocytic cancers was designated by FDA as an orphan drug in 2014 and received FDA approval in 2015, but FDA has nevertheless unlawfully denied Bendeka its statutorily mandated exclusivity.

2. This will not be the first time this Court addresses FDA's refusal to follow the plain language of the Orphan Drug Act. In the widely publicized 2014 decision, *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014), Judge Ketanji Brown Jackson held in almost identical circumstances that the "plain language of the exclusivity provision of the Orphan Drug Act requires the FDA to recognize exclusivity for any drug that the FDA has designated and granted marketing approval." *Id.* at 237. In that case, Judge Jackson held unlawful FDA's attempt to impose an additional requirement for orphan drug exclusivity

that a pharmaceutical company, which had *already been granted an orphan drug designation,* prove that its drug was clinically superior to older, similar drugs. Judge Jackson recognized that the exclusivity issue presented a straightforward *Chevron* "step 1" question, and that FDA's extra-statutory limits on exclusivity were fundamentally in conflict with the statute. *See id.* at 229. Judge Jackson invited FDA to change its regulations governing orphan drug *designations* if the agency sought a different result in future cases. *Id.* at 230-31.

3. Rather than appeal from Judge Jackson's ruling or rewrite its regulations to conform to the Orphan Drug Act, FDA decided to ignore the ruling. FDA published a notice in the Federal Register explaining its intent to treat that decision as limited to its facts, and to "continue to apply its existing regulations." *Policy on Orphan-Drug Exclusivity; Clarification*, 79 Fed. Reg. 76,888 (Dec. 23, 2014). FDA's decision to ignore *Depomed* is what has led to this case.

4. Even though FDA granted Bendeka orphan drug designation on July 2, 2014, and approved Bendeka on December 7, 2015, FDA denied Bendeka exclusivity in a March 24, 2016 letter ruling taking essentially the same position it took in *Depomed*. *See* Letter from Gayatri R. Rao, Director, FDA Office of Orphan Drug Development, to John Manthei, Latham & Watkins LLP (Mar. 24, 2016) [hereinafter *Letter Ruling*]. *First*, the letter ruling explained FDA's position that *Depomed* was wrongly decided. *Id.* at 39 ("[T]he *Depomed* court erred in not deferring to FDA's statutory interpretation …."); *id.* at 32 ("We are not bound to follow the *Depomed* decision, and we do not believe that the *Depomed* court's conclusion is compelled by the statute …." (internal citation omitted)); *id.* at 9 ("Because FDA concluded that the decision was inconsistent with FDA's clinical superiority framework and the important policy interests at stake, the Agency has continued to implement its long-standing clinical superiority framework for designation and exclusivity decisions."). *Second*, FDA defended its regulatory scheme: FDA

acknowledged that it had indeed granted orphan drug designation for Bendeka, but argued that Congress's exclusivity incentive for orphan drugs is not particularly important compared to other incentives in the statute. *See id.* at 10, 34. Thus, FDA argued that, despite granting orphan drug designation, the agency was free to deny exclusivity at the end of the process. *Id.* at 32-40. *Third*, despite FDA's conclusion when it designated Bendeka as an orphan drug that Bendeka presented a plausible hypothesis of clinical superiority over a similar drug named Treanda, FDA reversed course in 2016. FDA now concluded that, although Bendeka is safe and effective, Eagle had not proffered sufficient evidence that Bendeka is in fact clinically superior to Treanda under the regulatory requirement this Court found unlawful in *Depomed*. *Id.* at 32.

5. There is no doubt that FDA disagrees with the policy behind Congress's structure of the Orphan Drug Act. But FDA is not free to simply disregard the plain language of that statute. Had FDA respected Judge Jackson's ruling in 2014, this case would not be necessary. Unfortunately, FDA's defiance of this Court's prior order leaves Plaintiff no choice but to file this suit.

PARTIES

6. Plaintiff Eagle is a specialty pharmaceutical company with its headquarters and principal place of business at 50 Tice Boulevard, Suite 315, Woodcliff Lake, New Jersey 07677. Eagle focuses on developing and commercializing injectable drug products, primarily for the treatment of rare diseases and conditions in the critical care and oncology areas.

7. Defendant Sylvia Burwell is the Secretary of Health and Human Services and is ultimately responsible for implementation and execution of the Federal Food, Drug, and Cosmetic Act ("FDCA"), the Orphan Drug Act, and associated regulations. The Secretary

exercises those authorities through FDA, an agency within the U.S. Department of Health and Human Services.

8. Defendant U.S. Department of Health and Human Services is an executive department of the United States with its headquarters and principal place of business at 200 Independence Avenue, SW, Washington, D.C. 20201.

9. Defendant Robert Califf is the Commissioner of FDA and is directly responsible for FDA's implementation and execution of the FDCA, the Orphan Drug Act, and associated regulations. In that role, Dr. Califf heads FDA and reports to Defendant Burwell.

10. Defendant FDA is a federal agency within Defendant U.S. Department of Health and Human Services. FDA has responsibility, *inter alia*, for approving and regulating drugs sold within the United States, including through application of the Orphan Drug Act. The headquarters and principal place of business of FDA is 10903 New Hampshire Avenue, Silver Spring, Maryland 20903.

JURISDICTION AND VENUE

11. This Court has subject matter jurisdiction over Plaintiff's claims pursuant to 28 U.S.C. §§ 1331 and 1361, as well as 5 U.S.C. § 706. This Court has authority to grant declaratory relief pursuant to 28 U.S.C. § 2201.

12. This Court has personal jurisdiction over Defendants, as each is an agency or official of the United States Government.

13. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(e) because Defendants Burwell and the U.S. Department of Health and Human Services reside within the district of Washington, D.C.

LEGAL AND REGULATORY FRAMEWORK

A. The Drug Approval Process

14. Under the FDCA, before a new drug may be introduced into interstate commerce, it must be specifically approved by FDA through one of several available pathways. *See* 21 U.S.C. § 355. Obtaining FDA approval is a complex process that can take years and cost millions of dollars. Upon FDA's approval of a drug, the drug becomes approved for the particular intended use, or "indication," for which FDA has found the drug to be safe and effective. *See* 21 C.F.R. § 201.57(c)(2).

B. The Orphan Drug Act

15. The Orphan Drug Act was enacted on January 4, 1983 to incentivize the development of drugs for rare diseases and conditions. Pub. L. No. 97-414, § 1(b), 96 Stat. at 2049; *see also* H.R. Rep No. 97-840, at 1. The Orphan Drug Act amended the FDCA at 21 U.S.C. §§ 360aa–360ee. By enacting the Orphan Drug Act, Congress provided financial incentives to encourage investment in the development of drugs that would otherwise not be developed because the market for their use was too small to be profitable.

16. The main financial incentive established by Congress through the Orphan Drug Act is a promise of a seven year period of marketing exclusivity for designated orphan drugs that are ultimately approved for rare diseases or conditions. During this period of exclusivity, FDA may not approve another marketing application for "such drug" for "such disease or condition." 21 U.S.C. § 360cc(a). This exclusivity period is commonly known as "orphan drug exclusivity."

17. For a drug sponsor to obtain orphan drug exclusivity, FDA must first designate the drug as an orphan drug for a particular rare disease or condition and then grant approval for the drug for that rare disease or condition. *Id.*

18. Section 526 of the Orphan Drug Act (21 U.S.C. § 360bb) establishes the process by which a drug may receive orphan designation and permits FDA to promulgate regulations implementing the statutory designation process. That section permits a drug sponsor to request that FDA designate a drug as an "orphan drug," and requires FDA to grant a timely request if it finds that: (a) the drug is being investigated for a rare disease or condition; and (b) if the drug is approved, the approval will be for the use of the drug for that rare disease or condition. 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). Thus, the Orphan Drug Act requires FDA to grant timely requests for orphan drug designation if the drug that is the subject of the request is being investigated for a disease or condition that affects fewer than 200,000 persons in the United States and FDA finds that any future approval of the drug will be for that disease or condition.

19. Once a drug is designated as an orphan drug, the drug sponsor becomes eligible for a number of benefits. Most importantly, a designated orphan drug is entitled to market exclusivity once it completes the FDA approval process demonstrating that the drug is safe and effective:

> Except as provided in subsection (b), if [FDA] (1) approves an application filed pursuant to [21 U.S.C. § 355] … for a drug designated under [21 U.S.C. § 360bb] for a rare disease or condition, [FDA] may not approve another application ... for such drug for such disease or condition for a person who is not the holder of such approved application … until the expiration of seven years from the date of the approval of the approved application[.]

21 U.S.C. § 360cc(a).

20. The seven year period during which FDA is prohibited from approving another application for "such drug" for "such disease or condition" is often referred to as a period of "marketing exclusivity" for the orphan drug applicant because no new entity is permitted to manufacture or sell the drug in interstate commerce for the orphan indication during that time.

Congress's decision to grant orphan drug holders seven years of marketing exclusivity upon approval was the result of purposeful consideration of the extent of benefits needed to incentivize drug manufacturers to advance treatments for orphan diseases. *See* H.R. Rep. No. 100-473, at 6 (1987) (discussing that Congress weighed the potential benefits and drawbacks of offering seven years of market exclusivity).

21. Once FDA has approved an orphan-designated drug, there are only two circumstances under which the Orphan Drug Act permits FDA to approve a third party's marketing application for the same drug for the same orphan indication: (1) if the drug sponsor cannot sufficiently supply the market and meet the needs of the orphan patient population; or (2) if the third party obtains the written consent of the orphan drug sponsor. 21 U.S.C. § 360cc(b).

22. Congress also supplied other incentives to develop orphan drugs, including: eligibility for research grants pursuant to 21 U.S.C. § 360ee; exemption from certain application fees pursuant to 21 U.S.C. § 379h(a)(1)(F); exemption from product and establishment fees in certain circumstances after approval pursuant to 21 U.S.C. § 379h(k); tax credits for qualified clinical research pursuant to 26 U.S.C. § 45C; exclusion from the branded pharmaceutical fee pursuant to the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 9008, 124 Stat. 119, 859-62 (2010) (codified in notes preceding 26 U.S.C. § 4001); and exclusion from the requirement to offer discounted prices to certain covered entities pursuant to 42 U.S.C. § 256b.

C. FDA Regulations Implementing the Orphan Drug Act

Orphan Drug Designation

23. Congress expressly authorized FDA to promulgate implementing regulations regarding the *designation* process, *see* 21 U.S.C. § 360bb(d), and FDA has done so.

24. Under FDA's regulations, FDA will grant a timely submitted request for orphan drug designation if the drug is intended for a rare disease or condition, and there is sufficient

information to establish that a medically plausible basis exists to expect the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition. *See* 21 C.F.R. §§ 316.24(b), 316.25.

25. The regulations further provide that FDA will refuse to grant an orphan drug designation if "[t]he drug is otherwise the same drug as an already approved drug 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(3). The regulations define "same drug," in relevant part, as "a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug." 21 C.F.R. § 316.3(b)(14)(i).

26. Thus, FDA must determine whether a new drug with the same active moiety as an existing drug presents a "plausible hypothesis that [the new] drug may be clinically superior to the first drug" at the time of orphan drug designation, 21 C.F.R. § 316.20(a), and otherwise meets the statutory factors for such a designation, *id.* § 316.25(a)(3).

Orphan Drug Exclusivity

27. In contrast to the Orphan Drug Act's *designation* provision, Congress did not authorize FDA to promulgate regulations implementing the Act's *exclusivity* provision. *See* 21 U.S.C. § 360cc; *see also Depomed*, 66 F. Supp. 3d at 222 (noting that FDA was not delegated authority to promulgate implementing regulations for the Orphan Drug Act's exclusivity provision). FDA did so nonetheless.

28. While FDA's orphan drug exclusivity regulations mirror the Orphan Drug Act in certain respects, they are different in material ways. First, FDA's regulations generally provide that FDA will not recognize the exclusivity rights of a previously designated orphan drug if

another drug with the same active moiety (or otherwise meeting the "same drug" criteria in the regulations) has previously been approved. 21 C.F.R. § 316.34(a). In particular, for a drug that received orphan designation based on a plausible hypothesis of clinical superiority over a previously approved drug with the same active moiety, FDA's regulations improperly require the sponsor to later *prove* that its drug is in fact "clinically superior" to the previously approved drug. *See* 21 C.F.R. §§ 316.31(a), 316.34(c). In other words, FDA has given itself authority found nowhere in the statute to withhold the statutory orphan drug exclusivity Congress utilized to incentivize the development of these drugs.

29. FDA continues to apply this extra-statutory requirement for proof of clinical superiority despite the fact that the same requirement was expressly rejected by Judge Jackson in *Depomed*. Moreover, FDA's orphan drug exclusivity regulations—amended *after* the relevant actions in the *Depomed* case—now codify the precise requirement that Judge Jackson found to be unlawful.

30. In *Depomed*, Judge Jackson considered FDA's denial of orphan drug exclusivity for Depomed's drug, Gralise. Even though FDA had previously designated Gralise as an orphan drug based on a plausible hypothesis of clinical superiority over a previously approved "same drug," FDA refused to grant exclusivity upon approval. *Depomed*, 66 F. Supp. 3d at 231. FDA's justification was that the sponsor had failed to actually demonstrate the clinical superiority of Gralise over the previously approved "same drug." *Id.* at 226.

31. Judge Jackson rejected FDA's justification and held that the Orphan Drug Act *automatically* conferred orphan drug exclusivity to Depomed upon Gralise's approval. Judge Jackson explained that "the plain language of the exclusivity provision of the Orphan Drug Act requires the FDA to recognize exclusivity for any drug that the FDA has designated and granted marketing approval." *Id.* at 237. Thus, where a drug satisfies both of those criteria, the drug "is

entitled to exclusivity and ... the FDA must recognize as much without requiring proof of clinical superiority or imposing any additional conditions on [the applicant]." *Id.* (emphasis added). Judge Jackson noted that, while the agency may have some discretion to limit which drugs ultimately obtain exclusivity, it must do so through the earlier *designation* process, not at the time of approval. *Id.* at 235-36. Indeed, FDA's designation regulations require applicants to present a plausible hypothesis of clinical superiority over any previously approved "same drug" in order to obtain designation. 21 C.F.R. § 316.25(a)(3). If FDA believes these regulations should be amended, it can do so through the rulemaking process.

32. Requiring FDA to impose any limitations at the *designation* stage comports with the Orphan Drug Act's incentive structure by allowing applicants to rely on the promise of future exclusivity when they make the decision to move forward with drug development. *Depomed*, 66 F. Supp. 3d at 234; *see also* H.R. Rep. No. 99-153, at 5-6 (1984), *reprinted in* 1985 U.S.C.C.A.N. 301 (specifying that the Orphan Drug Act is intended to "give drug company sponsors some certainty as to the drug approval process at FDA and the market conditions they will face upon approval"); H.R. Rep. No. 100-473, at 5-6 (explaining that the seven year exclusivity period has been a valuable incentive to companies to develop orphan drugs because it "assure[s] such a company that it could offset some or all of its costs of development by recouping *all* possible revenues from the sale of the drug during the seven year period of exclusivity").

33. FDA filed a notice of appeal of *Depomed* on November 6, 2014. Notice of Appeal, *Depomed Inc. v. U.S. Dept of Health and Hum. Servs.*, Case No. 14-5271 (D.C. Cir. Nov. 6, 2014). However, it withdrew the appeal the very same day, prior to briefing. Unopposed Voluntary Motion to Dismiss Appeal, *Depomed Inc. v. U.S. Dept of Health and Hum. Servs.*,

Case No. 14-5271 (D.C. Cir. Nov. 6, 2014). Instead, FDA has attempted to circumvent Judge Jackson's decision and the statutory mandate by issuing a notice in the Federal Register announcing its intention to continue to apply the post-approval clinical superiority condition that Judge Jackson found to be unlawful. *Policy on Orphan-Drug Exclusivity; Clarification*, 79 Fed. Reg. 76,888 (Dec. 23, 2014). In the notice, FDA stated that "[f]ollowing the *Depomed* decision, under the court's order, FDA recognized orphan-drug exclusivity for GRALISE for the treatment of post-herpetic neuralgia." *Id.* Nonetheless, FDA stated:

> It is the Agency's position that, given the limited terms of the court's decision to GRALISE, FDA intends to continue to apply its existing regulations in part 316 to orphan-drug exclusivity matters. FDA interprets section 527 of the [FDCA]and its regulations (both the older regulations that still apply to original requests for designation made on or before August 12, 2013, as well as the current regulations) to require the sponsor of a designated drug that is the 'same' as a previously approved drug to demonstrate that its drug is 'clinically superior' to that drug upon approval in order for the subsequently approved drug to be eligible for orphan-drug exclusivity.

Id. In accordance with this notice, FDA has acted and continues to act in direct conflict with both the Orphan Drug Act and Judge Jackson's holding in *Depomed*.

STATEMENT OF FACTS

A. Bendeka

34. Eagle is the developer of the drug Bendeka (bendamustine hydrochloride) Injection, which is an intravenous chemotherapy agent. Bendeka was approved by FDA on December 7, 2015 for the treatment of two rare lymphocytic cancers (specifically, chronic lymphocytic leukemia ("CLL") and indolent B-cell non-Hodgkin lymphoma ("NHL") that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen), each of which affects fewer than 200,000 persons in the United States. Both of these patient populations are made up primarily of advanced age patients with debilitating disease loads, many of whom also suffer from compromised heart and/or kidney function.

35. Eagle has the same active ingredient as another drug, Treanda (bendamustine hydrochloride) for Injection, although it is formulated very differently. Treanda is owned and marketed by Cephalon, Inc., a subsidiary of Teva Pharmaceuticals Industries Ltd. (collectively, "Teva"). Treanda is approved for the treatment of CLL and indolent B-cell NHL in two forms: (1) a powder that must be reconstituted to liquid form with sterile water, and then diluted in 500 mL of either 0.9% Sodium Chloride Injection, USP (normal saline) or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP (dextrose/saline) before it is intravenously administered to the patient; and (2) a liquid that does not require reconstitution, but that similarly must be diluted in 500 mL of normal saline or dextrose/saline before being intravenously administered. Both forms of Treanda take 30 minutes to administer to CLL patients and 60 minutes to administer to indolent B-cell NHL patients.

36. As part of its development work for Bendeka, Eagle obtained considerable feedback from healthcare providers that identified areas for improvement on Treanda. This work showed a general dissatisfaction with the length of time required to administer Treanda, and the large volume of fluid and high amount of sodium that came with it. Additionally, it was identified that, because Treanda's powder formulation must be reconstituted into a liquid and then diluted by the clinician, it is prone to dosing errors that could cause increased toxicity or reduced efficacy. Eagle also identified other areas for improvement and included them in its formulation.

37. Although Bendeka has the same active ingredient as Treanda, Eagle performed extensive research and development to formulate Bendeka to provide new benefits to patients. Eagle's unique formulation renders Bendeka superior to Treanda in multiple respects:

(1) Bendeka reduces the administration time required for treatment by 66-83% (20-50 minutes) compared to the Treanda products, reducing what patients perceive to be

one of the most burdensome aspects of chemotherapy—length of treatment time. For example, over the two consecutive days of treatment required for indolent B-cell NHL therapy, a patient taking Bendeka can save more than an *hour and a half* of time that would have been spent in the treatment chair with Treanda.

(2) Bendeka eliminates the 885-1769 mg sodium load associated with the Treanda products, and reduces the amount of fluid that must be injected into the patient by 90%. The reduced sodium and volume are particularly beneficial for the many CLL and indolent B-cell NHL patients who are suffering from renal and cardiovascular comorbidities. For example, patients with congestive heart failure have reduced cardiac output and, as a result, clinicians place great importance on managing their sodium and fluid intake during chemotherapy. Likewise, chronic kidney disease disrupts the body's ability to properly balance water and, accordingly, restrictions on sodium and fluid intakes are generally recommended for these patients, particularly those in advanced stages.

(3) Bendeka addresses a cause of many dosing errors by eliminating the need for reconstitution of the Treanda powder. Bendeka's formulation comes in a stable ready-to-dilute form.

(4) Bendeka contains no N, N-dimethylacetamide ("DMA"), which is a solvent in Treanda liquid that, according to FDA, can cause the plastic in certain common medical devices to dissolve on contact, leading to device failure, possible product contamination, and the potential infusion of the dissolved plastic into the patient. By eliminating DMA, Eagle thereby increased Bendeka's compatibility with common medical devices relative to liquid Treanda.

(5) Bendeka also offers better stability and a longer shelf-life with reduced propylene glycol ("PG") ester impurities, reducing the likelihood of patients receiving a degraded, impure product relative to liquid Treanda.

38. Accordingly, the Bendeka product provides substantial improvements over the Treanda products that result in clinical superiority through greater patient safety and a major contribution to patient care.

39. As part of the FDA approval process, Eagle was required to conduct a human study to show that the differences in Bendeka's formulation would not impact the drug's safety or effectiveness. Eagle conducted an 83-subject study, which demonstrated the bioequivalence[1] of Bendeka to Treanda as well as the safety and tolerability of the novel Bendeka formulation.

40. Eagle dedicated significant resources, including making an approximately $30 million investment, to formulate and test Bendeka.

B. FDA Granted Orphan Drug Designation for Bendeka

41. Eagle submitted requests for orphan drug designation for Bendeka for indolent B-cell NHL on March 5, 2014 and for CLL on March 14, 2014. Because Bendeka has the same active moiety and is approved for the same orphan indications as Treanda, Bendeka is considered to be the "same drug" as Treanda under FDA's designation regulations despite the differences between the formulations of the two drugs. 21 C.F.R. §§ 316.24(b), 316.25(a)(3), 316.3(b)(14). Accordingly, Eagle's designation requests included two lengthy submissions establishing a plausible hypothesis that Bendeka, if approved, would be clinically superior to Treanda based on its improved formulation. These submissions cited dozens of scientific studies and other sources

[1] Generally speaking, two drugs are considered bioequivalent if there is "[no] significant difference in the rate and extent to which the active ingredient ... becomes available at the site of drug action when administered at the same molar dose under similar conditions." 21 C.F.R. § 320.1(e).

of clinical information to establish that if Eagle were to obtain approval of a bendamustine product with the particular novel characteristics being proposed, that product would be clinically superior to Treanda. The characteristics Eagle proposed in that submission were the exact characteristics of now-approved Bendeka: a formulation that takes less time to administer, requires less fluid and sodium to be injected into the patient, eliminates the causes of certain Treanda preparation and dosing errors, and reduces impurities. Relying on an extensive review of the scientific literature, Eagle provided scientific justifications for why each of these characteristics would provide "greater safety in a substantial portion of the target populations," and/or "a major contribution to patient care" in satisfaction of FDA's clinical superiority standard. 21 C.F.R. § 316.3(b)(3)(ii)-(iii). The submissions also described the data that Eagle intended to generate during the Bendeka drug development and approval process.

42. FDA granted orphan drug designation for Bendeka for both CLL and indolent B-cell NHL on July 2, 2014.[2] In FDA's letters granting designation, FDA acknowledged, "[y]our designation is based on a plausible hypothesis that your drug may be clinically superior to the same drug that is already approved for the same orphan indication. *See* 21 C.F.R. § 316.3(b)(3) & (14) (defining 'clinically superior' and 'same drug' in this context)." FDA did not specify that it had found any of the bases Eagle had presented in its designation request to be inadequate or implausible.

43. Although FDA's orphan drug designation entitled Bendeka to exclusivity upon approval, in an abundance of caution, Eagle nonetheless submitted additional information the

[2] The indolent B-cell NHL designation was granted for "treatment of follicular lymphoma, treatment of small lymphocytic lymphoma, treatment of lymphoplasmacytic lymphoma, treatment of splenic marginal zone lymphoma, treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoma tissue (MALT), and treatment of nodal marginal zone lymphoma (collectively indolent B-cell non-Hodgkin's lymphoma)." Collectively, these diseases are referred to as "indolent B-cell NHL."

following year regarding FDA's extra-statutory clinical superiority requirement. Because FDA evaluates that requirement in a regulatory black box—there is no guidance document or regulation that purports to govern what type of additional information or data is necessary—Eagle repeatedly reached out to the agency to ensure that the data it submitted during the designation process and in the Bendeka approval process would be regarded as sufficient. FDA refused to provide any additional detail on these topics. When Eagle requested a meeting to determine whether the agency would require additional data or information beyond what Eagle had notified FDA in its designation requests that it planned to generate and submit in the Bendeka approval process, FDA denied the request. The agency stated that it would not address the issue of clinical superiority for exclusivity purposes until *after* approving Bendeka as safe and effective.

C. FDA Approved Bendeka and Withheld Orphan Drug Exclusivity

44. FDA approved Bendeka as safe and effective for the treatment of CLL and indolent B-cell NHL on December 7, 2015. Although both indications had been orphan-designated, FDA did not provide Eagle with written notice recognizing exclusivity at the time of approval or any time thereafter. Neither did FDA publish information about orphan exclusivity in the "Approved Drug Products With Therapeutic Equivalence Evaluations" (the "Orange Book") which FDA regulations require of the agency when a drug is approved for a designated orphan drug that qualifies for exclusive approval. 21 C.F.R. § 316.34(b).

45. Two days after the Bendeka approval, on December 9, 2015, Eagle contacted FDA to inquire about the status of FDA's expected publications regarding Bendeka's orphan drug exclusivity. FDA informed Eagle that it was moving forward with another analysis of whether Eagle had demonstrated the clinical superiority of Bendeka over Treanda. In subsequent

correspondence, Eagle informed FDA that the Orphan Drug Act required FDA to recognize orphan drug exclusivity for Bendeka, beginning on the date that FDA approved the drug for its orphan-designated indications. Eagle also informed FDA of its belief that, in any event, the information it had already submitted demonstrated clinical superiority, and Eagle offered to provide additional information to FDA as needed. However, throughout these communications, the agency continued to withhold any guidance as to what specific measures would be required in order for Bendeka to receive orphan drug exclusivity under FDA's current regulatory scheme.

46. Nevertheless, over the next three months, Eagle provided supplemental information to FDA in an effort to satisfy any potential outstanding concerns regarding Bendeka's clinical superiority. On January 29, 2016, Eagle attended an in-person meeting with FDA to present the benefits of Bendeka and the requirements of the Orphan Drug Act, as well as to answer any questions from the agency. Shortly thereafter, on February 8, 2016, Eagle submitted a supplemental analysis of the clinical trial data that it had submitted to FDA as part of the Bendeka approval process, which showed Bendeka's greater safety and major contribution to patient care through a demonstrably lower incidence of adverse advents.

47. However, on March 24, 2016, FDA issued a formal letter ruling to Eagle denying orphan drug exclusivity for Bendeka on the basis that (a) Eagle had not provided sufficient evidence that Bendeka is clinically superior to Treanda, and (b) Bendeka is thus not entitled to exclusivity under the Orphan Drug Act. FDA stated that it was not bound to follow *Depomed*, and it reasserted the very arguments for its authority to impose the clinical superiority demonstration requirement that Judge Jackson found unpersuasive in *Depomed*. In sum, FDA stated: "[W]e continue to believe that the *Depomed* court erred in not deferring to FDA's

statutory interpretation, and we therefore deny your request for exclusivity on that ground." Letter Ruling at 39.

48. Finally, the letter ruling rejected the same scientific underpinnings for each of the hypotheses of clinical superiority that FDA had accepted at the designation stage, reversing the position the agency took in granting the designation, when it *accepted* these premises and thereby induced Eagle to continue developing Bendeka as planned. In doing so, FDA claimed that Eagle had failed to meet the agency's secret and unknowable regulatory criteria for a demonstration of clinical superiority. *Id.* at 30 ("Eagle has not provided enough data to support that any of the supposed benefits of Bendeka over Treanda meets the applicable regulatory standard of clinical superiority."). The same day FDA issued its letter ruling, the agency approved at least two applications for drugs for the same rare diseases that will compete with Bendeka.

CLAIMS FOR RELIEF

CLAIM 1

(Violation of the Administrative Procedure Act)

49. Eagle reasserts and incorporates by reference all of the above allegations.

50. The Administrative Procedure Act prohibits Defendants from acting in a way that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law, or that is in excess of statutory jurisdiction or authority or short of statutory right. 5 U.S.C. § 706(2)(A), (C).

51. Notwithstanding that the plain language of the Orphan Drug Act and this Court's decision in *Depomed* require Defendants to grant orphan drug exclusivity upon approval of a previously designated orphan drug, Defendants have impermissibly denied Bendeka orphan drug exclusivity. Defendants' denial of orphan drug exclusivity for Bendeka upon approval of the

drug for its orphan-designated indications exceeds Defendants' statutory authority and is otherwise not in accordance with the law.

52. Defendants' approval of Bendeka for the treatment of CLL and indolent B-cell NHL, and their subsequent denial of the orphan drug exclusivity that such approval automatically triggered, constitutes final agency action. 5 U.S.C. § 704.

53. Eagle has exhausted its administrative remedies, or, to the extent that it has not, is not required to exhaust its administrative remedies because doing so would not further the goals that exhaustion is designed to further.

54. Eagle has no adequate remedy at law. 5 U.S.C. § 704.

CLAIM 2

(Violation of the Administrative Procedure Act)

55. Eagle reasserts and incorporates by reference all of the above allegations.

56. The Administrative Procedure Act prohibits Defendants from acting in a way that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law, or that is in excess of statutory jurisdiction or authority or short of statutory right. 5 U.S.C. § 706(2)(A), (C).

57. After granting Bendeka orphan drug designation based upon Eagle's submissions at the designation stage, Defendants later impermissibly reversed their position regarding what constitutes a clinically superior drug. In doing so, Defendants impermissibly applied a standardless post-designation requirement for proof of clinical superiority. Defendants' change in position, application of their post-designation requirement, and ultimate determination that Bendeka is not entitled to orphan drug exclusivity were arbitrary and capricious, and an abuse of discretion.

58. Defendants' approval of Bendeka for the treatment of CLL and indolent B-cell NHL, and their subsequent denial of the orphan drug exclusivity that such approval automatically triggered, constitutes final agency action. 5 U.S.C. § 704.

59. Eagle has exhausted its administrative remedies, or, to the extent that it has not, is not required to exhaust its administrative remedies because doing so would not further the goals that exhaustion is designed to further.

60. Eagle has no adequate remedy at law. 5 U.S.C. § 704.

PRAYER FOR RELIEF

WHEREFORE, Eagle respectfully requests that this Court enter judgment in its favor and prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that:

   a. Defendants' refusal to grant orphan drug exclusivity to Eagle for Bendeka exceeds their statutory authority, and is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law;

   b. Eagle is entitled to seven years of orphan drug exclusivity for Bendeka for the treatment of CLL and indolent B-cell NHL starting from December 7, 2015, the date Defendants approved Bendeka for these indications; and

   c. FDA's regulations at 21 C.F.R. §§ 316.3(b)(12), 316.31(a), 316.34(a), (c) are invalid under the FDCA, as amended by the Orphan Drug Act, insofar as they purport to permit Defendants to not recognize orphan drug exclusivity for Bendeka.

B. An order directing Defendants to recognize that Eagle 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, in accordance with 21 C.F.R. § 316.34(a), (b).

C. Injunctive relief effectuating Eagle's orphan drug exclusivity by enjoining Defendants from approving any other drug covered by Eagle's exclusivity for the treatment of CLL or indolent B-cell NHL until December 7, 2022.

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

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

Dated: April 27, 2016

Respectfully submitted,

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