IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

EAGLE PHARMACEUTICALS, INC., Plaintiff, 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 United States Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendants.	Civil Action No.: 16-0790-GK Judge Gladys Kessler PUBLIC VERSION

DEFENDANTS' RESPONSE TO PLAINTIFF'S
MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION

Pursuant to the Court's order dated August 9, 2016, and Rule 56 of the Federal Rules of Civil Procedure, defendants, the United States Department of Health and Human Services, Sylvia Burwell, in her official capacity as Secretary, the United States Food and Drug Administration, and Robert Califf, in his official capacity as Commissioner, (collectively, FDA), respectfully request that the Court deny the motion for summary judgment filed by plaintiff, Eagle Pharmaceuticals, Inc. (Eagle), sustain the FDA decision at issue, and enter judgment in FDA's favor.

In support of this motion, we rely on the administrative record submitted in this matter, the underlying administrative decision, and the following brief.

Respectfully submitted,

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August 19, 2016

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INTRODUCTION

Eagle asks the Court to create a monopoly for Eagle's drug, Bendeka, by finding that the drug is entitled to a seven-year period of market exclusivity. *See generally* Pl. Br. at 1–6, July 11, 2016, ECF No. 19. This desire for a monopoly is understandable; Eagle stands to reap a tremendous windfall if it can exclude potential competitors from the market. The problem, however, is that from a clinical standpoint, Bendeka is the same as an existing drug—one that was previously developed by another company and itself protected from competition for seven years. In other words, Eagle wants to obtain a successive seven-year monopoly for nothing more than a minor tweak to an existing therapy. Relying on its established regulatory framework, the FDA properly found that the Orphan Drug Act does not provide such super-monopolies, and that Eagle's drug is not entitled to the exclusivity that Eagle seeks.

In challenging this decision, Eagle contends that the plain language of the Orphan Drug Act, 21 U.S.C. §§ 360aa–ee, *mandates* exclusivity for Bendeka. Not so. Congress enacted the Orphan Drug Act to reward meaningful advances in drug development for "previously untreated rare diseases" with a seven-year exclusivity period. Because the language Congress used is ambiguous, FDA has interpreted this provision to confer only one seven-year period of exclusivity to the first sponsor to obtain approval of an orphan drug for a particular rare disease. This interpretation is consistent with both the text and the policy of the Orphan Drug Act—and has provided carefully crafted incentives for orphan drug development for over twenty years, resulting in an enormous jump in the number of available drugs for patients with rare diseases. Members of Congress have expressed this same interpretation of the statute on a number of occasions, as have two other courts.

Eagle's interpretation, by contrast, is based on a misreading of the statute's text and purpose. If accepted, it would turn the orphan-drug exclusivity provision into a gift that keep on giving

successive seven-year monopolies to formulation changes that provide no material benefit to patients over an existing drug. This reading would grant an exclusivity windfall to drug sponsors—to the detriment of seriously ill cancer patients who, as a result, must continue to pay monopoly prices for minor variations of the same drugs.

The Court should likewise reject Eagle's claims that FDA's process for deciding clinical superiority is constitutionally deficient along with its suggestion that FDA's scientific experts erred by concluding that Eagle's bendamustine product, Bendeka, is not clinically superior to a previously-approved bendamustine product, Treanda. FDA regulations afford considerable process to Eagle for seeking administrative review of the Agency's decision; Eagle's choice not to take advantage of that process does not make FDA's process constitutionally deficient. Further, FDA's scientific determination is entitled to the utmost deference, and Eagle fails to raise any credible challenge to the agency's determination that the Bendeka formulation does not provide clinically superior benefits to patients within the meaning of FDA's regulations.

For all these reasons, the Court should deny Eagle's motion for summary judgment, and enter judgment in favor of the FDA.

BACKGROUND

I. STATUTORY AND REGULATORY FRAMEWORK

The facts of this case are set against a complex statutory and regulatory regime, which requires some explanation.

A. Drug Approval Process

As a general matter, pharmaceutical companies seeking to market a new drug must obtain FDA approval by filing a new drug application (NDA) containing extensive scientific clinical data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b), (c). Sponsors of new

drug applications may be able to delay approval of other applications for the same drug by obtaining and listing patents and qualifying for statutory bars on FDA approval (*i.e.*, exclusivities), including, among others, seven-year orphan-drug exclusivity, five-year new chemical entity exclusivity (21 U.S.C. § 355(j)(5)(F)(ii)), and three-year exclusivity for certain new clinical studies (21 U.S.C. §§ 355(j)(5)(F)(iii) & (iv)).

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) amended the FDCA to add 21 U.S.C. § 355(b)(2) and 21 U.S.C. § 355(j), which provide abbreviated pathways for § 355(b)(2) NDAs and Abbreviated New Drug Applications (ANDAs), respectively. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions. H.R. Rep. No. 98-857 (June 21, 1984).

A stand-alone NDA is submitted under 21 U.S.C. § 355(b)(1) and supported entirely by studies that the sponsor owns or to which it has a right of reference. Like a stand-alone NDA, a section 355(b)(2) NDA must meet both the "full reports" requirement in 21 U.S.C. § 355(b)(1)(A) and the same safety and effectiveness standard as a 21 U.S.C. § 355(b)(1) NDA. Unlike a stand-alone NDA, in a section 355(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval may be provided by investigations (1) "not conducted by or for the applicant" and (2) "for which the applicant has not obtained a right of reference or use." A section 355(b)(2) applicant may rely on sources such as its own studies; published reports of studies to which the applicant has no right of reference; the Agency's findings of safety and/or effectiveness for one or more previously approved drugs (a "listed drug"); or a combination of these sources to support approval.

The Hatch-Waxman Amendments also permit manufacturers to submit ANDAs for generic versions of approved drug products. Rather than submit clinical data, ANDA applicants rely on FDA's previous finding that the product approved under the relied-upon NDA (also known as the reference listed drug) is safe and effective. To obtain approval, the ANDA applicant needs only to establish that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling (with certain permissible differences), and conditions of use as the reference listed drug, and that it is bioequivalent to that drug.

FDA approves § 355(b)(2) NDAs and ANDAs when they have met all requirements for approval and any applicable patent and exclusivity periods have expired or have otherwise ceased to be a barrier.

B. Orphan Drug Act

One year prior to enacting the Hatch-Waxman Amendments, Congress enacted the Orphan Drug Act (Public Law 97-414) in 1983 to provide incentives to develop drugs to treat rare diseases and conditions. *See* 21 U.S.C. § 360aa *et seq*. As defined in 21 U.S.C. § 360bb, 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.*

The Orphan Drug Act provides incentives such as tax credits for clinical testing, research grants, exemption from application user fees, and the possibility of seven years of orphan-drug exclusivity to address the failure of the market to provide the correct incentives for drug

development. *See* AR 5–6.[1] To obtain many of these incentives, sponsors of drugs for rare diseases must first seek and obtain "designation" for their drugs under 21 U.S.C. § 360bb; *see also* 21 C.F.R. §§ 316.31 and 316.34. 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 C.F.R. § 316.20(b)(3); *see generally* 21 C.F.R. §§ 316.20 and 316.21.

When a drug is otherwise the same (*i.e.*, contains the same active moiety or principal molecular structural features) as "an already approved drug" for the same use, the request for designation must contain "a plausible hypothesis that its drug may be clinically superior to the first drug." 21 C.F.R. § 316.20(a) and (b)(5). Thus, sponsors are able to secure the benefits of designation such as tax credits for clinical testing, which help defray the costs of development at an early stage of the process, without having to prove clinical superiority before testing is complete.

C. Orphan-Drug Exclusivity

One of the major incentives of the Orphan Drug Act—and the provision at issue here—is orphan-drug exclusivity. The statute generally grants seven-year orphan-drug exclusivity to designated drugs for orphan indications upon approval for those indications, during which FDA will not approve the same drug for the same indication from another sponsor. *See* 21 U.S.C. § 360cc. In doing so, the statute refers to the drug that is approved and to subsequent "such" drugs whose approvals for the same indication are blocked for seven years after the approval of the designated drug. The statute, however, is silent with respect to whether there may be multiple exclusivity periods for the same drug.

[1] "AR __" refers to the corresponding page in the administrative record filed in this case.

After extensive consideration of the Orphan Drug Act's text and purpose, FDA issued a final rule in 1992 to set out the agency's interpretation to implement the designation and exclusivity provisions of the Orphan Drug Act. Among other things, the 1992 final rule describes the rules that apply when a sponsor of a subsequent version of a drug seeks designation and exclusivity for the same indication as a previously approved drug by establishing the clinical superiority framework. Under this "clinical superiority" framework, a sponsor seeking to market another version of an already approved drug must show that its version is clinically superior to that previously approved drug to avoid being the same "such drug" and potentially subject to being blocked by the already approved drug's orphan-drug exclusivity period. *See* 21 C.F.R. § 316.3(b)(14) (defining "same drug," and excluding a drug from that definition if it is clinically superior). A clinically superior drug, under this framework, is therefore considered to be different from the previously approved drug, even if they share the same chemical structure. In other words, a drug must be demonstrated to be clinically superior in order to "break" existing orphan-drug exclusivity of a previously approved same drug, as well as to obtain orphan-drug exclusivity in its own right.[2] This regulatory framework ensures that there will not be serial, potentially infinite, seven-year periods of orphan-drug exclusivity for the same drug (*i.e.*, a drug that is otherwise the same drug as a previously approved drug, is approved for the same indication as the previously approved drug, and has not been shown to be clinically superior).

FDA's regulations set out a two-step process for showing clinical superiority that is commensurate with the available level of data at each step. To obtain designation (typically sometime early in product development), the sponsor need only present a plausible hypothesis of clinical superiority. At this early stage, the sponsor will generally not have completed the studies

[2] FDA amended its clinical superiority framework in 2013 to clarify its long-standing view that this framework requires sponsors to demonstrate clinical superiority over a previously approved drug to obtain exclusivity. 78 Fed. Reg. at 35,132 (AR 1500).

necessary for approval, and would have difficulty actually demonstrating clinical superiority. Moreover, sponsors can take advantage of the early-stage development incentives associated with designation, like clinical trial tax credits, to complete the studies necessary for approval and for demonstrating superiority. Clinical superiority must then be *proven* at the approval stage to qualify for seven-year orphan-drug exclusivity to ensure that the drug receiving this benefit is not "the same drug" as the previously approved drug and to justify the significant monopoly benefits of exclusivity.

A sponsor may demonstrate clinical superiority by showing that, as compared to the previously approved drug, its drug provides a "significant therapeutic advantage" by providing greater effectiveness or safety or by making a "major contribution to patient care." 21 C.F.R. § 316.3(b)(3). To show greater effectiveness, sponsors will in most cases need direct comparative clinical trials. 21 C.F.R. § 316.3(b)(3)(i). For greater safety, FDA has explained that the standard is similar to the standard applicable for claims in prescription drug labeling. 57 Fed. Reg. at 62077 (AR 1419). FDA's regulation states that "[i]n some cases direct comparative clinical trials would be necessary." 21 C.F.R. § 316.3(b)(3)(ii).

FDA's regulation clarifies that major contribution to patient care is reserved for "unusual cases." 21 C.F.R. § 316.3(b)(3)(iii); *see also* 56 Fed. Reg. 3343 (AR 1409) (characterizing major contribution to patient care as "a narrow category"). FDA expressed particular concern that this standard "is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated." 56 Fed. Reg. at 3343 (AR 1409). The final determination is made on a case-by-case basis. 57 Fed. Reg. 62,079 (AR 1421).

To determine whether a sponsor has demonstrated clinical superiority, FDA's Office of Orphan Products Development (OOPD) consults with the specific review division that approved the

relevant applications. OOPD considers that consult and applies its own scientific, medical, and regulatory expertise in making a decision about clinical superiority.

D. The *Depomed* Decision

FDA has employed its clinical superiority regime for over twenty years, and that regime has withstood challenge. *See Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001). However, in 2013, a company called Depomed challenged the regime after its drug, Gralise (which was the same as a previously-approved drug, Neurontin), did not qualify for orphan-drug exclusivity. *Depomed, Inc. v. U.S. Dep't of Health & Human Servs*., 66 F. Supp. 3d 217, 220 (D.D.C. 2014). Among other things, Depomed argued that exclusivity was automatic under the plain language of the orphan-drug exclusivity provision because Gralise was both designated and approved for an orphan indication. *Id.* The Court agreed, and ordered FDA to recognize exclusivity for Gralise, noting that the case did "not raise the specter of the 'serial exclusivity' scenario," because the first approved drug in that case did not have exclusivity. *Id.* at 237. In doing so, the Court dismissed FDA's policy arguments because, in its view, FDA had control over the timing of designation and approval, and could thereby "easily remedy" its concerns about multiple exclusivity periods. *Id*. at 237. The Court also found that the facts in *Depomed* were *sui generis* and thus that the "absurd" result of serial exclusivity "rarely, if ever, actually occurs." *Id.* at 236–37.

FDA complied with the district court order for *Depomed*. After doing so, it published a notice in the Federal Register announcing that it disagreed with the decision and stating that it would continue to implement its long-standing clinical superiority framework (for both the older regulations applicable in *Depomed*, which cover applications where the request for designation was submitted before August 12, 2013, and the newer regulations) to designation and exclusivity decisions. *See* 79 Fed. Reg. 76,888 (Dec. 23, 2014) (AR 1510).

II. STATEMENT OF FACTS

In 2008, FDA approved Cephalon Inc.'s NDA 022249 for Treanda (bendamustine hydrochloride) for chronic lymphocytic leukemia (CLL) and NDA 022303 for indolent B-cell non-Hodgkin lymphoma (NHL). AR 10. Treanda received orphan drug exclusivity for each of these indications because Treanda was designated for these indications and was the first bendamustine approved for these indications. *Id.* The exclusivity periods were extended by six months by a period of pediatric exclusivity, so that the exclusivity period for the CLL indication expired on September 20, 2015, and the period for the NHL indication expired on May 1, 2016. *Id.*

Cephalon is now a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd., which markets Treanda. *Id*. In 2015, just when orphan exclusivity for Treanda was expiring, Treanda was Teva's second-highest grossing drug, with $741 million in sales.[3] Treanda was previously marketed in two different formulations: a lyophilized powder (reportedly about 15% of the market) and a solution (about 85% of the market). AR 492. Teva has since partnered with Eagle to market Bendeka, which it launched on January 28, 2016, with the expectation that it will replace the liquid version of Treanda. AR 11–12.[4] Notably, Eagle states that Bendeka is a "line extension developed for Teva to replace Treanda," that it expects "near-complete conversion to Bendeka," and has a "shared goal with Teva of 90% market share." Eagle Pharmaceuticals Corporate Overview (Aug. 2016), *available at* https://www.sec.gov/Archives/edgar/data/827871/000082787116000077/egrxinvestorpresentation.htm; Eagle Pharmaceuticals Corporate Overview June 2016, *available at*

[3] *See* Teva 2015 Annual Report at F-63, available at http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-financials.

[4] *See also* Eagle Pharmaceuticals, Inc. Form 8-K (Feb. 20, 2015), Item 1.01 Entry into a Material Definitive Agreement, *available at* http://www.sec.gov/Archives/edgar/data/827871/000110465915012666/a15-5072_18k.htm.

http://investor.eagleus.com/sites/eaglepharm.investorhq.businesswire.com/files/doc_library/file/EGRX_Investor_Presentation_06_06_16_FINAL.pdf, at 4 (Eagle June Overview).

Eagle holds NDA 208194 for Bendeka, which is also a bendamustine product approved for the same CLL and NHL indications as Treanda. AR 11. It is the same drug as Treanda because it contains the same active moiety (bendamustine), but has a different formulation: 50 mL to be administered over 10 minutes for Bendeka, in comparison to 500 mL to be administered between 30 and 60 minutes for Treanda. AR 10. Eagle requested orphan-drug designation for Bendeka for both the NHL and CLL indications; because Bendeka is the same drug as Treanda, FDA required Eagle to present a plausible hypothesis of clinical superiority. AR 63–84; AR 85–127. On July 2, 2014, FDA granted orphan-drug designation for Bendeka for NHL and CLL after concluding that Eagle had provided a plausible hypothesis that the lower volume of fluid in Bendeka could result in greater patient safety. AR 328–32. The designation letters sent to Eagle stated that in order to obtain orphan-drug exclusivity upon approval, the sponsor would need to demonstrate, at approval, that the proposed drug (Bendeka) is clinically superior to the already approved same drug (Treanda). AR 328, 331.

Rather than submitting a full suite of non-clinical and clinical studies as would be required for a stand-alone NDA, Eagle filed a § 355(b)(2) application referencing FDA's finding of safety and efficacy for Treanda, and conducted a single clinical study in 81 patients to show that its formulation was bioequivalent to Treanda. AR 11. Eagle was blocked from approval by Treanda's orphan-drug exclusivity until September 20, 2015 for CLL, and May 1, 2016 for NHL. AR 10. Teva, however, waived its orphan-drug exclusivity for Treanda for the NHL indication. AR 11. Accordingly, on December 7, 2015, FDA approved Bendeka for both CLL and NHL. *Id.*

In an attempt to obtain its own orphan-drug exclusivity period, Eagle submitted information in support of its claim that Bendeka is clinically superior to Treanda on several different grounds. AR 426–83; 493–504. Eagle also relied on the *Depomed* decision and argued that Bendeka was automatically entitled to exclusivity under the statute even without proving clinical superiority over Treanda. AR 432–33. Eagle met with FDA officials on January 29, 2016 to discuss its claim of clinical superiority. AR 484–92.

In a comprehensive letter decision issued on March 24, 2016, FDA rejected Eagle's arguments. *See generally* AR 1. Specifically, after carefully evaluating all the evidence, FDA found that Eagle had failed to demonstrate clinical superiority for Bendeka, meaning that the drug did not qualify for orphan-drug exclusivity under FDA's established regulatory framework. *See id*. In making this decision, FDA carefully evaluated each of nine separate bases on which Eagle claimed clinical superiority. AR 13–32. FDA also rejected Eagle's *Depomed* arguments, explaining that the statute is ambiguous and that FDA's rules give proper effect to its language and purpose. AR 37–38. As FDA noted, its existing clinical superiority framework avoids serial exclusivity, while providing appropriate incentives to develop clinically superior versions of already approved drugs. AR 36.

Separately, Teva attempted to delay generic approvals of ANDAs referencing Treanda. FDA denied a citizen petition from Teva and approved two ANDAs referencing Treanda for the CLL indication on March 24, 2016. *See* AR 1557–72. These ANDAs are approved for the lyophilized version of Treanda, which reportedly makes up about 15% of the bendamustine market. FDA has since approved two additional ANDAs referencing Treanda. *See* Electronic Orange Book, *available at* http://www.accessdata.fda.gov/ scripts/cder/ob/ docs/tempai.cfm (Orange Book).

Eagle filed this lawsuit on April 27, 2016, seeking a declaration that Eagle is automatically entitled to seven years of orphan-drug exclusivity, and that FDA's regulations implementing the

clinical superiority framework are invalid. Eagle also alleges that FDA's process for deciding clinical superiority for Bendeka was constitutionally deficient, and challenges FDA's scientific determination that Bendeka is not clinically superior to Treanda.

ARGUMENT

I. STANDARD OF REVIEW

Eagle has brought this case under the Administrative Procedure Act (APA). Pursuant to § 706 of the APA, the Court may set aside agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). As courts have repeatedly explained, this standard is "a narrow one," *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971) (citations omitted), and "highly deferential," *Am. Horse Prot. Ass'n v. Yeutter*, 917 F.2d 594, 596 (D.C. Cir. 1990). The reviewing court must ensure that the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (citations and quotation marks omitted). At the same time, however, it must "presume the validity of agency action," *Am. Horse Prot. Ass'n*, 917 F.2d at 596, and may not "substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. Indeed, as this Court has explained, "[t]he proper inquiry is not . . . whether there is sufficient evidence in the record to support the opposing conclusion, but rather whether the choice made by the agency has a rational basis in the evidence." *Cumberland Pharms. Inc. v. FDA*, 981 F. Supp. 2d 38, 51 (D.D.C. 2013) (internal quotes and citations omitted).

When, as here, an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded even greater deference. *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) (The FDA is

"peculiarly suited" to evaluate conflicting scientific reports, a matter "not . . . well left to a court without chemical or medical background," because it "necessarily implicates complex chemical and pharmacological considerations."). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (*quoting Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *see also Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise.").

Meanwhile, if the agency's decision turns on the interpretation of a statute, the Court must apply the canonical two-step framework articulated in *Chevron, USA., Inc. v. NRDC*, 467 U.S. 837 (1984). Under this framework, the Court must first determine "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842–43. But if the statute is silent or ambiguous on the specific issue, the Court must defer to any agency interpretation that is based on a permissible construction of the statute. *Id.* at 843. An agency's construction is permissible "unless it is arbitrary or capricious in substance, or manifestly contrary to the statute." *Mayo Found. For Med. Educ. & Research v. United States*, 562 U.S. 44 (2011) (citations and internal quotation marks omitted).

II. THE ORPHAN DRUG ACT DOES NOT CREATE AUTOMATIC EXCLUSIVITY FOR SUBSEQUENT SAME DRUGS LIKE BENDEKA

First off, Eagle is wrong to insist that the terms of the Orphan Drug Act *entitle* its drug to exclusivity. They do not.

The statute, at 21 U.S.C. § 360cc(a), sets forth two conditions that a drug must satisfy to obtain exclusivity. However, Congress did not define how broadly that exclusivity extends—and did not specify what happens after a drug's exclusivity expires. These gaps required FDA to promulgate substantive rules based on the statute's structure and purpose. Eagle may be unhappy that these rules deny automatic exclusivity to Bendeka—a drug that FDA has scientifically determined to be the same as one that was previously approved and protected by a period of orphan-drug exclusivity. But the case on which Eagle builds its argument was wrongly decided, and Eagle cannot show error in FDA's approach.

A. The Exclusivity Provision Requires Interpretation

The gaps in section 360cc—and the need for agency clarification—become apparent when we consider the language that Congress used in the section's first paragraph.

Congress provided that FDA's approval of an orphan drug—that is, a drug designated to treat a disease or condition affecting less than 200,000 people—would preclude FDA from "approv[ing] another application . . . for such drug for such disease or condition . . . until the expiration of seven years . . . ." 21 U.S.C. § 360cc(a). The implication is that the creator of an orphan drug can expect that FDA will not allow another "such drug" to enter the market for seven years.[5] Immediately, however, two things are unclear from Congress's formulation.

[5] The second part of section 360cc, section 360cc(b), lists instances when FDA may disregard, or break, previously-granted exclusivity. *See* 21 U.S.C. § 360cc(b). However, that section does not speak to the conditions for *granting* exclusivity, and so is not relevant here.

First, what did Congress mean when it said "such drug"? The term appears to suggest a drug that is the same as the "drug" referred to in the first part of the paragraph. But Congress was silent on what makes two drugs the same. Two drugs may have the same chemical structure; they may operate on the same physiological pathways; or they may have the same effects. From early on, sponsors disagreed about what Congress meant. *See Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 313 (D.D.C. 1987) (noting that the statute does not define what makes two drugs the same).

This first question about section 360cc's scope leads to the second: namely, what should FDA do with drugs "such" as the protected orphan drug *after* the "expiration of seven years"? One possibility is that section 360cc looks forward into perpetuity, and sets out the *entirety* of exclusivity protections that a drug and all future "such drug[s]" can receive. Under this reading, once protections for a drug expire, the FDA may approve applications for *all future* "such drug[s]" without any further restriction—meaning that, as a corollary, no future "such drug[s]" may receive their own exclusivity periods. This reading is consistent with the "expiration" of exclusivity after seven years. *See* 21 U.S.C. § 360cc(a). Alternatively, section 360cc can be read to carry no future implication—meaning all those other "such drug[s]" could be eligible for their *own* seven-year protection periods, creating potentially limitless, sequential blocks of exclusivity for what is essentially the same drug. This latter interpretation is, in essence, the one Eagle urges. *See generally* Pl. Br. at 17–26. Critically, however, neither of these readings is *compelled* by section 360cc's language. Indeed, although Congress's reference to an "expiration" of exclusivity supports FDA's interpretation, section 360cc does not explicitly address the point.

Congress, of course, could have resolved these questions. It could have, for example, specified that the grant of exclusivity for a drug creates a one-time bar for all other drugs with the same chemical structure, and then cannot be used to benefit drugs with the same chemical structure

again. Or it could have provided that exclusivity creates seven years of market protection for a drug that is designated and approved, and can be invoked repeatedly for all future "such" drugs in perpetuity, essentially providing for an indefinite period of exclusivity for each orphan drug. It did neither. Instead, it stayed silent.

To be sure, Congress *did* later indicate what it thought section 360cc meant in considering later revisions to the statute. In fact, that legislative history is replete with statements suggesting that Congress viewed exclusivity as a benefit that would only apply *once* to a particular drug. *See, e.g.*, 136 Cong. Rec. H. 5799 ("The primary incentive in the [statute] is the grant of 7 years of market exclusivity to the *first* company that develops a new drug for a rare disease.") (statement of Rep. Nielson) (July 30, 1990) (emphasis added); 136 Cong. Rec. H. 11931 (Oct. 23, 1990) (statement of Rep. Bliley) ("The primary incentive in the act is the grant of 7 years of market exclusivity to the first company that develops a new drug for a rare disease."); 132 Con. Rec. S. 11944 (Aug. 15, 1986) (statement of Sen. Hatch) ("[U]nder the present act, only one company receives a 7-year exclusive marketing right"); *see also* 137 Cong. Rec. H. 73 (Jan. 3, 1991) (memorandum of disapproval of proposed legislation from President George Bush) ("Under current law, firms may apply to develop the same orphan drug, but only the first firm to have its drug approved receives market exclusivity.").

Similarly, early decisions that examined section 360cc viewed its language as ambiguous with respect to what makes two drugs the same for purposes of exclusivity, but fairly clear in its suggestion that the seven-year exclusivity period "is reserved for the *first* manufacturer to receive full FDA approval of its drug as safe and effective for commercial sale." *Genentech*, 676 F. Supp. at 304 (also noting that FDA had a "statutorily imposed" "responsibility" to set down "a "universal rule for determining whether two drugs are 'different' for purposes of the Orphan Drug Act") (emphases added); *see also Baker Norton*, 132 F. Supp. 2d at 36–37 (observing that the framework creates a

regime where "market exclusivity rights are *limited in time* to seven years, and granted only for a particular drug for a particular use") (emphasis added). Though the question of whether the unambiguous language of section 360cc actually permitted multiple exclusivity periods was not squarely presented in those cases, it is notable that the Courts' understanding of the section accorded with FDA's interpretation and Congress's understanding.

Taken together, this history strongly suggests that the best reading of section 360cc is one that does not permit multiple exclusivity periods for the same drug. Nonetheless, because Congress did not translate this intent into the statute's unambiguous text, no conclusion about the scope and availability of exclusivity for a second-in-line drug (like Bendeka) can be drawn from the statute alone; it does not automatically flow from the statute, as Eagle contends.[6] Agency interpretation is required.

B. FDA Promulgated Reasonable Rules To Interpret The Statute

Because Congress did not translate its clear intent into the language of section 360cc, the task of interpreting the section fell to FDA. *See, e.g.*, *Genentech*, 676 F. Supp. at 313 (noting that it is FDA's responsibility to define the scope of Orphan Drug Act exclusivity).

As the Supreme Court famously explained in *Chevron*, where a "statute is silent or ambiguous with respect to the specific issue," the agency has great discretion to deal with the issue in any way that "is based on a permissible construction" of the statute's text. *Chevron*, 467 U.S. at 842–43 (1984). Absent "unambiguous statutory language to the contrary or unreasonable resolution

[6] In this way, section 360cc is similar to another statutory provision which Courts in this Circuit have recognized to be ambiguous regarding the number of exclusivity periods it provides. *See, e.g.*, *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1065 n.4 (D.C. Cir. 1998) (stating that, for a 180-day exclusivity statute, "the statute might conceivably be read to confer this 180-day [exclusivity] period on a second or third applicant in some situations"); *Apotex Inc. v. FDA*, 414 F. Supp. 2d 61, 68-70, 74 (D.D.C. 2006) (stating that the 180-day exclusivity statute "is silent regarding the issue of how many exclusivity periods may arise in connection with a single drug product . . . . because of that silence, the provision lends itself to multiple interpretations, and hence is ambiguous under *Chevron* step one").

of language that is ambiguous," the agency's "interpretation governs." *United States v. Eurodif S.A.*, 555 U.S. 305, 316 (2009); *see also Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 665 (2007). Put another way, congressional silence constitutes "an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation." *Chevron*, 467 U.S. at 842-44; *see also Eurodif*, 555 U.S. at 316 (noting that "[t]he whole point of *Chevron* is to leave the discretion provided by the ambiguities of a statute with the implementing agency").

Following this established practice, as well as explicit direction from the Court's decision in *Genentech*, which instructed FDA to interpret the ambiguity of section 360cc, FDA promulgated comprehensive implementing rules clarifying, among other things, the scope of exclusivity protections. *See generally* 21 C.F.R. § 316.31 (defining "[s]cope of orphan-drug exclusive approval"); 21 C.F.R. § 316.3 (defining various terms and provisions); *Orphan Drug Regulations, Proposed Rule*, 56 Fed. Reg. 3,338 (FDA, Jan. 29, 1991); *Orphan Drug Regulations, Final Rule*, 78 Fed. Reg. 35,117 (FDA, June 12, 2013). These rules—which have become known as the clinical superiority framework—resolve the questions that Congress did not precisely address: exactly how, when, and to which drugs section 360cc applies.

Specifically, FDA interpreted the grant of exclusivity under section 360cc to bar subsequent "approval . . . of the *same drug* for the same use or indication for [seven] years[.]" 21 C.F.R. § 316.3(b)(12) (emphasis added). And it defined "same drug" to mean "a drug that contains the same active moiety[[7]] as a previously approved drug and is intended for the same use as the previously approved drug," *unless* "the subsequent drug can be shown to be clinically superior to the first" (in which case the two "will not be considered to be the same"). 21 C.F.R. § 316.3(b)(14)(i)

[7] The term "active moiety" is defined in 21 C.F.R. § 316.3(b)(2). In layman's terms, for small molecule drugs such as bendamustine, the term means the portion of the drug that is likely to be responsible for the activity of the molecule, and ignores certain parts of the molecule that generally result in clinically insignificant changes to its chemical structure (such as salt and ester bonds).

(defining "same drug"). Finally, FDA determined that section 360cc provides only *one* period of exclusivity for a drug—and, by implication, cannot be invoked in a way that would restrict approval of other "such" drugs *after* the "expiration of seven years." Thus, FDA stated that a "designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication." 21 C.F.R. § 316.3(b)(12).

In practice, these definitions mean that FDA will grant exclusivity to the first company with a drug that is designated and approved with a particular active moiety for a specific indication. A subsequent drug with the same active moiety that is clinically superior is not blocked from approval for the same orphan indication by this first drug's exclusivity period, and is also eligible for its own exclusivity period. A subsequent drug with the same active moiety that is not clinically superior is blocked by that exclusivity period, and may not obtain its own exclusivity period before or after expiration of the first drug's exclusivity period.

This rule, FDA explained, reflects careful policy tradeoffs. 57 Fed. Reg. at 62,077 (AR 1419). As it stated, it developed the rule "by seeking as much as possible to protect the incentives of the Orphan Drug Act without allowing their abuse," and ultimately achieved "the best balance possible between protecting exclusive marketing rights and fostering competition." *Id.*; *see also* 78 Fed. Reg. at 35,127 (AR 1495) (noting that multiple periods of exclusivity for the same drug would "be at odds with the Orphan Drug Act"). The alternative would be a regime where companies could "[o]btain infinite, successive 7-year periods of exclusivity for" essentially the same drug, which would not meaningfully contribute to patient care and be at odds with the purposes of the Orphan Drug Act. 78 Fed. Reg. at 35127 (AR 1495). Indeed, as noted above, FDA's construction appears to be exactly what Congress had in mind when it passed the Orphan Drug Act.

After their passage, these regulations were challenged and upheld in the context of determining whether an existing exclusivity period blocked approval of a drug with the same active moiety. *See Baker Norton*, 132 F. Supp. 2d at 36 (upholding FDA's clinical superiority framework, stating: "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.") (internal quotations omitted). In doing so, the Court observed with approval that the framework creates a regime where "market exclusivity rights are limited in time to seven years, and granted only for a particular drug for a particular use." *Id.* at 36–37. Thus, the Court not only found the FDA's regulations defining what constitutes the same drug reasonable, but did so, in part, on the basis of the effect that the definition had on exclusivity protections. *Id.*

The upshot is that, under the FDA's rules that interpret the statutory ambiguity in section 360cc, Eagle's drug is *not* automatically eligible for exclusivity. It is undisputed that Bendeka has the "same active moiety" as Treanda, a drug that was approved in 2008, and whose relevant periods of exclusivity only expired in 2015 and 2016. *See* AR 10. Accordingly, as a matter of law, Eagle can *only* receive seven years of exclusivity if it can show that Bendeka is clinically superior—and therefore a different drug.

C. *Depomed* Misread The Statute

Eagle does not dispute that the *scope* of exclusivity established by section 360cc is ambiguous and requires interpretation. *See* Pl. Br. at 21. Nevertheless, Eagle urges the Court to follow the recent *Depomed* decision, in which this Court found FDA's rules improper under *Chevron*'s first step. *See id.* at 18–26. Respectfully, the Court should not do so: *Depomed* was wrongly decided, and its reasoning is unsound.

In *Depomed*, this Court concluded that FDA's rules are improper under the first step of *Chevron* because—in the Court's view—those rules created conditions for granting exclusivity that are inconsistent with the statute's unambiguous language. *See Depomed*, 66 F. Supp. 3d at 229. In the Court's view, the statute, on its face, stipulates only two conditions for granting exclusivity—a drug must be designated as an orphan drug, and it must be approved. *Id.* at 230. Once those conditions are satisfied, the Court reasoned, the statute leaves FDA no discretion; it is required to grant exclusivity regardless of whether a drug is the first, second, or tenth version of the same drug in line. *Id.* at 231–33.

In reaching its conclusion that the plain text compelled exclusivity, the Court acknowledged that the statute *is* ambiguous about the *scope* of exclusivity. *See id.* at 232 (finding that the use of the term "such drug" creates ambiguity about the scope of section 360cc's protections). However, the Court found that this ambiguity is wholly separate from the question of whether exclusivity can be granted in the first instance—and reasoned that the ambiguity therefore did not give FDA authority to impose any requirements not expressly specified in the statute. *Id.* Noting that the statute *already* enumerates conditions under which exclusivity would not exist, the Court declined to impute an additional exception. *See id.* at 233 (discussing 21 U.S.C. § 360cc(b)).

On its face, *Depomed*'s analysis is flawed in a number of respects. As an initial matter, the Court was wrong to assume that the *conditions* for exclusivity are wholly distinct from exclusivity's *scope*. The two are, in fact, intertwined. For example, assume FDA grants exclusivity to drug A. Another company requests approval for drug B. FDA must now determine whether A's exclusivity blocks it from approving B. That answer depends on how FDA defines the scope of A's exclusivity—that is, it depends on how FDA determines whether B constitutes the same "such drug" as A. If B *is* blocked, then it necessarily will not be eligible to obtain its *own* exclusivity. From the

standpoint of the company that produces drug B, the way FDA defines the scope of A's exclusivity (through the definition of "such drug") affects the exclusivity for B. The Court's reasoning in *Depomed* elided this relationship by construing the statute as a mathematical construct. *See Depomed*, 66 F. Supp. 3d at 230; Pl. Br. at 18–19. But statutes are not discrete mathematical equations, and their terms have to be read holistically. *Cf. PDK Labs. Inc. v. DEA*, 362 F.3d 786, 796 (D.C. Cir. 2004) (noting that a statute's terms should be read in context, considering its place in the overall statutory scheme and the problem that Congress sought to solve). Respectfully, the Court in *Depomed* failed to appreciate this fact.

Similarly, the *Depomed* Court erred by concluding that Congress's failure to address how exclusivity should work when there is a previously-approved same drug demonstrated "breadth" in the statute, rather than "ambiguity." 66 F. Supp. 3d at 231. In drawing that conclusion, the Court cited the Supreme Court's decision in *PGA Tour, Inc. v. Martin*, 532 U.S. 661, 689 (2001). However, that case does not bear the weight that the Court placed on it. In *PGA Tour*, the Supreme Court applied the Americans with Disabilities Act to require an accommodation for a disabled golfer, stating that Title III expressly applied to "golf courses" and that even if the statute were not so express, "the fact a statute can be applied in situations not expressly anticipated by Congress does not demonstrate ambiguity [but] . . . . breadth." (quoting *Pennsylvania Dept. of Corrections v. Yeskey*, 524 U.S. 206, 212 (1998)). In reaching this conclusion, the Supreme Court noted the Act's "broad mandate" and its "comprehensive character." *Id.* at 675.

Here, by contrast, there is no broad, remedial reason to impose the statutory requirements expansively. In passing the Orphan Drug Act, Congress recognized the need to reward certain

orphan drugs with exclusivity to incentivize development of drugs for presently untreated patients,[8] and it drafted a statute to provide a benefit that has an "expiration" period after seven years of exclusivity. 21 U.S.C. § 360cc(a). Serial exclusivity—of the type condoned by *Depomed*—would undercut this statutory purpose by awarding super-monopolies to drugs that have shown no material benefit to patients. Moreover, such a construction would be contrary to the established principle that monopolies should be construed narrowly. *See, e.g., Louisville Bridge Co. v. United States,* 242 U.S. 409, 417 (1917) (articulating "the universal rule that grants of special franchises and privileges are to be strictly construed in favor of the public right, and nothing is to be taken as granted concerning which any reasonable doubt may be raised").

Likewise, the Court in *Depomed* was wrong to find that the exceptions to exclusivity specified in section 360cc(b) foreclose FDA's interpretation of section 360cc(a). *See Depomed,* 66 F. Supp. 3d at 233; Pl. Br. at 20. Section 360cc(b) provides two instances for when FDA may break exclusivity: (1) when the drug's sponsor cannot make sufficient quantities of a protected drug available; and (2) when the sponsor has waived its exclusivity (as Teva did for Eagle in this case). 21 U.S.C. § 360cc(b). But, as FDA emphasized in its decision letter, these exceptions "pertain to the *breaking* of" *previously-granted* exclusivity. AR 35. They do not speak to *granting* exclusivity in the first instance. *Depomed* failed to recognize this distinction—and it appears lost on Eagle. *See Depomed*, 66 F. Supp. 3d at 233 (stating that Congress "specifically enumerated the circumstances in which exclusivity *would not result* despite the fact that a drug had been designated and approved" (emphasis added)). But the distinction is crucial. The simple fact is that section 360cc(b) speaks to a different issue entirely than the conditions for granting exclusivity—and therefore does not preclude

[8] *See Genentech,* 676 F. Supp. at 305, 312 ("The legislative history is replete with references to the fundamental need to provide treatment for presently untreated patients.") (citing H.R. Rep. 153, 99th Cong, 1st Sess.).

FDA from promulgating regulations that affect those conditions. The *Depomed* Court erred in finding otherwise, and this Court should not repeat that error.

Further, contrary to *Depomed*'s reasoning, Congress's statement that FDA "may not approve" certain new drug applications during the pendency of the same drug's exclusivity period does not remove FDA's discretion to interpret section 360cc. The phrase "may not approve" does not remove the ambiguity of section 360cc concerning the scope of exclusivity or whether there may be multiple exclusivity periods. Indeed, this Court has repeatedly deferred to FDA's interpretation of other ambiguous statutory provisions that used similar restrictive language. *See, e.g.*, *Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d 174, 176 (D.D.C. 2010), *aff'd*, 625 F.3d 760 (D.C. Cir.) (upholding FDA's approach to five-year exclusivity); *Apotex*, 414 F. Supp. 2d at 74 (upholding FDA's patent-by-patent approach to 180-day exclusivity).

Last but not least, *Depomed* short-circuited the *Chevron* step-one analysis by focusing almost exclusively on the statute's text without adequately accounting for the legislative history, structure, and purpose. *Chevron* directs courts to parse congressional intent using all "the traditional tools of statutory construction." 467 U.S. at 837 n.9; *King v. Burwell*, 135 S. Ct. 2480, 2490 (2015) (interpreting "an Exchange established by the State" to include federal exchanges: "But when read in context, 'with a view to [its] place in the overall statutory scheme,' the meaning of the phrase 'established by the State' is not so clear."); *Robinson v. Shell Oil Co*., 519 U.S. 337, 341 (1997) ("The plainness or ambiguity of statutory language is determined by reference to the language itself, the specific context in which that language is used, and the broader context of the statute as a whole."); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 (1990) (interpreting the patent provisions of the Hatch-Waxman Amendments as "not plainly comprehensible on anyone's view" and enlisting "the structure of the 1984 Act taken as a whole" to hold that the statute is ambiguous);

see also Bell Atl. Tel. Cos. v. FCC, 131 F.3d 1044, 1047 (D.C. Cir. 1997) ("The traditional tools include examination of the statute's text, legislative history, and structure . . . as well as its purpose."). As noted previously (and explained in more detail in the next section), FDA's interpretation is consistent with Congress's understanding of the Orphan Drug Act's purpose and with the entire new-drug regime. Respectfully, the Court was wrong to dismiss these considerations when interpreting the statute.

Given the errors in *Depomed*'s reasoning, FDA was justified in not following it here. Indeed, *Depomed*'s order was binding on the FDA only in *that* case, but does not bind the agency going forward. Eagle appears to suggest that it was somehow improper for the FDA to *not* treat *Depomed* as binding for all future instances. *See* Pl. Br. at 3–4. But that is simply untrue. *Depomed* is one district court case, and does not create a nationwide precedent. Indeed, *Depomed* is not even binding on this Court. FDA did the exemplary thing: after complying fully with the court's order, it published a notice in the Federal Register announcing to all *future* parties that it disagreed with *Depomed*'s reasoning, and would continue to follow its prior practice. The FDA ensured that no one would be surprised by the approach FDA was taking, and reserved for another day the possibility of correcting *Depomed*'s reasoning. This was entirely proper.

To be sure, Eagle also proffers some other cases in support of its *Chevron* step-one argument. In particular, Eagle cites *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1064-1065 (D.C. Cir. 1998) and *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120 (D.C Cir. 2006) to argue that FDA's rules are improper because they seek to rewrite the plain language of the act. *See generally* Pl. Br. at 26–29. This argument is unpersuasive; *Mova* and *Ranbaxy* dealt with challenges to *different* regulations that related to *a different* statutory provision, 21 U.S.C. 355(j)(5)(B)(iv)—a provision that provides a 180-day period of market exclusivity to generic drug manufacturers that satisfy certain conditions. *See*

Mova, 140 F.3d at 1064–65; *Ranbaxy Labs.*, 469 F.3d at 124–26. The language of section 355, which those cases examined, is different than the language of section 360cc, and the regulations that FDA implemented bear no similarity to the regulations here. *See Mova*, 140 F.3d at 1064–65; *Ranbaxy Labs.*, 469 F.3d at 124–26; *see* AR 39 (discussing differences between *Mova* and this case). Indeed, Eagle ultimately cites the cases for the unremarkable assertion that agencies are precluded from rewriting the clear language of the statute. *See* Pl. Br. at 26–29. We do not contend otherwise. The question here, however, is whether the text of section 360cc *is* clear—and neither *Mova* nor *Ranbaxy* help answer that.

Simply put, the language of section 360cc *is not* clear. In this way, this case resembles the vast majority of instances in which courts in this circuit and elsewhere have found the various provisions of the FDCA—including provisions providing for exclusivity benefits—ambiguous, and deferred to the FDA's reasonable interpretation of those provisions under *Chevron* step two. *See Actavis*, 625 F.3d at 764 (upholding FDA's implementation of 5-year exclusivity over a plain-language challenge: "Where Actavis sees clarity we see ambiguity."); *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 85-86 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (upholding FDA's view that the three-year exclusivity statute was silent on the question whether exclusivity was warranted for changes unrelated to a supplement to an application when they were approved at the same time as the supplement). Rather than follow *Depomed*'s—respectfully, erroneous—reasoning, the Court should follow the principles of deference applied in those cases, and recognize that FDA has authority to clarify the ambiguity in the statute's text.

D. FDA's Regulations Are Consistent With The Statute's Intent And Structure

Once the Court rejects Eagle's cramped reading of the statute, the question becomes whether FDA's rules reasonably give effect to the Orphan Drug Act's purpose. Contrary to what Eagle claims, it is evident that they do. *See generally* Pl. Br. at 21–26.

As FDA explained in its decision letter, the central purpose of the Orphan Drug Act is to incentivize drug development for otherwise untreated patients. *See Genentech*, 676 F. Supp. at 305, 312 ("The legislative history is replete with references to the fundamental need to provide treatment for presently untreated patients."); *see also* H.R. Rep. 153, 99th Cong, 1st Sess. ("The Committee hopes and anticipates that the amendment . . . will encourage the development of new orphan drugs for use in previously untreated rare diseases."). Interpreting section 360cc in a way that makes exclusivity available to only the *first* company that produces a particular drug is a reasonable way to accomplish this purpose. After all, seven years of market monopoly is a serious carrot: companies have motivation to exclude all competitors. If exclusivity were available to *any* manufacturer who produces a drug, regardless of whether the drug was approved previously, companies would have no reason to invest in developing superior drugs. Rather, they could just sit back and make minor tweaks to existing orphan drugs, knowing that they could eventually benefit from exclusivity after the original drug's exclusivity period expired. Such a regime does not foster innovation, or serve patients. By contrast, awarding the monopoly to only the *first* orphan drug developer, as FDA does, sharpens the incentives so that only products that provide meaningful benefits to patients over a previously approved drug receive the reward.

Eagle challenges this explanation, claiming that FDA did not identify "genuinely relevant authority" when explaining that the purpose of the Orphan Drug Act is to incentivize drug development for presently untreated patients. Pl. Br. at 21. This argument is unavailing. The Court

in *Genentech* has previously described the Orphan Drug Act as having exactly that purpose, as FDA pointed out in its letter decision. AR 2 n.6 (quoting *Genentech*, 676 F. Supp. at 312 ("The legislative history is replete with references to the fundamental need to provide treatment for presently untreated patients.")). *Genentech* cited the report of the House Committee on Energy and Commerce accompanying the 1985 Amendments to the Orphan Drug Act. *See* 676 F. Supp. at 305 (citing H.R. Rep. 153, 99th Cong, 1st Sess.). This report stated: "The Committee hopes and anticipates that the amendment . . . will encourage the development of new orphan drugs for use in *previously untreated rare diseases*." H.R. Rep. 153, 99th Cong, 1st Sess. (emphasis added). FDA's clinical-superiority framework achieves this purpose by incentivizing meaningful drug development, not products that embody only minor variations of an already approved drug.

Similarly, Eagle incorrectly insists that the legislative history does not support FDA's "position that exclusivity was intended to be limited to the first drug to treat a patient population." Pl. Br. at 22. FDA's decision explicitly points to one statement demonstrating that Congressional understanding: "The primary incentive in the act is the grant of 7 years of market exclusivity to the *first* company that develops a new drug for a rare disease." 136 Cong. Rec. H. 5799 (statement of Rep. Nielson) (July 30, 1990) (emphasis added). AR 2. As we noted previously, other similar statements abound. *See* 136 Cong. Rec. H. 11931 (Oct. 23, 1990) (statement of Rep. Bliley) ("The primary incentive in the act is the grant of 7 years of market exclusivity to the first company that develops a new drug for a rare disease."); 132 Con. Rec. S. 11944 (Aug. 15, 1986) (statement of Sen. Hatch) ("under the present act, only one company receives a 7-year exclusive marketing right"); *see also* 137 Cong. Rec. H. 73 (Jan. 3, 1991) (memorandum of disapproval of proposed legislation from President George Bush) ("Under current law, firms may apply to develop the same orphan drug, but only the first firm to have its drug approved receives market exclusivity.").

Most critically, Eagle's suggestion that the Orphan Drug Act should be construed to provide sequential periods of exclusivity would lead to absurd results. Under Eagle's approach, a company seeking exclusivity can continue to submit applications for minor variations of its orphan-designated drug and, when approved, automatically obtain successive seven-year orphan-drug exclusivity periods. Such a sponsor may not even need to conduct clinical trials to gain approval. AR 4. Eagle wants the longest marketing exclusivity period under the FDCA to be construed as automatic, and to continue indefinitely with only minimal future effort from the sponsor, while the sponsor continues to reap the financial rewards of a monopoly. Given Congress's reference to the "expiration" of the exclusivity period for "such drug" in section 360cc, and other legislation providing pathways for approval of more affordable generic and biosimilar versions of drugs, *see* 21 U.S.C. § 355(j) and 42 U.S.C. § 262(k), it is not plausible that Congress intended to incentivize the creation of orphan drugs without *any* limits.

Eagle claims that all of these concerns were rejected by the Court in *Depomed*. *See* Pl. Br. at 24–25. But *Depomed* analyzed these arguments in a different posture. Specifically, the Court in *Depomed* found that these concerns did not create ambiguity in (what it found to be) an unambiguous statute. *See Depomed*, 66 F. Supp. 3d at 234. *Depomed* never found that the concerns were illegitimate or did not support legitimate policy choices: it only rejected FDA's ability to craft that policy based on its erroneous "plain meaning" reading of section 360cc. Significantly, *Depomed* analyzed the statute in the abstract—the facts of that case did not give the Court a chance to see the long-term effect of its holding in practice. *See* 66 F. Supp. 3d at 237 (dismissing concerns about serial exclusivity as irrelevant because the facts of that case did not raise the issue). Here, there is no need for speculation. The facts of this case illustrate exactly why *Depomed* was wrong to dismiss FDA's arguments, given the very real serial exclusivity that Eagle seeks.

Simply put, *Depomed*'s (and Eagle's) reading of the statute would grant additional exclusivity periods for a drug with the *same* active moiety and indication as a previously approved drug. Thus, despite expiration of Treanda's seven-year exclusivity period for bendamustine, Eagle (and Teva) would get seven years of exclusivity for a different formulation of the same drug, bendamustine, and if Eagle or Teva were to subsequently develop a different formulation, that, too, would also be eligible for exclusivity upon expiration of Bendeka's seven-year period, opening the door to infinite periods of exclusivity and resulting in perpetually high prices. There is no corollary for such exclusivity anywhere in the FDCA.

This result would be especially egregious here; the second sponsor has collaborated with the first in an attempt to extend the prior exclusivity on bendamustine to fourteen years, and thereby deprive cancer patients of competitively-priced therapies during this exceptionally long period.[9] Indeed, the companies are very open about their goal to completely convert patients from Treanda to Bendeka and thereby continue to block competition as if the exclusivity period for Treanda had never expired. *See* Eagle June Overview at 4. This result is contrary to the purpose of the Orphan Drug Act to incentivize meaningful drug development.

Ironically, the exclusivity period that Eagle seeks would block approval not only of applications referencing Bendeka, but of all applications for bendamustine, including generics. AR 36–67. The approvals of four different ANDAs for the protected indications would be affected.[10] Under the clinical superiority regulations, Eagle's failure to prove clinical superiority means that its drug is the "same drug" as Treanda, and, under Eagle's reading, FDA would be broadly prohibited from approving any other "same drug," *i.e.*, bendamustine, for the same indication during Eagle's

[9] A 2015 article reports that Treanda was one of the top five most expensive medications that Medicare covers, costing the government $332 million. AR 651–52.

[10] *See* Orange Book (search for "bendamustine") (noting FDA approval of ANDAs for Hospira, Accord, Innopharma, and Glemark).

exclusivity. *See* 21 C.F.R. § 316.3(b)(14); AR 9 n.50 (noting that the exclusivity period granted by *Depomed* affected 12 ANDAs, contrary to the court's conclusion that such exclusivity would not affect products already on the market). By contrast, if Eagle had proven clinical superiority, its drug would be deemed a different drug and would not block approvals of drugs that are the same as Treanda. AR 36–37. Eagle's interpretation would thus turn the statute on its head by rewarding a sponsor with a broader scope of exclusivity (*i.e.*, to all "same drugs," including the previous drug) for *failing* to demonstrate clinical superiority than it would for a drug that has demonstrated clinical superiority. That result is plainly inconsistent with the purpose of the Orphan Drug Act to incentivize meaningful drug development.

Seeking to mitigate the absurdity of its position, Eagle suggests that FDA could solve the serial-exclusivity problem by changing how it decides to grant orphan-drug designations in the first instance. *See* Pl. Br. at 25. In particular, relying on *Depomed*, Eagle contends that FDA could require that drug sponsors prove that drug versions are actually clinically superior (rather than just proffer a hypothesis of clinical superiority) as a condition of designation. *See id.* (citing *Depomed*, 66 F. Supp. 3d at 234–36). This is not an effective solution, and is not in keeping with the statutory structure and purpose.

The only logical reading which gives effect to all of the statutory language is a two-step process: (1) an initial designation decision based on a plausible hypothesis of clinical superiority; and (2) a final decision for which this hypothesis must be proven. As FDA explained in its decision letter, a request for designation must occur before filing an application, 21 U.S.C. § 360bb(a)(1), and such early designation allows sponsors to take full advantage of the major benefits of designation, which are designed to be useful at this early stage of designation: approximately two million dollars in application fee exemptions, as well as tax credits for clinical trials. AR 34 ("[T]he Congressional

scheme [] assumes that designation will take place at [an] early time so that sponsors can enjoy many of the benefits when they matter most.").

FDA liberally grants designation on a mere showing of a plausible hypothesis of clinical superiority so that sponsors may take advantage of the benefits of designation early in the drug approval process. *See* 21 C.F.R. § 316.20(a); *see also Genentech*, 676 F. Supp. at 304 (referring to designation benefits as "development-phase benefits of the Act"). By contrast, under Eagle's (and *Depomed*'s) late-designation theory, sponsors would have to prove clinical superiority before obtaining the benefit from the very tax credits and fee exemptions that are intended to support their work to demonstrate clinical superiority. As a result, "a sponsor would be unable to take advantage of one of the very incentives designation was intended to provide in the first place—tax credits for clinical trials." AR 34. This view would effectively read the benefits out of the statute, and undermine the important timing structure for those benefits.

Eagle has no answer to these concerns. Rather, Eagle argues that Congress could not have intended that the benefits must come early in the designation stage to later prove clinical superiority because FDA, not Congress, imposed a clinical superiority requirement. Pl. Br. at 23–24. But clinical studies are typically relied on both to obtain approval and to support clinical superiority, as was true in this case. *See, e.g.*, AR 493–502 (arguing for clinical superiority based on its clinical trial to show bioequivalence). There is no real dispute that the Congressional scheme assumes early designation to support later approval, and FDA's requirement to demonstrate clinical superiority at that later time fits carefully in that scheme.

In any event, all of Eagle's objections to the manner in which FDA has chosen to implement the Orphan Drug Act are defeated by the fact that Congress has publicly *approved* that implementation. Over the years, members of Congress have repeatedly revisited the Act, and

commended its success in serving patients. *See, e.g.*, 159 Cong Rec E 13 (Jan. 4, 2013) ("The Act has been very successful. Over the thirty years between then and now, hundreds of orphan drugs have been approved and millions of Americans with rare diseases have been helped.") (statement of Rep. Waxman commemorating thirtieth anniversary of Orphan Drug Act).[11] Notably, though Congress has made changes to *other* portions of the Orphan Drug Act over the years, it *never* amended the language of section 360cc or otherwise changed the exclusivity regime. *See* 21 U.S.C.S.§ 360cc (describing amendments in 1993, 1997, and 2002). In doing so, Congress has effectively confirmed that FDA correctly understood Congress's intent, and that its regulations are effective and proper. This approval defeats Eagle's legal claims.

III. FDA PROPERLY APPLIED ITS CLINICAL SUPERIORITY FRAMEWORK

Turning away from its facial challenge to the FDA's rules, Eagle next asserts that the manner in which FDA *applied* the clinical superiority standard was legally deficient. In particular, Eagle alleges that FDA applied the standard without explaining what kind of evidence would establish that one drug is clinically superior to another, and it claims that FDA deprived Eagle of due process by not providing prior notice of its ultimate decision. *See* Pl. Br. at 29–30. Like Eagle's other arguments, these lack merit. FDA's procedures were not only lawful, but they accorded Eagle all the process it was due.

A. FDA's Clinical Superiority Standard Is Sufficiently Defined

First, Eagle is incorrect to claim that FDA's clinical superiority standard lacks definitional content and that it is impossible to know what type of evidence is sufficient to demonstrate clinical superiority. Pl. Br. at 29; 38. FDA routinely must decide whether product-specific evidence

[11] This success is easy to see. Following enactment of the Orphan Drug Act in 1983, FDA's program has enabled the development and marketing of more than 400 drugs and biologic products for rare diseases—by contrast, fewer than ten such products came to market between 1973 and 1983. *See* Developing Products for Rare Diseases & Conditions, *available at* http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.

submitted by sponsors meets general standards such as "safe" and "effective." *See, e.g.*, 21 U.S.C. § 355(d)(4), (5). These types of scientific decisions are necessarily fact-specific, and the generality of the standards does not render them "fundamentally flawed." Rather, Congress entrusts expert agencies to make such decisions. *PDK Labs. v. U.S. Drug Enforcement Admin.*, 438 F.3d 1184, 1194–95 (D.C. Cir. 2006) (interpreting *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) to allow federal agencies to clarify a statutory term on a case by case basis).

As relevant here, FDA has given guidance on its clinical superiority standard in its regulation. For instance, the agency described an example of a change that could result in greater safety: the elimination of an ingredient or contaminant that is associated with relatively frequent adverse events. 21 C.F.R. § 316.3(b)(3)(ii). The preamble to FDA's regulation describes several factors that may bear on FDA's consideration of whether a drug provides a major contribution to patient care, including convenient treatment location, duration of treatment, patient comfort, reduced treatment burden, advances in ease and comfort of drug administration, longer periods between doses, and potential for self-administration. 57 Fed. Reg. 62,078. Eagle is well aware of such factors, which it described to FDA in a meeting on January 29, 2016. AR 466. Further, sponsors (including Eagle) may file and have filed requests under the Freedom of Information Act to understand how FDA applies these standards in particular cases. Information about FDA's clinical superiority decisions is also publicly available.[12]

Thus, FDA's clinical superiority standard is not infirm for the reasons that Eagle cites. Pl. Br. at 38. In *Pearson*, for example, the court acknowledged that "The agency is entitled to proceed case by case or, more accurately, sub-regulation by sub-regulation, but it must be possible for the

[12] *See, e.g.*, A New "Greater Safety" Orphan Drug Clinical Superiority Precedent: PURIXAN (July 5, 2016), *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/orphan-drugs/ (discussing a "scorecard of precedents where FDA determined that an orphan drug is clinically superiority to another drug that is otherwise the same drug for the same orphan condition").

regulated class to perceive the principles which are guiding agency action." *Pearson v. Shalala*, 164 F.3d 650, 661 (D.C. Cir. 1999). Here, the principles guiding FDA's clinical superiority decisions are readily apparent in FDA's regulation and preamble. Eagle is unhappy that Bendeka does not meet the standard, but that does not make the standard itself deficient.

Eagle also argues that FDA "fault[ed] the evidence that FDA previously apparently accepted at the designation stage" when it denied clinical superiority, Pl. Br. at 29, and asserts that "no facts relevant to FDA's determination changed between designation and final approval that would undermine Bendeka's clinical superiority over early treatments," *id*. at 6. But Eagle conveniently overlooks the fact that the two standards are not the same. FDA liberally grants designation to provide sponsors an opportunity to obtain benefits at an early stage in drug development in order to maximize the ability of such benefits to help them test and develop their drug. FDA requires only a plausible hypothesis of clinical superiority at this early stage, and applying this standard based on the scientific facts known at the time, FDA agreed that Eagle had presented a hypothesis that Bendeka's lower volume plausibly might provide greater safety to patients. AR 314, 326. At the approval stage, however, FDA requires sponsors to prove that their drug is clinically superior to a previously approved drug if the two drugs are otherwise the same. Not only is the standard different, but additional facts became available. [redacted] Contrary to Eagle's assertions, FDA properly applied two different standards upon two different factual records and reasonably concluded that Eagle did not prove clinical superiority for Bendeka.

B. FDA Afforded Eagle Due Process

Eagle is likewise wrong to claim that FDA's procedures violated its due process rights. FDA's existing process fully complies with principles of due process.

As a legal matter, a plaintiff making a due process challenge must demonstrate that (1) it has a constitutionally protected property interest; and (2) that the procedures employed deprived the plaintiff of that interest without constitutionally adequate procedure. *See, e.g., Propert v. Dist. of Columbia*, 948 F.2d 1327 (D.C. Cir. 1991). As FDA has explained in a different matter, however, exclusivity is not a protected property interest. AR 1482-83 ("The seven-year period of exclusive marketing is not a property right but is a prohibition against action by FDA. It does not affirmatively grant any rights or privileges to the 'pioneer' sponsor.") (FDA decision in Docket No. 86P-0452, at 2-3 (Mar. 6, 1987)). Eagle cites cases concerning other types of government benefits, but these benefits are administered under other statutory regimes, and are not analogous to the exclusivity periods under the FDCA. Pl. Br. at 34. Indeed, Eagle may have spent $30 million on developing Bendeka (although some of this may have been recovered through tax credits from designation), *id.* at 36, but that expenditure does not reflect a lost investment: Eagle has a fully approved NDA for a drug that is expected to earn $750 million annually.[13]

But even assuming that Eagle can get past the first prong of the test, it still cannot demonstrate that FDA's procedures were deficient. The adequacy of an agency's procedures are evaluated using the three-factor test articulated in *Mathews v. Eldridge*, 424 U.S. 319, 334-35 (1976), which consider (1) the private interest that will be affected by the agency action; (2) the risk of erroneous deprivation and the probable value of any additional process; and (3) the government's

[13] In a recent statement, Eagle predicts that Bendeka will earn $750 million annually, and that Eagle will earn between $125 -$150 million annually through 2019 under its agreement with Teva. Eagle Pharmaceuticals Corporate Overview (Aug. 2016), *available at* https://www.sec.gov/Archives/edgar/data/827871/000082787116000077/egrxinvestorpresentation.htm.

interest (including the burdens) that any such additional process would entail. On the first factor, as noted, Eagle has not established a property or other viable interest in a seven-year exclusivity period.

For the second factor, FDA's existing process provides assurance against the risk of erroneous deprivation. Sponsors may and do regularly communicate with FDA officials, as Eagle did. Eagle even met with the Director of FDA's Office of Orphan Drug Development in its attempt to convince FDA that Bendeka is clinically superior. AR 484-92. Had it wanted, Eagle could have submitted additional information to FDA if it believed that it could address gaps that FDA identified in its clinical superiority decision. Eagle could have also filed a citizen petition under 21 C.F.R. § 10.30, or requested internal agency review under 21 C.F.R. § 10.75. Eagle's claim that it had "no opportunity to contest or cure the agency's findings of evidentiary deficiency," Pl. Br. at 37, rings especially hollow because Eagle has not even tried to use the agency's existing administrative avenues to contest the findings.

Eagle would prefer a process similar to that for approval of new drugs, in which FDA sends sponsors "complete response letters" and other communications before approval that list deficiencies in the application. Pl. Br. at 32. But Congress specifically requires FDA to give applicants notice if it determines that a ground for denying approval of a new drug application in 21 U.S.C. § 355(d) applies. *See* 21 U.S.C. § 355(c)(1)(B). Similarly, FDA must give notice and an opportunity for a sponsor to provide its views when FDA seeks to invoke the exception to exclusivity in 21 U.S.C. § 360cc(b)(1) for insufficient quantities of the drug. No such specific notice requirement attaches to determinations of orphan-drug designation or exclusivity.

Like many other drug companies, Eagle would like FDA to give advance notice of its exclusivity decisions. Pl. Br. at 36. Eagle cites numerous cases that are not relevant to this context. *Id.* at 36–37. For FDA exclusivity decisions, courts have routinely denied such requests for advance

notice. *AstraZeneca Pharmaceuticals v. FDA*, 872 F. Supp. 2d 60, 74-76 (D.D.C. 2012) (denying request for determination of 3-year exclusivity as unripe); *Mylan Pharmaceuticals Inc. v. FDA*, 789 F. Supp. 2d 1 (D.D.C. 2011) (dismissing claim seeking advance exclusivity determination as unripe); *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 1, 13 (D.D.C. 2008) (denying attempt to obtain an early decision on 180-day exclusivity before ANDA approval).

Similarly, one Court has rejected a claim that a plaintiff was denied due process when FDA declined to provide an early decision on whether it would approve a competitor's drug application. *Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 163 (D.D.C. 2006). The plaintiff argued that if FDA approved an ANDA at the same time that it issued its decision, it (the plaintiff) would not have a meaningful opportunity to be heard. *Id.* The Court rejected the plaintiff's due process claim, stating that "in the event that the petition is denied, the plaintiff will then be entitled to seek judicial review of that decision." *Id.* The *Biovail* Court was confident that this timing was sufficient to satisfy the "fundamental requirement" of due process—"the opportunity to be heard at a meaningful time and in a meaningful manner." *Id.* (quoting *Mathews*, 424 U.S. at 333)). So too here: Eagle has no claim to advance notice of an exclusivity determination, and must await FDA's decision, after which it may challenge the decision judicially or through FDA's existing administrative processes. Due process requires no more.

Nor is there any value to the additional process that Eagle says is constitutionally required; Eagle is free now as it would have been at an earlier time to bring additional information to FDA if Eagle believes that information could address gaps that FDA identified in its decision.

As to the third factor, FDA has a valid interest in maintaining its deliberative process protection for exclusivity matters. Eagle asserts that "it would cost the agency close to nothing" to give pre-deprivation notice because FDA already makes determinations about evidentiary

deficiencies in the applicant's claims for clinical superiority. Pl. Br. at 37. The detailed type of pre-deprivation notice that Eagle apparently seeks, however, would compromise FDA's deliberations on important matters and potentially subject it to judicial review of not-yet-final decisions.

Eagle also asserts that FDA should publish its clinical superiority decisions, Pl. Br. at 31, but FDA has resource limitations given the sheer volume of such decisions for designation and exclusivity, including the significant amount of redactions that would need to be made for the confidential information in those decisions.[14] Indeed, Eagle's own information related to clinical superiority is entirely redacted from the public version of FDA's decision in this case. And, as Eagle knows because it has filed such requests, redacted versions of FDA's designation memoranda may be obtained through FOIA requests, and requesters may be required to pay fees for such requests to help offset the burden placed on FDA staff.

The fact is, Eagle had opportunities to challenge FDA's clinical superiority decision administratively, but Eagle chose not to bring additional information to FDA, file a citizen petition, or request internal agency review. Nor does Eagle assert that there is any such additional information that FDA should consider, such that any additional process is needed. Eagle's avoidance of existing process does not make the agency's decision constitutionally deficient.

IV. FDA PROPERLY EXERCISED ITS SCIENTIFIC EXPERTISE TO FIND THAT BENDEKA IS NOT CLINICALLY SUPERIOR TO TREANDA

Once the Court disposes of Eagle's legal challenges, all that remains is a set of fact-specific challenges to FDA's finding that Bendeka was not clinically superior to Treanda. In particular, Eagle urges the Court to find FDA's conclusion arbitrary on four basic grounds. None of these has merit.

[14] FDA's regulation at 21 C.F.R. § 316.28 requires FDA to publish orphan drug designations and list certain information, which does not include the basis for the decision.

A. FDA Did Not Depart From Past "Practice"

Eagle first complains that FDA provided advance notice of its intent to deny exclusivity in two other situations, and that it was arbitrary for FDA to not do so here. Pl. Br. at 39-40. Neither of these two situations, even if they could be considered a "practice," support Eagle's claim. Eagle cites a document describing FDA's notification to Eagle that it had not provided data to demonstrate clinical superiority in its NDA submission for a different drug. Pl. Br. at 32 (citing AR 685). In that situation, at the time the drug was approved, Eagle had not previously contacted OOPD with any clinical superiority evidence, so OOPD notified Eagle that clinical superiority had not yet been proven and that it would need to provide evidence, as OOPD typically does when the sponsor does not initiate communication after the drug is approved. AR 685 (describing first arguments regarding clinical superiority as after approval). By contrast, for Bendeka, Eagle had already contacted OOPD, pre-approval, with extensive evidence and arguments about why it believed that Bendeka was clinically superior to Treanda. *See, e.g.*, AR 41-62; 1632-43; 1707-41; 1779-89. Post-approval, FDA continued to have questions for Eagle about clinical superiority, and it was evident from the correspondence and discussions that clinical superiority had not yet been proven because this was an issue that FDA was actively considering. *See, e.g,* AR 486 (noting that FDA asked questions at multiple points during January 29, 2016 meeting); AR 493 (supplemental submission to address FDA's questions at the meeting). Thus, FDA did not inform Eagle that further submissions would be necessary; Eagle had already made submissions that FDA was actively considering.

Eagle also cites FDA's notice to a different sponsor that its drug had not demonstrated clinical superiority. Pl. Br. at 32-33. But rather than a pre-deprivation notice, the notice described in that situation was an actual deprivation notice. [15] In that situation, as here, the sponsor was free to

[15] *See* http://www.hpm.com/pdf/blog/Procysbi-13.pdf at 5 (noting that sponsor had been informed that it had not demonstrated clinical superiority).

provide additional evidence to FDA for consideration, and did so successfully. *Id.* at 10. This situation only illustrates that any risk of erroneous deprivation can be readily corrected by FDA's existing process, not that the process is constitutionally defective.

B. FDA Adequately Explained Its Clinical Superiority Decision

Eagle next takes issue with FDA's determination that Eagle did not provide sufficient evidence to demonstrate greater safety or a major contribution to patient care, and that it is "impossible for this Court to review whether Eagle's showing met the applicable threshold." Pl. Br. at 41. FDA, however, explained in detail its basis for finding that Bendeka did not meet the clinical superiority standard. [redacted]

[redacted] FDA acknowledged that example in its decision letter, but did not agree that the cited level of "improved patient satisfaction" would itself be a major contribution to patient care. As its name implies, the major-contribution-to-patient-care standard requires a "major" contribution to patients. Eagle's own drug, Ryanodex, met this standard by enabling reconstitution and administration of a drug used in emergency, life-threatening situations in one minute, as opposed to 50. AR 31. Such a difference in time, FDA explained "can mean the difference between life and death." *Id.* [redacted] Here, FDA is the expert agency charged with making such scientific and regulatory determinations, and its decision is entitled to the utmost deference. *See Weinberger*, 412 U.S. at 653–54.

C. FDA Properly Found That Bendeka Did Not Provide Substantially Greater Safety

Eagle also argues that FDA takes a *per se* approach to finding greater safety if a sponsor eliminates a reconstitution step, and that it erred by not doing so here. Pl. Br. at 41 (citing AR 1743). Again, Eagle is wrong.

Eagle cites a document from the administrative record that was attached to a consult request that gave examples of situations in which FDA has not required head-to-head clinical trials to demonstrate greater safety. This document does not say that eliminating a reconstitution step *always* makes a product clinically superior, but merely states that "various review divisions" "*have consider*[*ed*]," in certain contexts, eliminating a reconstitution step to confer greater safety. Moreover, the rationale of that approach was that the oral solution was now "manufactured under [good manufacturing practice] and is thus safer than the product that requires reconstitution (assuming all else is comparable)." AR 1743. [redacted].[16] Notably, the review division did not conclude that the product at issue was clinically superior, noting that "[b]oth lyophilized powder and liquid preparations require mixing in a biologic-safety cabinet." AR 1747.

Taking a different tack, Eagle accuses FDA of not addressing its argument that eliminating DMA provides greater safety. [redacted]

[16] [redacted]

[redacted].[17]

D. FDA Properly Concluded That Reduced Sodium Does Not Constitute Clinical Superiority

Finally, Eagle argues that FDA ignored a scientific article that contains evidence of a "substantial portion" of renal comorbidities with CLL and indolent B-cell NHL patients who would benefit from reduced sodium intake. Pl. Br. at 43-44. [redacted] Eagle does not dispute FDA's analysis of those two references, but now brings a *different* reference to the Court's attention that Eagle cited for a different proposition to FDA: "development of [chronic kidney disease] and congestive heart failure are known to be age-related." *Id.* Eagle now asserts that this reference shows that 11% of CLL and NHL patients have renal impairment, and then crunches the data presented in the article to assert that

[17] Moreover, Treanda is also available as a lyophilized powder that does not contain DMA, and Bendeka cannot show greater safety over that version.

49% of CLL and 38% of NHL patients have creatinine clearance levels below those of healthy adults. Pl. Br. at 43 and n.8.[18]

This additional information and argument about renal comorbidity do not advance Eagle's claim. The 11% of patients with renal impairment (creatinine clearance levels of < 40 mL/min) are not even supposed to take Bendeka, the labeling of which states: "BENDEKA (bendamustine hydrochloride) Injection should not be used in patients with CrCL < 40 mL/min." AR 412. Eagle has not addressed how Bendeka provides greater safety to such patients for whom it is not even indicated.

[redacted]

In the end, none of the factual arguments Eagle makes demonstrates that FDA's conclusion was in any way arbitrary or capricious. Rather, Eagle's claims all boil down to the suggestion that the Court should substitute Eagle's analysis of the evidence for that of the scientific experts at FDA. The Court should not do so. Instead, it should reject Eagle's challenges, and sustain FDA's decision.

CONCLUSION

For these reasons, we respectfully request that the Court deny Eagle's motion for summary judgment, and enter judgment in favor of the FDA.

[18] Eagle brought an early version of this reference to FDA's attention two years previously, asserting as it does now that it showed that renally compromised patients comprised a substantial portion of the CLL and NHL populations, but Eagle did not give any figures at that time. AR 44.

Respectfully submitted,

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August 19, 2016

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

EAGLE PHARMACEUTICALS, INC., Plaintiff, 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 United States Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendants.	Civil Action No.: 16-0790-GK Judge Gladys Kessler

[PROPOSED] ORDER

Upon consideration of the parties' cross-motions for summary judgment, all other relevant materials, and upon due deliberation, it is hereby

ORDERED that plaintiff's motion for summary judgment is DENIED; and it is further

ORDERED that defendants' motion for summary judgment is GRANTED; and it is further

ORDERED that judgment shall be entered for defendants.

SO ORDERED.

Dated: _____, 2016
Washington, DC

_____
United States District Judge