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 U.S. Food and Drug Administration;

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Defendants.

Case No. 1:16-cv-00790-GK

Judge Gladys Kessler

Oral Argument Requested

MOTION FOR SUMMARY JUDGMENT OF PLAINTIFF EAGLE PHARMACEUTICALS, INC. (REDACTED PUBLIC VERSION)

Plaintiff Eagle Pharmaceuticals, Inc. ("Eagle") respectfully moves this Court for summary judgment pursuant to Federal Rule of Civil Procedure 56(c). In support of this motion, Eagle relies upon the agency administrative record and the attached memorandum, which demonstrates that Eagle is entitled to judgment as a matter of law. The Court should hold that the decision of Defendant U.S. Food and Drug Administration ("FDA") that Eagle challenges in this case is arbitrary, capricious, not in accordance with law, and contrary to Eagle's constitutional right to procedural due process.

Respectfully submitted,

Dated: July 11, 2016

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MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT OF PLAINTIFF EAGLE PHARMACEUTICALS, INC. (REDACTED PUBLIC VERSION)

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INTRODUCTION

Plaintiff Eagle Pharmaceuticals, Inc. ("Eagle") is entitled to summary judgment because Defendant U.S. Food and Drug Administration ("FDA") has violated the plain language of the Orphan Drug Act by refusing to recognize the seven-year period of market exclusivity mandated by that Act for Eagle's drug, Bendeka. The principal issue in this case is not novel. FDA has already litigated it in this very Court and lost, declining to pursue an appeal in favor of trying the same arguments again in front of a new judge. *See Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014). This Court should conclude that FDA's refusal to follow the plain language of the Act was unlawful for the same reasons Judge Ketanji Brown Jackson found in *Depomed.* And even if FDA had a viable legal interpretation of the statute (it does not, as *Depomed* demonstrated), FDA's decision to deny Bendeka's statutory exclusivity was in any event arbitrary and capricious, and contrary to Eagle's constitutional right to procedural due process, in violation of the Administrative Procedure Act.

Congress enacted the Orphan Drug Act in 1983 to induce pharmaceutical companies to develop so-called "orphan drugs"—drugs that treat rare conditions and diseases that would ordinarily be unprofitable due to their limited market. *See* Orphan Drug Act, Pub. L. No. 97-414, § 1, 96 Stat. 2049, 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa–360ee) (making statutory findings); *see also* H.R. Rep No. 97-840, at 1 (1982). The most important of Congress's statutory incentives is a seven-year period of market exclusivity, known as "orphan drug exclusivity," during which FDA may not approve competitors' marketing applications for the same drug.

Under the Act, a pharmaceutical company may request that FDA designate a potential drug for a rare disease or condition as an "orphan drug." 21 U.S.C. § 360bb. This designation generally occurs at an early stage of the drug development process. To receive such a

designation, the pharmaceutical company must show that its potential new drug is being developed for a rare disease or condition and, if approved, would be for use in that disease or condition. *Id.* § 360bb(a). Under the statute, once FDA grants the orphan drug ***designation***, the sponsor can move forward, invest, and complete drug development with the assistance of various statutory benefits, s*ee* 21 U.S.C. § 379h(a)(1)(F) (waived fees); 26 U.S.C. § 45C (tax credits), and the knowledge that, at the end of the arduous FDA drug approval process, the sponsor will be entitled to a seven-year period of marketing exclusivity, *see* 21 U.S.C. § 360cc. *See* Orphan Drug Act § 1(b)(4), (6) (finding that "because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to . . . incur a financial loss" and that "it is in the public interest to provide . . . incentives for the development of orphan drugs"). Under the unambiguous terms of the statute, when a previously designated orphan drug receives FDA approval, it is automatically entitled to a seven-year period of exclusivity. 21 U.S.C. § 360cc(a).

Here, *FDA does not dispute* that: (1) Eagle's drug Bendeka for treatment of two rare lymphocytic cancers *was* ***designated by FDA as an orphan drug in 2014***; and (2) *Bendeka received FDA marketing approval as "safe and effective" for those cancers in 2015*. Thus, under the plain text of the statute, Bendeka is automatically entitled to exclusivity. But FDA has unlawfully refused to recognize that statutorily mandated exclusivity.

FDA is fully aware that its actions contravene this Court's precedent. In the widely publicized 2014 *Depomed* decision, Judge Jackson held in almost identical circumstances that the "plain language of the exclusivity provision of the Orphan Drug Act requires the FDA to recognize exclusivity for any drug that the FDA has designated and granted marketing approval." 66 F. Supp. 3d at 237. In that case, FDA attempted to withhold orphan drug exclusivity for a

drug that—like Bendeka—had *already been designated and approved*, by imposing an additional requirement on the sponsor to demonstrate, at the end of the FDA drug approval process rather than at the earlier orphan drug designation stage, that its drug would be "clinically superior" to older, similar drugs. *Id.* at 220. But Judge Jackson correctly recognized that the exclusivity issue presented a straightforward *Chevron* "step 1" question, and held that FDA's extra-statutory limits on exclusivity were fundamentally in conflict with the statute. *See id.* at 229. Judge Jackson invited FDA to change its regulations governing orphan drug *designations* if the agency sought a different result in future cases. *Id.* at 230-31.

What FDA did next is remarkable. Rather than appeal Judge Jackson's ruling or rewrite its regulations to conform to the Orphan Drug Act, FDA published a notice in the Federal Register explaining that the agency *would not comply* with *Depomed's* legal holding for other orphan drug products and would instead "continue to apply its existing regulations"—a practice euphemistically known as administrative "non-acquiescence." *Policy on Orphan-Drug Exclusivity; Clarification*, 79 Fed. Reg. 76,888 (Dec. 23, 2014). This sort of "non-acquiescence" has been sharply criticized in this District and elsewhere: as this Court has observed, once it rules on an issue directly affecting an agency, "it is no longer reasonable for that agency to totally ignore the only existing case law (which it failed to appeal) simply because it thinks it was erroneously decided." *Dong v. Smithsonian Inst.*, 943 F. Supp. 69, 73-74 (D.D.C. 1996) (Kessler, J.); *see also, e.g.*, *Hosp. of Univ. of Pa. v. Sebelius*, 847 F. Supp. 2d 125, 139 (D.D.C. 2012) (Bates, J.) (criticizing Defendant Department of Health and Human Services' "unacceptable non-acquiescence" and stating that its "stubborn repetition" of an argument rejected by both this court and the D.C. Circuit was "objectionable" and "unacceptable"); *Duggan v. Bowen*, 691 F. Supp. 1487, 1501, 1503-04, 1503 & n.22 (D.D.C. 1988) (Sporkin, J.)

(criticizing Defendant Department of Health and Human Services' practice of non-acquiescence, which "condemns worthy plaintiffs to litigate the same issues again and again," and certifying a nationwide class in part to ensure compliance with the court's judgment); *Ass'n of Admin. Law Judges, Inc. v. Heckler*, 594 F. Supp. 1132, 1143 (D.D.C. 1984) (Green, J.) (criticizing Defendant Department of Health and Human Services' practice of non-acquiescence and calling it of "questionable legality"); *Am. Mining Cong. v. U.S. Army Corps of Eng'rs*, 962 F. Supp. 2, 5 (D.D.C. 1997) (Harris, J.) (criticizing the practice of "administrative nonacquiescence" as unfair to those subject to the agency's unlawful regulation and concluding that, "[i]f the government believes that the Court has misinterpreted the law, the appropriate remedy is congressional action or appellate review").

FDA's decision to ignore Judge Jackson's legal holding in *Depomed* is what has led to this case. FDA denied Bendeka exclusivity in a March 24, 2016 letter ruling (the Letter Ruling), explicitly taking the position that *Depomed* was wrongly decided. FDA argued:

- "[T]he *Depomed* court erred in not deferring to FDA's statutory interpretation . . . ." FDA0039.
- "We are not bound to follow the *Depomed* decision, and we do not believe that the *Depomed* court's conclusion is compelled by the statute . . . ." FDA0032.
- "Because FDA concluded that the [*Depomed*] decision was inconsistent with FDA's clinical superiority framework and the important policy interests at stake, the Agency has continued to implement its long-standing clinical superiority framework for designation and exclusivity decisions." FDA0009.

FDA then again defended its unlawful regulatory scheme, taking essentially the same legal position that was rejected in *Depomed*: the agency argued that, even after it has designated

an orphan drug, it has the power to reverse course and deny exclusivity *at the end of the approval process* (once a drug is fully developed), FDA0032-40, notwithstanding the agency's repeated recognitions that exclusivity is *the critical statutory* ***incentive*** provided by Congress in the Orphan Drug Act to induce pharmaceutical companies to invest in and develop orphan drugs in the first place. *See, e.g.*, *Orphan Drug Regulations*, 56 Fed. Reg. 3338, 3341 (Jan. 29, 1991) ("Exclusive marketing is the Orphan Drug Act's primary incentive for the development of orphan drugs."); *id.* at 3343 (calling it the "chief incentive"). Judge Jackson explained in detail in *Depomed* why each of FDA's arguments is inconsistent with the statutory text and structure. In short, FDA is administering a statutory regime it wishes it had, rather than the one Congress actually created.

Even aside from FDA's disregard for the Orphan Drug Act's plain language, its decision to deny Bendeka exclusivity violated the Administrative Procedure Act in multiple respects. FDA's argument is essentially this: FDA's regulations provide that Eagle was required to present evidence that Bendeka was "clinically superior" to other drugs on two occasions—first at the initial designation stage, and again at the end of FDA's drug approval process. Although Bendeka cleared the first hurdle and was granted orphan drug designation, FDA0328-32, FDA concluded that Eagle did not submit "sufficient evidence" at the end of the process to reaffirm that Bendeka's drug was indeed "clinically superior" to other alternatives. *See, e.g.*, FDA0017; FDA0019; FDA0025; FDA0028-30. But, as the administrative record now demonstrates, FDA acted in a purely *ad hoc* manner, without articulating and applying a discernable standard as mandated by well-established D.C. Circuit precedent. *See, e.g.*, *Pearson v. Shalala*, 164 F.3d 650, 660 (D.C. Cir. 1999) (concluding that an agency cannot regulate on the basis of "I know it when I see it" because it "must be possible for the regulated class to perceive the principles

which are guiding agency action"). Notably, no facts relevant to FDA's determination changed between designation and final approval that would undermine Bendeka's clinical superiority over earlier treatments. Compared to those earlier treatments, Bendeka is administered in much smaller volume and over a much shorter amount of time (***10* minutes** of intravenous delivery, as opposed to up to ***60 minutes*** for alternative drugs—a reduction of up to 83.33%). While FDA evidently relied on at least the volume difference to make its initial determination of clinical superiority, FDA, with no contrary facts, then determined these factors did not render Bendeka clinically superior—taking the counterintuitive position that regularly wasting 50 minutes of a gravely ill patient's day—while significant volume of unnecessary liquid is injected into the patient—is no big deal. FDA0022-23. As anyone who has ever sat through treatment with a cancer patient can attest, that defies common sense.

More fundamentally, FDA never shared or explained the rationale for its initial determination of clinical superiority at the designation stage, and never identified—despite repeated requests that it do so—what type of information would be sufficient or necessary to demonstrate clinical superiority at the end of the process. Eagle was forced to guess at what might meet FDA's "sufficient evidence" threshold—despite the fact that FDA already had in its possession (but did not disclose) an analysis that would have provided Eagle with important guidance. Had this information been shared before FDA made its final decision, Eagle would have had a chance to address what FDA believed were insufficiencies in the record. But Eagle never got that chance; instead, the agency rejected Eagle's entitlement to exclusivity by employing undisclosed criteria and without ever articulating what evidence was necessary. As demonstrated below, this conduct is quintessentially arbitrary and capricious in violation of the Administrative Procedure Act and also fundamental tenets of procedural due process.

BACKGROUND

A. The Orphan Drug Act

In enacting the Orphan Drug Act, Congress provided financial incentives to induce pharmaceutical companies to develop drugs that would otherwise not be developed because the market for their use was too small to be profitable. Orphan Drug Act § 1(b); *see also* H.R. Rep No. 97-840, at 1. The principal incentive in the Act is a promise of a seven-year period of marketing exclusivity. During that seven-year period, FDA may not approve another marketing application for "such drug" for "such disease or condition." 21 U.S.C. § 360cc(a). As set forth below, the entitlement to exclusivity attaches at the time of designation, and vests *automatically* upon FDA's approval of the designated drug as "safe and effective." *Id.*

1. Orphan Drug Designation

The orphan drug process begins with the *designation* of a drug as an orphan drug. A sponsor submits a request for designation, which the statute requires FDA to grant if the drug is being "investigated" for, and would ultimately be used to treat, a rare disease or condition. *Id.* § 360bb. The statute defines a "rare disease or condition," in relevant part, as a disease or condition that "affects less than 200,000 persons in the United States." *Id.* § 360bb(a)(2).

Once a drug developer obtains designation, it is automatically entitled to a bundle of incentives/benefits, which are collectively designed to ease the cost and financial risk associated with drug development for a small orphan drug market. In addition to a promise of future marketing "exclusivity" upon drug approval, these benefits include tax credits for qualified clinical research, 26 U.S.C. § 45C, and waivers of certain application fees, 21 U.S.C. § 379h(a)(1)(f).

2. Orphan Drug Exclusivity

Most importantly, once a drug is designated as an orphan drug, the statute mandates that the drug is entitled to market exclusivity upon approval of the designated drug as safe and effective under 21 U.S.C. § 355:[1]

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

21 U.S.C. § 360cc(a) (emphasis added). Subsection (b), in turn, provides the only two exceptions from this exclusivity: (1) when FDA finds that the sponsor cannot assure the availability of sufficient quantities of its drug; and (2) when the sponsor waives its exclusivity in writing. 21 U.S.C. § 360cc(b).

Thus, under the statute's plain language, FDA is *required* to recognize orphan drug exclusivity upon approval of a previously designated orphan drug, *unless* one of the two statutory exceptions applies.

B. FDA's Orphan Drug Regulations

Congress expressly authorized FDA to promulgate implementing regulations regarding the ***designation*** phase of the orphan drug process. *See id.* § 360bb(d). Under FDA's designation regulations, FDA will grant a timely submitted request for designation if the drug is intended for a rare disease or condition, and there is a medically plausible basis to expect the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition. *See* 21 C.F.R. §§ 316.24(b), 316.25. The regulations further provide that FDA will refuse to grant a

[1] 21 U.S.C. § 355 concerns FDA approval of new drugs as safe and effective. All new drugs must be approved as safe and effective by FDA before being marketed in interstate commerce.

designation if "[t]he drug is otherwise the ***same drug*** as an already approved drug for the same rare disease or condition and the sponsor has not submitted a ***medically plausible hypothesis for the possible clinical superiority of the subsequent drug***." 21 C.F.R. § 316.25(3) (emphasis added). As relevant here, FDA's regulations define "same drug" to mean any drug with the same "active moiety" (a term that, for present purposes, is synonymous with active ingredient) intended for the same use or indication, and that is not "clinically superior" to an older drug with the same active moiety.[2] *See* 21 C.F.R. § 316.3(b)(14)(i). When evaluating whether a sponsor has shown a "medically plausible hypothesis of clinical superiority," FDA makes record-based scientific judgments, some of which are extremely detailed. *See* FDA0312-16 (explaining what was sufficient and insufficient to meet the threshold). Indeed, the plausible hypothesis threshold has been a genuine bar to orphan drug designation in past cases. *See, e.g.*, FDA0565 (noting that the "sponsor was required to provide a plausible hypothesis of clinical superiority" and was "unable to obtain designation"). Under this framework, the regulations purport to prohibit a true "copycat" drug from obtaining an orphan drug designation, and thus preclude the possibility that such a drug would later obtain orphan drug exclusivity.

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

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[2] "Clinically superior" is defined in the regulation as when "a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways: (i) Greater effectiveness than an approved drug . . . ; or (ii) Greater safety in a substantial portion of the target populations . . . ; or (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care." 21 C.F.R. § 316.3(b)(3).

FDA's orphan drug exclusivity regulations purport to give FDA the authority, found nowhere in the statute, to reexamine its decision previously made at the designation stage and to withhold the statutory exclusivity Congress utilized to incentivize the development of these drugs in the first place. Specifically, FDA's regulations provide that FDA "will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug." *See* 21 C.F.R. § 316.34(c). The regulations do not specify what evidence is necessary to make the "demonstration" for this second determination. Thus, FDA has authorized itself to revoke the key statutory incentive—the promise that an orphan drug designee will have exclusivity upon approval. Instead, FDA now only informs designees that it *might* grant exclusivity at the end of the process, after all the effort has already been made to develop the drug. FDA continues to apply this extra-statutory requirement for proof of clinical superiority despite the fact that the same requirement was expressly rejected by Judge Jackson in *Depomed*.

C. *Depomed*

In *Depomed*, FDA denied orphan drug exclusivity for Depomed's drug, Gralise. 66 F. Supp. 3d at 219-20. Just as is the case here, FDA designated Gralise as an orphan drug based on a plausible hypothesis of clinical superiority over a previously approved drug with the same active ingredient; FDA then refused to grant exclusivity upon approval. *Id.* at 231. FDA's justification was that Depomed had ultimately failed to submit sufficient evidence to affirm the clinical superiority of Gralise over the previously approved "same drug." *Id.* at 226.

In 2014, Judge Jackson rejected FDA's justification and held that the Orphan Drug Act *automatically* conferred orphan drug exclusivity to Depomed upon FDA's award of marketing approval because FDA had previously designated Gralise as an orphan drug. Judge Jackson explained that "[t]he plain language of the exclusivity provision of the Orphan Drug Act requires

the FDA to recognize exclusivity for any drug that the FDA has designated and granted marketing approval." *Id.* at 237. Thus, where a drug satisfies both of those criteria, the drug "is *entitled to exclusivity and ... the FDA must recognize as much* without requiring [additional] proof of clinical superiority [after the designation stage] or imposing any additional conditions on [the applicant]." *Id.* (emphasis added). Judge Jackson noted that, while the agency may have some discretion to limit which drugs ultimately obtain exclusivity, it must do so through the earlier *designation* process, not at the time of approval. *Id.* at 235-36. Indeed, as discussed above, FDA's designation regulations already require FDA to evaluate at the *designation* stage whether applicants have submitted sufficient scientific evidence supporting a medically plausible hypothesis of clinical superiority over any previously approved drug incorporating the same active ingredient in order to obtain designation. 21 C.F.R. § 316.25(a)(3). Requiring FDA to impose any limitations at the *designation* stage comports with the Orphan Drug Act's incentive structure by allowing applicants to rely on the promise of future exclusivity when they make the decision to move forward with drug development. *Depomed*, 66 F. Supp. 3d at 234; *see also* H.R. Rep. No. 99-153, at 6-7 (1984), *reprinted in* 1985 U.S.C.C.A.N. 301 (specifying that the Orphan Drug Act is intended to "give drug company sponsors some certainty as to the drug approval process at FDA and the market conditions they will face upon approval"); H.R. Rep. No. 100-473, at 5-6 (explaining that the seven-year exclusivity period has been a valuable incentive to companies to develop orphan drugs because it "assure[s] such a company that it could offset some or all of its costs of development by recouping *all* possible revenues from the sale of the drug during the seven-year period of exclusivity").

FDA filed a notice of appeal of *Depomed* on November 3, 2014. Notice of Appeal, *Depomed Inc. v. U.S. Dept of Health and Hum. Servs.*, Case No. 14-5271 (D.C. Cir. Nov. 3,

2014). However, it withdrew the appeal days later, prior to briefing. Unopposed Voluntary Motion to Dismiss Appeal, *Depomed Inc. v. U.S. Dept of Health and Hum. Servs.*, Case No. 14-5271 (D.C. Cir. Nov. 6, 2014). Rather than pursue the appeal, FDA issued a notice in the Federal Register announcing its intention to continue to apply the post-designation clinical superiority condition that Judge Jackson held to be unlawful. *Policy on Orphan-Drug Exclusivity; Clarification*, 79 Fed. Reg. 76,888 (Dec. 23, 2014). In the notice, FDA stated that "[f]ollowing the *Depomed* decision, under the court's order, FDA recognized orphan-drug exclusivity for GRALISE for the treatment of post-herpetic neuralgia." *Id.* Nonetheless, FDA stated:

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

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

D. Procedural History

Eagle is the developer of the drug Bendeka (bendamustine hydrochloride) injection, which is an intravenous chemotherapy agent for the treatment of patients with chronic lymphocytic leukemia (CLL) and certain patients with indolent B-cell non-Hodgkin lymphoma (NHL). *See* FDA394; FDA0312-13; FDA0323. Both of these patient populations are unquestionably orphan populations—they consist of fewer than 200,000 persons in the United States—and are made up primarily of advanced-age patients with debilitating disease loads,

many of whom also suffer from compromised heart and/or kidney function. FDA0044; FDA0312-13; FDA0323.

1. FDA Granted Orphan Drug Designation To Eagle's Drug, Bendeka

Eagle submitted a request for orphan drug designation for Bendeka for indolent B-cell NHL on March 5, 2014 and one for CLL on March 14, 2014. FDA1644-64; FDA1665-85. Because Bendeka has the same active ingredient as the previously approved drug Treanda that is marketed by Cephalon, Inc., a subsidiary of Teva Pharmaceutical Industries Ltd. (collectively, Teva), Eagle's designation requests cited dozens of scientific studies and other sources of clinical information establishing a medically plausible hypothesis that Bendeka is clinically superior to Treanda. FDA1644-64; FDA1665-85.

Treanda is also a drug for treatment of indolent B-cell NHL and CLL that comes in two forms: (1) a powder that must be reconstituted to liquid form with sterile water and then diluted in 500 mL of a sodium-containing liquid before it is intravenously administered to the patient; and (2) a liquid that does not require reconstitution, but that similarly must be diluted in 500 mL of a sodium-containing liquid. FDA0042; FDA0045. Although Bendeka has the same active ingredient as Treanda, Eagle performed extensive research and development to formulate Bendeka in a clinically superior manner to benefit patients. This work showed concern with the ***length of time*** required to administer Treanda, and the large volume of fluid and high amount of sodium that must be injected into the patient, particularly for the largely elderly patients with the rare diseases at issue. Eagle identified multiple areas for improvement:

- Bendeka "requires 80-90% less infusion chair time for cancer patients, providing greater flexibility and reduced pain and discomfort for patients receiving chemotherapeutic infusions," and saving patients up to 50 minutes per treatment. FDA0309.

- Bendeka "requires 80-90% less volume to be administered, providing reduced likelihood of edema, site irritation, and extravasation." *Id.*
- Bendeka "requires a significantly decreased sodium chloride load (up to a 90% reduction), providing greater safety especially for patients with cardiac comorbidities and renally compromised patients." FDA0310. Indeed, Eagle was able to demonstrate that Bendeka can be administered to the patient with essentially *no* sodium. FDA0017.
- Bendeka "exposes patients to fewer degradation product impurities," including "dimethylacetamide (DMA)," a "solvent with known toxicities." FDA0311. (Notably, FDA subsequently issued a safety alert regarding DMA in Treanda liquid—the drug FDA is here claiming is the "same" as Bendeka. FDA1828-37.)
- Bendeka "is a liquid ready-to-dilute formulation" which does not "require[] reconstitution." FDA0311.

FDA, at one point, seemed to agree that Bendeka was clinically superiority to Treanda. FDA granted Eagle's requests for orphan drug designation on July 2, 2014. FDA0328, FDA0331. The administrative record shows that FDA internally concluded that:

[redacted]

While FDA sent Eagle letters notifying the company of its orphan designations on July 2, 2014, those letters did not disclose this analysis or any explanation of the grounds FDA relied upon to

grant the designations. Indeed, Eagle did not see this analysis until the administrative record was produced in this matter.

2. FDA Approved Bendeka As Safe And Effective, But Then Months Later Unlawfully Refused To Recognize Bendeka's Exclusivity

Although Eagle was automatically entitled to exclusivity upon approval after receiving orphan designation for Bendeka, Eagle nonetheless endeavored to work cooperatively with FDA to satisfy the agency's unlawful post-designation clinical superiority requirement. Because FDA's regulations provide no genuine standard or other guidance for what further evidence is necessary to satisfy that requirement, Eagle repeatedly reached out to the agency by email and telephone in the months following its designation to find out whether any additional proof would be required to demonstrate clinical superiority beyond the extensive information already submitted. FDA1803; FDA1804; FDA1807-11. Unfortunately, FDA provided no such information. Instead, Eagle was forced to shoot in the dark, providing periodic supplemental information to the agency that Eagle guessed the agency might find valuable. FDA1815-18; FDA1819-20.

FDA approved Bendeka as safe and effective for the treatment of CLL and indolent B-cell NHL on December 7, 2015. FDA0394. Although both indications had been orphan-designated, FDA did not provide Eagle with written notice recognizing exclusivity at the time of approval or any time thereafter.

Two days after the Bendeka approval, Eagle contacted FDA to inquire about the status of Bendeka's orphan drug exclusivity and to offer to provide additional information to FDA as needed. FDA1815-18. In subsequent correspondence, Eagle again offered to discuss what additional information Eagle could provide to further FDA's inquiry. FDA1820-21; FDA1874-75; FDA0429. Receiving no guidance from FDA, Eagle proposed holding an in-person meeting.

FDA1879. FDA finally allowed a meeting on January 29, 2016, FDA0455-83, by which point the record shows the agency appears to have already decided to deny orphan drug exclusivity, FDA0518-24 (memorandum dated January 21, 2016 concluding that "Eagle Pharmaceuticals has not demonstrated clinical superiority of their Bendeka … product over the approved Treanda … product"). At the meeting, FDA said nothing about its intent to deny Bendeka exclusivity and did not notify Eagle of any particular evidentiary deficiencies in the record. *See* FDA0484-92.

Without any prior notice or explanation, on March 24, 2016, FDA issued a formal Letter Ruling to Eagle denying orphan drug exclusivity for Bendeka on the basis that Eagle had not provided "sufficient evidence" that Bendeka is clinically superior to Treanda. FDA stated that it was not bound to follow *Depomed*, and it reasserted the very arguments for its authority to impose the clinical superiority demonstration requirement that Judge Jackson found unpersuasive in *Depomed*. In sum, FDA stated: "[W]e continue to believe that the *Depomed* court erred in not deferring to FDA's statutory interpretation, and we therefore deny your request for exclusivity on that ground." FDA0039. Finally, the Letter Ruling announced for the very first time the scientific basis for FDA's grants of orphan drug *designation* nearly two years prior, and reversed positions the agency took when it granted the designations and thereby induced Eagle to continue developing Bendeka as planned. In doing so, FDA claimed that Eagle had failed to meet the agency's secret and unknowable regulatory standard for a demonstration of clinical superiority. FDA0030 ("Eagle has not provided enough data to support that any of the supposed benefits of Bendeka over Treanda meets the applicable regulatory standard of clinical superiority.").

STANDARD OF REVIEW

Under Fed. R. Civ. P. 56(a), summary judgment is appropriate when the pleadings and the evidence demonstrate that "there is no genuine dispute as to any material fact and the movant

is entitled to judgment as a matter of law." Where, as here, final agency action under the Administrative Procedure Act, 5 U.S.C. §§ 50 *et seq.* ("APA") is involved, summary judgment "serves as the mechanism for deciding, as a matter of law, whether the agency action is supported by the administrative record and otherwise consistent with the APA standard of review." *Roberts v. United States*, 883 F. Supp. 2d 56, 62-63 (D.D.C. 2012). Under the APA, a court must set aside agency action that is arbitrary and capricious, an abuse of discretion, in excess of statutory authority, contrary to a constitutional right, or otherwise not in accordance with law. *See* 5 U.S.C. § 706(2)(A), (C), (D), (E).

ARGUMENT

I. FDA'S DECISION TO WITHHOLD ORPHAN DRUG EXCLUSIVITY FOR BENDEKA VIOLATED THE ORPHAN DRUG ACT

FDA denied orphan drug exclusivity for Bendeka in violation of the Orphan Drug Act and in open disregard for this Court's decision in *Depomed*. By its plain terms, the Orphan Drug Act prohibits FDA from approving marketing applications for subsequent drugs—resulting in a period of marketing exclusivity for the approved drug—when ***two conditions*** are met: (1) FDA has previously designated the drug as an orphan drug for an orphan indication; and (2) FDA approves the drug for that orphan indication. Bendeka satisfies both of those conditions. Congress created only two exceptions to this exclusivity mandate, and FDA does not assert that either applies here. Under both the Act's plain language and *Depomed*, that should end the discussion. FDA does not seriously contend otherwise, instead arguing that the plain language should not control and that *Depomed* was wrongly decided.

A. As This Court Already Held In *Depomed*, The Plain Text Of The Orphan Drug Act Mandates Exclusivity For Designated Orphan Drugs That Are Subsequently Approved As Safe and Effective By FDA

Because this issue involves a question of statutory interpretation, the Court's review is conducted under the two-step *Chevron* test. *See Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984). Under the first step, the court first must consider "whether Congress has directly spoken to the precise question at issue." *Amarin Pharm. Ir. Ltd. v. FDA*, 106 F. Supp. 3d 196, 205 (D.D.C. 2015) (quoting *Chevron*, 467 U.S. at 842), *appeal dismissed*, 2015 WL 9997417 (D.C. Cir. Dec. 9, 2015). If so, the court and the agency "must give effect to the unambiguously expressed intent of Congress." *Arizona v. Thompson*, 281 F.3d 248, 253 (D.C. Cir. 2002) (quoting *Chevron*, 467 U.S. at 842-43). Only if the statute is ambiguous or silent on an issue does the court proceed to *Chevron*'s second step, where it evaluates the agency's interpretation to determine whether "it is reasonable and consistent with the statutory purpose." *Bell Atl. Tel. Cos. v. FCC*, 131 F.3d 1044, 1049 (D.C. Cir. 1997).

Here, this Court's analysis should begin and end with *Chevron's* first step, because the Orphan Drug Act "unambiguously requires marketing exclusivity when the FDA has designated an orphan drug and has approved that drug for marketing." *Depomed*, 66 F. Supp. 3d at 229. As Judge Jackson described, "the text of the Act's exclusivity provision (§ 360cc(a)) employs the familiar and readily diagrammable formula, 'if x and y, then z.'" *Id.* at 230. Section 360cc(a) states, with two enumerated exceptions:

> [I]f the [FDA]—**[x]** approves an application filed pursuant to [section 505 of the FDCA] . . . **[y]** for a drug designated under . . . [21 U.S.C. § 360bb] for a rare disease or condition **[z]** the [FDA] may not approve another application under [section 505 of the FDCA] . . . for such drug for such disease or condition for a person who is not the holder

> of such approved application . . . until the expiration of seven years from the date of approval of the approved application.

There is no dispute here that **[x]** FDA designated Bendeka as an orphan drug under 21 U.S.C. § 360bb for a rare disease or condition, and that **[y]** FDA approved an application filed pursuant to section 505 of the FDCA for Bendeka. Nor is there any dispute that the two enumerated statutory exceptions are inapplicable here. Thus, there is no ambiguity that **[z]** FDA is prohibited from approving another application for "such drug" for "such disease or condition" for seven years from the date Bendeka was approved. After a drug is designated as an orphan drug, FDA's statutory role in granting orphan drug exclusivity is almost purely ministerial, as the agency itself seemed to recognize in the preamble to its 1991 proposed orphan drug rule: "Section 527 of the act ***automatically vests*** a 7-year period of orphan-drug exclusive approval on the date that the agency issues a marketing approval for a designated orphan drug. For this reason, no further action by FDA to bring about exclusive approval is necessary." *Orphan Drug Regulations*, 56 Fed. Reg. 3338, 3341 (1991) (emphasis added). Yet FDA has refused to recognize the required exclusivity for Bendeka.

B. FDA's Attempts To Justify Its Deviation From The Statute's Plain Text And To Discredit *Depomed* All Fail

In its Letter Ruling, FDA raised a number of justifications for its assertion that *Depomed* is incorrect and the exclusivity provision should not apply as written. FDA is bound in this case by these purported justifications for its decision, *Mova Pharmaceuticals Corp. v. Shalala*, 140 F.3d 1060, 1067 (D.C. Cir. 1998), and they are all demonstrably wrong.

First, FDA argues (at FDA0033) that the exclusivity provision is ambiguous because the statute does not explicitly address whether a previously designated drug is entitled to exclusivity when FDA has previously granted orphan exclusivity to a similar drug. But as Judge Jackson

correctly found, there is no ambiguity in the statute regarding whether a previously designated orphan drug is entitled to exclusivity upon approval. 21 U.S.C. § 360cc(a); *Depomed*, 66 F. Supp. 3d at 230. The statute implements the exclusivity entitlement through a *prohibition* on FDA's authority to approve certain drug applications whenever an orphan-designated drug is approved—there is no latitude for FDA to escape that prohibition unless one of Congress's two specific enumerated exceptions is met (which is indisputably not the case here). *See* 21 U.S.C. § 360cc(b); *Depomed*, 66 F. Supp. 3d at 230.

What FDA is essentially attempting to do here is add a new exception to the two statutorily enumerated exceptions in section 360cc(b). If Congress wanted to recognize another exception of the type FDA supports, it would and could have codified that exception, as it did with the existing exceptions and as it has done in other drug contexts. *See, e.g.*, 21 U.S.C. § 360cc(b) (containing exceptions to the prohibition on approval when FDA finds that the orphan drug sponsor cannot assure the availability of sufficient quantities of the drug or when the sponsor waives its exclusivity); 21 U.S.C. § 379h(k) (providing that an orphan drug that is "designated" and "approved" "shall be exempt from product and establishment fees under this section, ***if the drug meets all of the following conditions***" (emphasis added)). But Congress did no such thing. Indeed, it is black letter law that "[w]hen Congress provides exceptions in a statute, . . . [t]he proper inference . . . is that Congress considered the issue of exceptions and, in the end, limited the statute to the ones set forth." *United States v. Johnson*, 529 U.S. 53, 58 (2000); *see also NRDC v. EPA*, 489 F.3d 1250, 1259-60 (D.C. Cir. 2007) (holding that where Congress provides certain enumerated exceptions in a statute, an agency "may not, consistent with *Chevron*, create an additional exception on its own"); *Sierra Club v. EPA*, 294 F.3d 155, 160 (D.C. Cir. 2002) (if statute "details the conditions in which EPA may extend the attainment

deadline," "[w]e cannot but infer from the presence of these specific exemptions that the absence of any other exemption . . . was deliberate, and that the Agency's attempt to [create an exemption] is contrary to the intent of the Congress").

Second, FDA also seems to argue (at FDA0038) that its clinical superiority requirement is authorized by ambiguity in the term "such drug" in section 360cc(a). FDA0038; *see* 21 U.S.C. § 360cc(a) (providing that "the Secretary may not approve another application under section [355 of this title] … for *such drug*" (emphasis added)). Judge Jackson explained exactly why FDA's argument is misplaced: the term "such drug" in that statutory provision is relevant only to the *scope* of the exclusivity prohibition that section imposes on FDA, not to whether FDA must recognize the sponsor's exclusivity at all. *See Depomed*, 66 F. Supp. 3d at 232 ("Properly understood, the term 'such drug' in the exclusivity provision operates only to define the scope of the limit on the FDA's approval authority once a 'designated drug' has been 'approved' as required for exclusivity to attach."). In other words, if an orphan drug designation is granted and the drug is later approved (as is the case for Bendeka), then FDA is flatly prohibited from granting approval to any other "such drug." The only decision for FDA to make under section 360cc(a) is determining exactly which drugs it is barred from approving as a result of Bendeka's exclusivity—*i.e.*, which other pending drug applications qualify as "such drug" and thus fall within the scope of Bendeka's exclusivity.

Third, FDA claims (at FDA033), without citing any genuinely relevant authority, that mandating exclusivity for all approved, designated drugs is inconsistent with the "purpose" of the Orphan Drug Act. According to FDA (at FDA0033, FDA0035), that purpose is to treat "presently untreated patients," and therefore the Act must be interpreted to support the agency's limitation on exclusivity for drugs that would treat an already treated drug population.

Judge Jackson correctly rejected this argument as well. *See Depomed*, 66 F. Supp. 3d at 234-36. The purpose of the Orphan Drug Act is defined in its statutory text—"to facilitate the development of drugs for rare diseases and conditions." Orphan Drug Act pmbl. Congress could have limited the Act's incentive to the *first* drug to treat a particular patient population, as it did in other statutory contexts not applicable here, but it chose not to do so. *Cf.* 21 U.S.C. § 355(j)(5)(B)(iv) (limiting 180-day exclusivity to "first applicant"). Indeed, FDA's position is inconsistent with the thrust of its own unlawful regulatory structure, which *explicitly contemplates orphan drug exclusivity for already treated patients*. 21 C.F.R. § 316.31(a) (allowing exclusivity for clinically superior orphan drugs to treat the same orphan disease or condition as the previously approved drug). FDA's Letter Ruling makes vague references to the Act's legislative history, FDA0033, but FDA does not and cannot cite any such history that actually supports its position that exclusivity was intended to be limited to the first drug to treat a patient population. And even if such legislative history existed, under D.C. Circuit precedent it cannot be used to *create* ambiguity in otherwise clear statutory text. *Recording Indus. Ass'n of Am., Inc. v. Verizon Internet Servs., Inc.*, 351 F.3d 1229, 1237 (D.C. Cir. 2003) ("Legislative history can serve to inform the court's reading of an otherwise ambiguous text; it cannot lead the court to contradict the legislation itself."); *United States ex rel. Totten v. Bombardier Corp.*, 380 F.3d 488, 494–95 (D.C. Cir. 2004) ("[T]here would be no need for a rule—or repeated admonition from the Supreme Court—that there should be no resort to legislative history when language is plain and does not lead to an absurd result, if the rule did not apply precisely when plain language and legislative history may seem to point in opposite directions."). Besides, there is plenty of legislative history that shows Congress had the purpose of incentivizing development of *all* orphan drugs, even ones that make incremental improvements for an already treated patient

population. *See, e.g.*, H.R. Rep No. 97-840, at 7 (discussing the prevalence of adverse side effects associated with existing orphan drugs); 127 Cong. Rec. E1370 (daily ed. Mar. 26, 1981) (statement of Rep. Barnes) (discussing the need for improved drugs for Tourette syndrome); Staff of H. Comm. on Energy & Commerce, 97th Cong., Preliminary Rep. of the Survey on Drugs for Rare Disease 17 (Comm. Print 1982) (stating that, of the 34 already-marketed orphan drugs studied as part of the consideration of orphan drug legislation, "18 were for orphan indications for which other drugs were already on the market"); *Orphan Drugs: Hearing on H.R. 1663 Before the Subcomm. on Health & the Env't of the H. Comm. on Energy & Commerce*, 97th Cong. 39 (1981) (statement of J. Richard Crout, Director, Bureau of Drugs, FDA) (describing the need for a uniform version of a dye used before surgery, which individual doctors were making themselves using constituent chemicals obtained from suppliers); *id.* at 74, 79-80 (statement of Lewis A. Engman, President, Pharmaceutical Manufacturers Association) (discussing the development of a capsule for the treatment of a form of extreme sensitivity to sunlight for which topical medications were already available); *id.* at 122-23 (statement of William N. Hubbard, Jr., President, Upjohn Company) (describing the development of an anti-clotting drug that was similar to an existing one except that it did not increase bleeding tendencies in patients undergoing surgery).

Fourth, FDA says (at FDA0034) that the plain text reading of the statute is inconsistent with the "structure of the designation, exclusivity, and approval statutes" because "the 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." Specifically, FDA points to "tax credits for human clinical testing." *Id.* FDA's argument is apparently that Congress's clinical trial incentives would be useful for a drug sponsor to use to establish that its drug was

truly "clinically superior," and that Judge Jackson's conclusion that FDA must evaluate clinical superiority only at the *designation* stage before those incentives are available would frustrate Congress's intent. But that was of course not Congress's intent—Congress did not establish the "clinical superiority" test—FDA did, *after* Congress had enacted the Orphan Drug Act. Congress intended the clinical trial incentive to help offset clinical trials performed in the *drug approval process* under section 355 to show that a drug is safe and effective. The incentives had nothing to do with FDA's subsequent "clinical superiority" provision in its regulations.

More generally, there is no doubt that Congress created orphan exclusivity as an incentive to induce the private sector *to investigate and develop* drugs for rare diseases. *See, e.g.*, H.R. Rep No. 97-840, at 5, 11; 129 Cong. Rec. E 59 (daily ed. Jan. 6, 1983) (statement of Rep. Walgren). Indeed, FDA acknowledges that exclusivity is the "primary" and "chief" incentive Congress created for that purpose. 56 Fed. Reg. at 3341. It would make no sense at all if FDA could refuse to recognize the promised entitlement *after* the drug *was already fully developed* and had completed FDA's drug approval process, as FDA has done in this case.[3]

Finally, FDA claims (at FDA0036) that the plain language reading adopted by *Depomed* leads to "absurd" results in this case because it results in "serial exclusivity," by which FDA apparently means separate, sequential periods of exclusivity for similar drugs. As an initial matter, there is no indication that separate periods of exclusivity for similar drugs would "so defeat [the Act's] purpose that Congress could not have meant the statute to be read in

[3] For this reason, even *if* FDA could establish that there is ambiguity in the exclusivity provision—which it cannot—its implementation of the clinical superiority framework in a manner that completely undermines the key statutory incentive created by Congress is impermissible even under a *Chevron* step 2 analysis. *See, e.g.*, *Rettig v. Pension Benefit Guar. Corp.*, 744 F.2d 133, 155 (D.C. Cir. 1984) (holding that the agency's interpretation was unreasonable at *Chevron* step 2 because it was inconsistent with the "overwhelming purpose" of the statute even though it furthered "secondary" purposes).

accordance with its plain language." *Depomed*, 66 F. Supp. 3d at 234. Congress intended to incentivize the creation of orphan drugs; conferring exclusivity on a new drug that has gone through designation and approval obviously creates such an incentive.

In any case, when rejecting FDA's absurdity argument in *Depomed*, the Court correctly concluded that to the extent such "serial exclusivity" is a genuine problem, *it is one of FDA's own making* because of how FDA chooses to issue orphan drug *designations*. Judge Jackson instructed that FDA could avoid this result by utilizing its authority to control the conditions for designation of an orphan drug under section 360bb. *Id.* at 230-31.

> For example, the FDA could require designation applicants to show clinical superiority ***before*** granting their product orphan-drug designation, a change in the regulations that would allow the FDA to maintain the benefits of its clinical superiority requirement and also forestall the hypothetical 'serial exclusivity' problem while at the same time avoiding any conflict with the plain language of the statute's exclusivity provision.

Id. at 235-36 (emphasis added). As discussed earlier, FDA already makes scientific record-based determinations at the designation stage. *Supra* pp. 8-9. Of course, if FDA wishes to alter the current designation threshold, it can consider doing so through notice and comment rulemaking. And although FDA may ***prefer*** to wait to make an ultimate decision on clinical superiority until after drug approval for its own policy reasons, it must implement its policy goals consistently with Congress's statutory structure. *Ranbaxy Laboratorties, Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006) (explaining that FDA "may not . . . change the incentive structure adopted by the Congress, for the agency is bound 'not only by the ultimate purposes Congress has selected, but by the means it has deemed appropriate, and prescribed, for the pursuit of those purposes.'" *Id.* (quoting *MCI Telecomms. Corp. v. AT&T Co.*, 512 U.S. 218, 231 n.4 (1994)); *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125 (2000) ("Regardless of how serious the problem an administrative agency seeks to address . . . it may not exercise its authority 'in a

manner that is inconsistent with the administrative structure that Congress enacted into law.'" (citation omitted)).

Relatedly, FDA argued in its Letter Ruling that recognizing exclusivity would be especially absurd here because Bendeka's exclusivity would block even Treanda generics. FDA0036-37. To the extent that FDA genuinely intends to take that position in this litigation, that result is obviously also one of FDA's own making, not an absurdity produced by the *statute*. As discussed, the Orphan Drug Act's exclusivity provision provides that once "a drug" has been designated for a "rare disease or condition" and approved, FDA "may not approve another application" for "such drug" for "such disease or condition" for seven years. 21 U.S.C. § 360cc(a). The statute *mandates* that FDA recognize Bendeka's exclusivity, but it is only because of how FDA has chosen to interpret the phrase "such drug" that the scope of that exclusivity could block Treanda generics. *See Depomed*, 66 F. Supp. 3d at 232; *Baker Norton Pharm. v. FDA*, 132 F. Supp. 2d 30, 34-38 (D.D.C. 2011) (concluding that FDA has some discretion to interpret the phrase "such drug" and thus determine the scope of exclusivity). FDA cannot justify departing from clear statutory text by itself causing a particular result under the statute and then claiming that the result is absurd.

In short, none of the reasons FDA provides for departing from the plain language of the statute are persuasive. This Court should therefore vacate FDA's Letter Ruling with instructions for FDA to grant exclusivity to Bendeka.

C. The D.C. Circuit Has Repeatedly Rebuked Similar Attempts By FDA To "Interpret" Congress's Unambiguous Exclusivity Instructions To Comport With The Agency's Policy Preferences

Depomed was not the only case where the courts have instructed FDA not to refashion Congress's drug exclusivity regimes to meet FDA's policy aims. The D.C. Circuit has at least twice rebuked similar attempts by FDA to thwart Congress's unambiguous command regarding

drug exclusivity in a similar context. Like with orphan drugs, Congress has provided various exclusivity periods to incentivize the market entry of generic drugs. When a new branded drug comes on the market through the New Drug Approval process, the sponsor submits any applicable patent information to FDA for publication in what is colloquially known as the "Orange Book." *See generally Ranbaxy*, 469 F.3d at 122. FDA is generally prohibited from approving any generic that would infringe patents listed in the Orange Book claiming the branded drug. 21 U.S.C. § 355(j)(2)(A)-(B), (j)(5). However, a generic applicant can attempt to avoid the statutory bar by submitting a "Paragraph IV" certification and providing notice to the branded patent-holder that a potentially blocking patent is invalid or will not be infringed by the generic; the statute then provides a 45-day window during which the patent-holder may bring a patent infringement suit against the applicant which, if filed, stays the applicant's FDA approval for the earlier of 30 months or the end of the patent litigation. *Id.* § 355(j)(5)(B)(iii). The statute rewards the first generic making such a certification (and thus risking a patent infringement action) by prohibiting FDA from approving any subsequent generic application for 180 days—a period of exclusivity commonly known as "180-day exclusivity." *Id.* § 355(j)(5)(B)(iv). The D.C. Circuit addressed FDA's attempt to restrict this exclusivity in two pertinent cases.

At the time of the D.C. Circuit's decision in *Mova*, the exclusivity provision prohibited FDA from approving any subsequent generic application for 180 days after the earlier of (a) the first commercial marketing of the drug by the generic filer or (b) a court decision finding the patent that is the subject of the paragraph IV certification to be invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv) (1997). Concluding on its own initiative that "Congress could not have intended for this provision to be read literally," FDA attempted to require, as a condition precedent to obtaining 180-day exclusivity, that the previous generic filer successfully defend

against a patent infringement suit. *Mova*, 140 F.3d at 1064-65. But, as in *Depomed*, the D.C. Circuit found that FDA's addition of this extra-statutory condition to exclusivity failed at *Chevron* step 1 because it was "gravely inconsistent with the text and structure of the statute." *Id.* at 1069. As here, the statutory language was clear: "if an applicant has already filed a paragraph IV ANDA, later applications shall be approved 'not earlier than one hundred and eighty days after' the commercial-marketing trigger or the court-decision trigger is satisfied." *Id.* By contrast, FDA's requirement "permits later applications to be approved even though neither trigger has been satisfied, simply because the first applicant's litigation has not yet come to a successful conclusion." *Id.*

Similarly, in *Ranbaxy* , the D.C. Circuit rejected at *Chevron* step 1 FDA's attempt to limit the exclusivity owed to two generic applicants making Paragraph IV certifications when a patent holder did not sue but instead requested that FDA remove the patents at issue from the Orange Book. 469 F.3d at 123-24. In these circumstances, FDA's regulations required the generic to amend its drug application to remove the Paragraph IV certification, eliminating the possibility for exclusivity. *Id.* FDA argued that, in the absence of litigation about the patent, the agency was free to remove patents from the Orange Book upon the patent holder's request even if it would deny exclusivity to a Paragraph IV filer. *Id.* The D.C. Circuit also rejected this extra-statutory attempt to limit exclusivity because "the statute [does] not require litigation to preserve a generic applicant's eligibility for exclusivity" and the elimination of such exclusivity would be inconsistent with structure of the statute. *Id.* at 125.

As in *Depomed*, *Mova*, and *Ranbaxy*, FDA here is impermissibly ignoring Congress's unambiguous command to grant exclusivity. To the extent that FDA's regulations purport to allow the agency to deny exclusivity to Bendeka, *see* 21 C.F.R. § 316.34(c), those regulations

cannot be squared with the plain language of the statute. Indeed, as is evident from the FDA's own Letter Ruling (at FDA0011, FDA0035, FDA0037), FDA's decision here was colored by its own (factually mistaken) views about what it regarded as the equities of granting market exclusivity to Eagle. As both *Depomed* and these other prior D.C. Circuit precedents demonstrate, FDA's job is not to question the wisdom of the exclusivity policies Congress enacted into law, or to pick market "winners" and "losers." Instead, FDA must faithfully apply the text of the statute.

II. IN ANY EVENT, FDA'S DETERMINATION THAT BENDEKA IS NOT CLINICALLY SUPERIOR TO TREANDA VIOLATES THE ADMINISTRATIVE PROCEDURE ACT IN MULTIPLE RESPECTS

Under FDA's extra-statutory framework, Eagle was required to present evidence that Bendeka was "clinically superior" to other drugs on two occasions—first at the initial designation stage, and again at the end of FDA's drug approval process. Although Bendeka cleared the first hurdle and was granted an orphan drug designation, FDA concluded that Eagle did not submit "sufficient evidence" at the end of the process to reaffirm that Bendeka was indeed "clinically superior" to other alternatives. But FDA never gave Eagle a genuine opportunity to understand what it would regard as "sufficient evidence" at the end of the process: FDA's clinical superiority standard is so lacking in definitional content that it is impossible for regulated entities to discern what evidentiary showing is required, FDA never shared or explained the rationale for its initial clinical superiority decision at the designation stage, and FDA never articulated what evidence could meet its ultimate clinical superiority standard. Instead, FDA simply denied Eagle's request for exclusivity at the end by faulting the evidence that FDA previously apparently accepted at the designation stage, without providing any opportunity to contest, rebut, or cure the agency's findings of evidentiary deficiency. FDA's failure to provide notice of its intention to deny Bendeka exclusivity and provide an opportunity

to cure was not in accordance with law and contrary to a constitutional right, 5 U.S.C. § 706, because it was inconsistent with longstanding principles of procedural due process. And even if FDA's secret decision-making could pass constitutional muster, its final clinical superiority determination was arbitrary and capricious for at least five reasons.

A. FDA's Clinical Superiority Framework Is Fundamentally Flawed

As discussed in detail *supra*, under FDA's orphan drug regulations, a drug sponsor must make two clinical superiority showings: one at the time of designation, and one at the time of drug approval. 21 C.F.R. §§ 316.20(a)(5), 316.34(c). As relevant here, FDA's regulations define "clinically superior" to mean that "a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways":

> (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
>
> (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

21 C.F.R. § 316.3(a)(3).

FDA provides no information, either in its regulations or otherwise during its decision-making process, regarding what is necessary to show "greater safety" or a "major contribution to patient care" (MC to PC) in order to obtain exclusivity. Under the plain text of the regulation, greater safety may (or may not) result, "for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects" and in "some cases" (but not others), "direct comparative clinical trials would be necessary." *Id.* § 316.3(a)(3)(ii). And MC to PC can be shown in "unusual cases" (a term that is not defined or quantified) with "a demonstration" (the evidence required in support of which remains a mystery) that the drug

makes a MC to PC. *Id.* at § 316.3(a)(3)(iii).[4] FDA has repeatedly refused to provide definitional content to the clinical superiority requirement. 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) ("The content of this evidence will depend on the nature of the superiority claimed."); 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) (rejecting request by commenter to provide more definitive standard, concluding: "There is no way to quantify such superiority in a general way. The amount and kind of superiority needed would vary depending on many factors, including the nature and severity of the disease or condition, the quality of the evidence presented, and diverse other factors."). And the agency admits that it evaluates clinical superiority on an essentially ad hoc basis. 57 Fed. Reg. 62,077 (claiming that the agency "does not believe that it can anticipate all or even most possible bases for categorizing some contributions as major and others as minor. Each will vary with the facts."); *id.* at 62,076-77 (asserting that MC to PC is a "determination [that] will have to be made on a case-by-case basis").

FDA's regulations do not require the agency to notify the sponsor of the basis of the agency's designation-stage clinical superiority determination, or implement a process for the agency to explain what additional information (if any) would be required to demonstrate clinical superiority at the exclusivity-determination stage. And FDA did not do so here, despite repeated attempts by Eagle to discern whether the agency would require any additional data to obtain exclusivity upon approval. FDA1803-04; FDA1807-11. *Likewise, FDA does not publish its determinations on clinical superiority, so it is not possible for regulated entities to discern what is required by analogy to other similar situations.*

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[4] Based on the precedents that industry has been able to piece together, FDA actually appears to rely on MC to PC as a relatively common basis for granting orphan drug exclusivity. *See* FDA Law Blog, "A New 'Greater Safety' Orphan Drug Clinical Superiority Precedent: PURIXAN" (July 5, 2016), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/07/a-new-greater-safety-orphan-drug-clinical-superiority-precedent-purixan-.html.

Instead, when FDA does not want to recognize exclusivity, it simply denies it at the end of the process based on a lack of "sufficient evidence," without providing any opportunity to contest the agency's findings of inadequacy. *See* FDA0030. FDA's black box approach to clinical superiority stands in marked contrast to the procedures the agency employs in similar related contexts. For example, in the context of FDA's review of whether a new drug is safe and effective, FDA has extensive communications with applicants to communicate issues that arise during the review process, including to "inform applicants promptly of its need for more data or information"—communication that is "intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment." 21 C.F.R. § 314.102(b). And in the event FDA later concludes that an applicant has not provided sufficient information to meet its standard for safety and effectiveness, FDA sends the applicant a "complete response letter" listing the "specific deficiencies that the agency has identified," and provides an opportunity to cure the deficiencies and/or request a hearing. 21 C.F.R. § 314.110.

FDA's clinical superiority framework provides none of those procedural safeguards. When regulated entities succeed in slightly lifting the veil of secrecy—through litigation, word-of-mouth, industry blogs, or by obtaining shreds of information through the Freedom of Information Act—it becomes apparent that FDA regulates clinical superiority inconsistently. For example, it appears that when the agency desires to recognize exclusivity, it will *informally* provide notice to the drug sponsor that additional information is required to demonstrate clinical superiority at the exclusivity-stage, and allow the sponsor an opportunity to develop and submit that information. FDA0685 (noting that drug sponsor was "notified by OOPD that they had not provided data to demonstrate clinical superiority in their NDA application," allowing submission of additional data and ultimately recognizing exclusivity); FDA, *Review of an Amended Request*

for Orphan Drug Designation for Procysbi at 5 (May 28, 2013) (noting that a "letter was issued to the sponsor explaining" that "the sponsor has not provided adequate information to support a claim for clinical superiority," that the sponsor was granted a meeting "to obtain guidance on how they might demonstrate clinical superiority," and that FDA ultimately granted exclusivity after obtaining additional requested data).[5] Yet in other cases—like this one—FDA provided no such opportunity.

FDA's clinical superiority framework is fundamentally broken. As explained in detail below, it is inconsistent with procedural due process and results in arbitrary and capricious decision-making.

B. FDA's Application Of Its Flawed Clinical Superiority Framework To Bendeka Deprived Eagle Of Procedural Due Process

An agency violates the Administrative Procedure Act when it acts "contrary to a constitutional right … privilege, or immunity" and "otherwise not in accordance with law." 5 U.S.C. § 706. "An essential principle of due process is that a deprivation of life, liberty, or property 'be preceded by notice and opportunity for hearing appropriate to the nature of the case.'" *Barkley v. U.S. Marshals Serv. ex rel. Hylton*, 766 F.3d 25, 31 (D.C. Cir. 2014) (quoting *Cleveland Bd. of Educ. v. Loudermill*, 470 U.S. 532, 542 (1985)). The "core requirements of due process" dictate that an agency must provide "adequate notice of why [a] benefit is being denied and a genuine opportunity to explain why it should not be." *Gray Panthers v. Schweiker*, 652 F.2d 146, 165 (D.C. Cir. 1980). FDA violated these core principles here by providing no such notice or opportunity before denying Eagle its statutory entitlement to exclusivity.

The first question under the due process clause is whether there is a constitutionally protected property interest at stake. *See Barkley*, 766 F.3d at 31. FDA's denial of exclusivity for

[5] *Available at* FDA Law Blog, http://www.hpm.com/pdf/blog/Procysbi-13.pdf.

Bendeka constituted a deprivation of Eagle's constitutionally protected property interest in exclusivity promised by the Orphan Drug Act. Although FDA has previously taken the remarkable position that "a manufacturer has no property right in its orphan-drug exclusivity," and thus is entitled to *no* due process protection should FDA attempt to rescind exclusivity, FDA1482-83, this Court has recognized that "property" covered by the due process clause "of course, extends beyond real estate or physical possession and can include rights to government benefits." *See Ass'n of Cmty. Orgs. For Reform Now (ACORN) v. FEMA*, 463 F. Supp. 2d 26, 33 (D.D.C. 2006). A party with "a legitimate claim of entitlement to" a benefit under a statute has a property right cognizable under the Due Process Clause of the Fifth Amendment. *NB ex rel. Peacock v. District of Columbia*, 794 F.3d 31, 41 (D.C. Cir. 2015) (quoting *Bd. of Regents v. Roth*, 408 U.S. 564, 577 (1972)). It has such a claim "if award of the benefit would follow from satisfaction of applicable eligibility criteria," *id.*, rather than being left to the government's "unfettered discretion," *id.* (quoting *Wash. Legal Clinic for the Homeless v. Barry*, 107 F.3d 32, 36 (D.C. Cir. 1997)). *See ACORN*, 463 F. Supp. 2d at 34 ("[I]t is well-established that government benefits create constitutionally-protected property interests if an applicant has a 'legitimate claim of entitlement to it,' rather than a mere expectation." (quoting *Roth*, 408 U.S. at 577)); *cf. Cushman v. Shinseki*, 576 F.3d 1290, 1297 (Fed. Cir. 2009) ("Every regional circuit to address the question . . . has concluded that applicants for benefits, no less than benefits recipients, may possess a property interest in the receipt of public welfare entitlements." (alteration in original) (quoting *Kapps v. Wing*, 404 F.3d 105, 115 (2d Cir. 2005)). An entitlement to orphan drug exclusivity attaches automatically upon designation, contingent only upon approval of the drug and, according to FDA's (unlawful) regulation, a showing of clinical superiority. *See* 21 U.S.C. § 360cc(a); 21 C.F.R. § 316.34(a).

The second question is what level of process is due. *Mathews v. Eldridge* provides the appropriate framework. 424 U.S. 319, 334-35 (1976). While *Mathews* provides agencies flexibility in the precise procedures they utilize in adjudicating an entitlement, "no case or commentator suggests that traditional trial-type procedural safeguards may be eliminated at the expense of the core requirements of due process[:] adequate notice of why the benefit is being denied and a genuine opportunity to explain why it should not be." *Gray Panthers*, 652 F.2d at 165; *see also Reeve Aleutian Airways, Inc. v. United States*, 982 F.2d 594, 599 (D.C. Cir. 1993) ("Obviously, when a notice requires its target to guess among several possible bases for adverse government action, it has not served those fundamental purposes."), *as amended on denial of reh'g* (Mar. 26, 1993); *ACORN*, 463 F. Supp. 2d at 34 ("[M]any courts have concluded that due process requires an agency to include in the notice provided to the applicant the reasons and factual support for the denial of benefits."). The specific process required in a given case depends on three factors:

> First, the private interest that will be affected by the official action; second, the risk of an erroneous deprivation of such interest through the procedures used, and the probable value, if any, of additional or substitute procedural safeguards; and finally, the Government's interest, including the function involved and the fiscal and administrative burdens that the additional or substitute procedural requirement would entail.

Mathews, 424 U.S. at 334-35; *see also Armstrong v. Manzo*, 380 U.S. 545, 552 (1965). The *Mathews* factors demonstrate that FDA was required to provide *notice* to Eagle that the agency intended to deny Eagle its statutory entitlement to exclusivity, and then provide Eagle an opportunity to rebut the agency's conclusions with additional evidence.

First, Eagle's private interest in its entitlement to orphan drug exclusivity is significant. As FDA has acknowledged, such exclusivity was the "primary incentive" associated with the orphan drug framework, *see* 56 Fed. Reg. 3338, 3341, and was the main goal underlying Eagle's investment in developing Bendeka. Indeed, the entire purpose of the exclusivity is to induce

pharmaceutical companies to spend the millions of dollars and years of effort required to develop a new orphan drug and bring it to market. Eagle, for example, spent approximately $30 million on developing Bendeka, which for a company of Eagle's size is a significant investment. The reliance interests are manifest.

Second, FDA's failure to provide pre-deprivation notice of its intent to deny Bendeka exclusivity created a great risk of an erroneous deprivation. "[M]any courts have acknowledged that the risk [of erroneous depravation] significantly increases as the notice given becomes less detailed and more vague." *ACORN*, 463 F. Supp. 2d at 34. In *Gray Panthers*, for example, the D.C. Circuit held that information the government provided to Medicare benefit claimants concerning the bases on which certain claims would be denied did "not give constitutionally adequate notice of why benefits are being denied," 652 F.2d at 167, where no plaintiff "received any precise indication as to why his or her claim was being denied prior to the final decision on review," *id.* at 156, and the "the reasons for claims denials" were "so unclear that it is virtually impossible for the average beneficiary to present a well-reasoned argument to the insurance company," *id.* at 167. Similarly, in *ACORN*, this court held that the plaintiffs were likely to prevail on their claim that the Federal Emergency Management Agency (FEMA) had provided unconstitutionally vague notices of benefit denials that precluded effective administrative appeals, commenting that a proper notice would include a "more detailed statement of FEMA's reasons for denying . . . benefits, including the factual and/or statutory basis for the decision." 463 F. Supp. 2d at 35. Likewise, other courts have consistently rejected agency attempts to deny benefits without articulating specific reasons in time for applicants to challenge the decisions. *See, e.g.*, *Kapps*, 404 F.3d at 124 ("Claimants cannot know *whether* a challenge to an agency's action is warranted, much less formulate an effective challenge, if they are not provided with

sufficient information to understand the basis for the agency's action."); *Barnes v. Healy*, 980 F.2d 572, 579 (9th Cir. 1992) ("Due process requires notice that gives an agency's reason for its action in sufficient detail that the affected party can prepare a responsive defense."). Here, FDA's action was worse—FDA provided ***no*** advance notice of its intent to deny Bendeka exclusivity, and no opportunity to contest or cure the agency's findings of evidentiary deficiency.

Finally, regarding FDA's interest, the fiscal and administrative burdens of providing pre-deprivation notice of its intent to deny orphan drug exclusivity would be negligible. In the normal course of adjudicating claims for orphan drug exclusivity, FDA *already* makes determinations about evidentiary deficiencies in the applicant's claims of clinical superiority. *See, e.g.*, FDA 0307-27; FDA0519. It would cost the agency close to nothing to communicate those findings to regulated parties in advance, so those parties could be adequately informed of the agency's claimed deficiencies in the record and then submit targeted evidence in support of their claims of entitlement. *See, e.g.*, *Barnes*, 980 F.2d at 579 (concluding that the burden an agency would face by communicating to regulated parties determinations it had already made would be "minimal"); *Dilda v. Quern*, 612 F.2d 1055, 1057 (7th Cir. 1980) (per curiam) (describing the burden of providing information about work the agency had already done as "trivial").

For these reasons, FDA's denial cannot be squared with the requirements of due process.

C. FDA's Application Of Its Flawed Clinical Superiority Framework To Bendeka Was Arbitrary And Capricious

The "core concern underlying the prohibition of arbitrary or capricious agency action" under the APA is "ad hocery." *Pacific Nw. Newspaper Guild, Local 82 v. NLRB*, 877 F.2d 998, 1003 (D.C. Cir. 1989) (internal quotation marks omitted). Although the standards for reasoned

decisionmaking under the APA are well established, three particular administrative law principles warrant emphasis here.

The agency must articulate adequate standards. The D.C. Circuit has consistently held that agencies must identify the standards that guide their analysis, as an agency's refusal "to define the criteria it is applying is equivalent to simply saying no without explanation." *See Pearson*, 164 F.3d at 660. When the agency seeks to render a decision based on a vague standard, the agency must provide "definitional content" to that standard. *Id.* It "must be possible for the regulated class to perceive the principles which are guiding agency action." *Id.* at 661; *see also id.* at 652, 660 (concluding that FDA failed to give sufficient definitional content when applying the standard "significant scientific agreement"). When an agency puts the burden of proof on a regulated party, "it must have a theory of what a prima facie case *is* before it rejects claims for failure to meet that standard." *City of Vernon v. FERC*, 845 F.2d 1042, 1048 (D.C. Cir. 1988). The agency must say what "elements are necessary *and sufficient* to make a prima facie case, instead of merely noting the absence of particular elements that may or may not be part of a prima facie case." *Id.* at 1048; *see also Amoco Prod. Co. v. FERC*, 158 F.3d 593, 596 (D.C. Cir. 1998) (remanding agency decision that revenues were not "significant," where agency failed to explain how much revenue should be regarded as significant); *Am. Lung Ass'n v. EPA*, 134 F.3d 388, 392-93 (D.C. Cir. 1998) (agency head must "describe[] the standard under which she has arrived at [her] conclusion" in order to facilitate judicial review). An agency that regulates on the basis of "I know it when I see it" does not engage in reasoned decisionmaking. *Pearson*, 164 F.3d at 660; *City of Vernon*, 845 F.2d at 1048.

The agency must explain departures from past precedent. "Reasoned decision making … necessarily requires the agency to acknowledge and provide an adequate explanation

for its departure from established precedent." *Dillmon v. Nat'l Transp. Safety Bd.*, 588 F.3d 1085, 1089-90 (D.C. Cir. 2009); *id.* ("[A]gency action is arbitrary and capricious if it departs from agency precedent without explanation."); *see also Jicarilla Apache Nation v. U.S. Dept. of Interior*, 613 F.3d 1112, 1120 (D.C. Cir. 2010) ("[W]e have never approved an agency's decision to completely ignore relevant precedent."); *Encino Motorcars, LLC v. Navarro*, -- S. Ct. --, 2016 WL 3369424, at *7 (S. Ct. June 20, 2016) ("[A]n unexplained inconsistency in agency policy is a reason for holding an interpretation to be an arbitrary and capricious change from agency practice." (internal quotation marks omitted)).

The agency must evaluate the pertinent evidence. "[A]n agency's refusal to consider evidence bearing on the issue before it constitutes arbitrary agency action within the meaning of § 706." *Butte Cnty., Cal. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010); *see also Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); *Comcast Corp. v. FCC*, 579 F.3d 1, 8 (D.C.Cir. 2009). "The substantiality of evidence must take into account whatever in the record fairly detracts from its weight." *Universal Camera Corp. v. NLRB*, 340 U.S. 474, 487–88 (1951); *Ass'n of Data Processing Serv. Orgs., Inc. v. Bd. of Governors of Fed. Reserve Sys.*, 745 F.2d 677, 683 (D.C. Cir. 1984) (concluding that "in their application to the requirement of factual support the substantial evidence test and the arbitrary or capricious test are one and the same").

FDA's Letter Ruling runs afoul of these principles and was therefore arbitrary and capricious for at least ***five*** reasons.

First, FDA did not acknowledge, much less explain, its departure from practice in past cases where the agency provided a drug sponsor with advance notice that the sponsor's showing of clinical superiority was deficient and gave the sponsor an opportunity to cure that deficiency.

See FDA0685; FDA, *Review of an Amended Request for Orphan Drug Designation for Procysbi* at 5. FDA's failure to provide the same procedural benefit to Eagle without adequate explanation is arbitrary and capricious. *See Schucker v. FDIC*, 401 F.3d 1347, 1355 (Fed. Cir. 2005) (agency acts arbitrarily and capriciously when it deviates without explanation from past practice of allowing rebuttal evidence).

Second, FDA repeatedly rejected Eagle's arguments for clinical superiority because of a failure to make a sufficient evidentiary showing to establish greater safety or a MC to PC. *See, e.g.*, [redacted] Of course, Eagle indisputably *did* provide materials in support of its assertion of clinical superiority on all of these points, *see* FDA1644-85, and FDA goes to great lengths in its Letter Ruling in an attempt to establish that Eagle's support was *not good enough*. But nowhere does FDA articulate standards for what *would* be good enough, rendering it

impossible for this Court to review whether Eagle's showing met the applicable threshold. *See Pearson*, 164 F.3d at 660; *City of Vernon*, 845 F.2d at 1048; *Amoco Prod. Co.*, 158 F.3d at 596.

To provide just one example, Bendeka indisputably reduces the treatment time necessary to administer the drug from 30-60 minutes to *10* minutes, a reduction in treatment time of 66.67-83.33% and savings of up to 50 minutes. FDA0022. In the real world, reducing treatment time by almost an hour is a very significant benefit to patients. And FDA has previously indicated that "duration of treatment; patient comfort; improvements in drug efficiency; advances in the ease and comfort of drug administration" could be sufficient benefits to establish a MC to PC. 57 Fed. Reg. 62076, 62079. [redacted]

Third, FDA flip-flopped on its treatment of the inherent safety benefits of eliminating reconstitution—a step where clinicians must convert a powder into an injectable liquid. [redacted] However, the record shows that FDA had previously considered a new drug that eliminates reconstitution to be *per se* safer than a similar drug requiring reconstitution, *without requiring a further clinical showing*. FDA1743 ("[V]arious review divisions in both CDER and CBER have consider [sic] an oral

solution requiring no reconstitution to be clinically superior to a powder that must be reconstituted into an oral solution because the oral solution is manufactured under GMP and is thus safer than the product that requires reconstitution (assuming all else is comparable).”). The reason why is obvious: reconstitution effectively serves as part of the manufacturing process for the drug that occurs outside of the strict manufacturing controls applicable to manufactures, inviting all kinds of human error by the clinician.[6] In such a circumstance, FDA concluded, “additional clinical trials (and certainly not head-to-head clinical trials) were not required.” *Id.* Despite explicitly recognizing that this precedent could be relevant—it was provided as an *example* to the review divisions in this administrative record—FDA failed to acknowledge it or explain its departure from it. *Jicarilla*, 613 F.3d at 1120 (“[W]e have never approved an agency’s decision to completely ignore relevant precedent.”).

Fourth, FDA failed to even *analyze* one of Eagle’s proposed bases for clinical superiority. Unlike Treanda liquid, Bendeka is formulated without N, N-dimethylacetamide (“DMA”)—a substance so potentially dangerous that FDA published a “safety alert” for healthcare providers warning of its risks. FDA1828. According to FDA’s warning, the DMA in Treanda liquid can cause components of certain critical medical equipment to ***literally dissolve on contact***, leading to “possible product contamination, and ***potential serious adverse health consequences***, including … ***the risk of small blood vessel blockage in patients***.” *Id.* (emphasis added); FDA1831-32. Use of Bendeka eliminates this risk entirely. But the Letter Ruling failed

[6] Indeed, Eagle recently became aware of another precedent where FDA found clinical superiority on similar grounds (again, Eagle learned of this through an industry blog, not voluntary release on FDA’s part). *See* FDA, Review of an Request for Orphan Drug Designation for Xaluprine at 2 (July 12, 2012), *available at* http://www.fdalawblog.net/Mercaptopurine%20-%20OOPD%20Memo.pdf (“[A]n oral liquid formulation… would be a ‘safer’ product than the approved tablet formulation by eliminating the need for compounding procedures and thus reducing or avoiding potential serious medication errors.”).

to even *address* Eagle's argument for greater safety on this basis. [redacted][7] That is also arbitrary and capricious. *See State Farm*, 463 U.S. at 43 (agency acts arbitrarily and capriciously when it fails to consider relevant information).

Fifth, FDA ignored evidence submitted by Eagle that should have established Bendeka's clinical superiority over Treanda based on greater safety in patients with renal and cardiovascular comorbidities due to reduced sodium intake. Bendeka reduces the sodium load to a patient by up to 1769 mg per day of treatment over both versions of Treanda. FDA0017. [redacted] *FDA entirely failed to address the third article submitted by Eagle*, FDA1206, which demonstrates that 11% of CLL and NHL patients studied had creatinine clearance levels showing renal impairment, and 49% of CLL patients and 38% of NHL patients had creatinine clearance levels below those of healthy adults, FDA1209.[8] Thus, renal comorbidities do exist in a substantial portion of the patient population.

[7] To the extent the Letter Ruling rejects Eagle's claim of increased safety, it does so on the basis of the existence of the DMA-free Treanda powder. FDA0028. But that is no answer, because Bendeka is also clinically superior under FDA precedent to the Treanda powder. *See supra* pp. 41-42 (explaining that FDA should have recognized Bendeka as clinically superior to Treanda powder on the basis of elimination of reconstitution).

[8] The 49% calculation is based on the total number of CLL patients (379) minus the number of CLL patients with creatinine clearance levels greater than or equal to 60 mL/min (193), which equals 186 patients. 186/379 is 49%. Similarly, the 38% calculation is based on the total number of NHL patients (561) minus the number of NHL patients with creatinine clearance

[redacted]

For at least these reasons, FDA's Letter Ruling was arbitrary and capricious and must be vacated and remanded.

CONCLUSION

For the foregoing reasons, Eagle's motion for summary judgment should be granted.

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levels greater than or equal to 60 mL/min (346), which equals 215 patients. 215/561 is 38%. Patients with creatinine clearance levels of up to even 80 mL/min present some degree of renal impairment. FDA1208. These figures conservatively include patients with levels only up to 60 mL/min.