IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMGEN INC.,	
Plaintiff,	
v.	Civil Action No. _____
THOMAS E. PRICE, M.D., in his official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,	
and	
SCOTT GOTTLIEB, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION,	
Defendants.	

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF AMGEN INC.'S MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

Catherine E. Stetson (D.C. Bar # 453221)
Susan M. Cook (D.C. Bar # 462978)
HOGAN LOVELLS US LLP
555 Thirteenth Street, NW
Washington, DC 20004

Counsel for Plaintiff Amgen Inc.

Dated: May 25, 2017

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases **Page(s)**

Statutes

INTRODUCTION

Seven years ago, in May 2010, the FDA asked plaintiff Amgen Inc. to conduct studies in several small pediatric populations with Amgen's SENSIPAR® (cinacalcet hydrochloride) Tablets, which helps regulate excess calcium in the blood of certain dialysis patients. Because pediatric studies often are difficult and resource-intensive, Congress put in place a valuable incentive for companies to respond when FDA requests such studies: six months of additional exclusivity and patent protection, which is extended to the drug sponsor upon "accept[ance]" by FDA of the sponsoring company's study reports. *See* 21 U.S.C. § 355a(b)(1). The statute also sets a deadline for FDA to "accept" the study reports: 9 months before the expiration of any affected patent. That deadline is June 8, 2017 for the critical patent covering SENSIPAR, and that impending deadline is the reason for this TRO motion.

Whether FDA will accept a drug sponsor's reports is not a difficult – or even a particularly substantive – question. The statute instructs the agency that its "*only* responsibility" is to confirm that (1) the studies were conducted in accordance with applicable scientific principles, (2) the studies "fairly respond" to the agency's request, and (3) the study reports were submitted in accordance with the agency's filing requirements. *Id.* § 355a(d)(3). The requested pediatric studies need not demonstrate that the drug is actually safe and effective in children to warrant pediatric exclusivity. Nor must they be sufficient to support a pediatric indication on the drug product's labeling. Nor must the studies even "*fully*" or "*completely*" respond to the agency's request. Congress's goal was simply to encourage drug sponsors to conduct pediatric studies, regardless of the results. Once a drug sponsor like Amgen tenders the *quid*, in other words, FDA is obligated to provide the *quo*.

Amgen expended years of work and approximately $10 million performing the pediatric studies FDA requested with SENSIPAR, despite considerable odds and numerous setbacks along the way. The company delivered the study reports – thousands of pages of them – to FDA on November 23 of last year. That started a clock for the agency, which had 180 days, or until May 22, to "accept" or reject the reports under the controlling statute. *Id.* § 355a(d)(3).

On May 22, FDA informed Amgen by letter that it did *not* accept the reports the company had so carefully performed, pursued, and assembled.

FDA's decision violated the Administrative Procedure Act in as many ways as that Act can be violated. *First*, the agency acted contrary to the plain terms of its governing statute by faulting Amgen for its failure to fulfill "*one criterion*" of several study requests, when the statute requires merely that the studies "fairly respond" to the agency's written request. *Second*, the agency also violated the statute by conflating the standard for accepting study reports with the different, separate, and more rigorous statutory standard for assessing a drug's safety. *Third*, by denying pediatric exclusivity, FDA deviated from its treatment of similarly situated sponsors and broke with the agency's longstanding practice, without explanation. *Fourth*, FDA's denial of pediatric exclusivity lacks any logical basis, because it is premised on Amgen's failure to achieve an impossible goal set by the agency – one that the agency itself cemented by refusing to accommodate amendments to the relevant study. And *fifth*, FDA violated Amgen's due process rights by changing the agency's interpretation of the statute without providing Amgen advance notice of its newfound interpretation.

Amgen is before this Court seeking emergency relief because there is another statutory clock that still continues to tick. The controlling statute states that the Secretary "shall not extend" the additional period of exclusivity if the accept-or-reject "determination . . . is made

later than 9 months prior to the expiration" of the relevant patent period. 21 U.S.C. § 355a(c)(2). A key patent covering SENSIPAR is set to expire on March 8, 2018 – meaning that June 8, 2017 is the statutory deadline for FDA to determine that it will accept Amgen's reports in order to preserve the company's entitlement to the additional patent exclusivity period. Amgen therefore requests a TRO or preliminary injunction by **June 6, 2017,** directing the agency to accept Amgen's reports no later than June 8, 2017, to preserve the status quo pending a favorable resolution by the agency or further order by the court.

The four factors governing injunctive relief strongly favor issuing an injunction in this case. First, Amgen's likelihood of success is strong. FDA's denial of pediatric exclusivity contravenes the plain language of the statute, undermines the incentive Congress crafted to encourage companies in Amgen's circumstances to conduct pediatric studies, contradicts the agency's past practices, and lacks any basis in reason. Moreover, both Amgen and the public interest will be irreparably harmed absent the requested injunctive relief – Amgen could stand to lose the full benefit of its pediatric exclusivity, and the public interest could be crushed by the agency's failure to recognize the incentives put in place by Congress to encourage pediatric studies. Neither FDA nor generic manufacturers will suffer any harm if injunctive relief is granted: The imminent statutory deadline, although critical to Amgen to preserve its rights, will not have any immediate effect on any third parties, who are barred from entering the marketplace until at least March 2018, when Amgen's key patent expires.

FACTUAL BACKGROUND

Statutory Framework

The Food, Drug, and Cosmetic Act (FDCA) mandates that all new prescription drugs obtain FDA approval before they can be marketed. 21 U.S.C. § 355(a). Manufacturers of brand name (also known as "innovator") drugs must demonstrate the safety and effectiveness of their products in order to gain FDA approval. Companies typically accomplish that by conducting pre-clinical and clinical studies and submitting the resulting data to FDA in a new drug application (NDA). 21 U.S.C. § 355(b)(1). Upon approval, a pioneer drug may be entitled to periods of marketing exclusivity and patent-related protections. Complaint ¶ 17. After any such periods of exclusivity and patent protections expire, FDA may approve competing manufacturers' generic drugs, which are essentially copies of the already approved innovator product. *Id.*

Most drugs are designed for and tested exclusively in adult populations. Conducting clinical trials in children is a daunting task: Pediatric patient populations are often small, potential liability is higher because of larger lifetime-damages awards, there are fewer experts with the requisite experience to run pediatric testing (such as the pediatric nephrologists involved in the studies at issue here), trial participation can be difficult for small children, parents are often reluctant to subject their children to the repeated blood draws associated with clinical studies, and there are unique consent and ethical issues at play. Complaint ¶ 18. For all of these reasons, drugs approved for use in the United States have long lacked sufficient pediatric

information for drug-labeling purposes.[1] This lack of information has, in turn, resulted in the persistent reality that most drugs are prescribed to children "off label" and without dosing instructions, which poses risks to pediatric patients. *Id.*

Six-month Pediatric Exclusivity

To remedy these deficiencies, Congress passed the Best Pharmaceuticals for Children Act (BPCA), which created an incentive for sponsors to undertake vital testing in pediatric populations. S. Rep. No. 105-43, at 51 (1997). The statute is straightforward: FDA issues a written request for pediatric studies if the agency "determines that information relating to the use of a … drug in the pediatric population may produce health benefits in that population." *Id.* § 355a(b)(1), (c)(1). The request, which is to be developed "after consultation with the sponsor" must be written, must include a timeframe for the studies" and must "request [that] … the sponsor … propose pediatric labeling resulting from such studies." *Id.* § 355a(d)(1)(A).

If a sponsor conducts the studies sought by FDA in the written request and submits reports of the study results to FDA, the agency has 180 days to either accept or reject the reports. FDA's "only responsibility" in accepting or rejecting the reports is to determine whether (1) "the studies fairly respond to the written request," (2) the studies "have been conducted in accordance with commonly accepted scientific principles and protocols," and (3) the studies "have been reported in accordance with the requirements of the [agency] for filing." *Id.* § 355a(d)(3). If each of the criteria is met, FDA must accept the reports, at which point the six-month extension of exclusivity and patent protection automatically applies. *Id.* at §§ 355a(b)(1), (c)(1) (exclusivities and patent protection extended if pediatric study reports are "accepted").

---

[1] *See* Karena J. Cooper, *Pediatric Marketing Exclusivity—As Altered by the Best Pharmaceuticals for Children Act of 2002*, 57 Food & Drug L.J. 519, 520 (2002).

Whether the studies ultimately *support* an indicated use for children – that is, whether they successfully demonstrate safety and efficacy – is irrelevant to FDA's decision to accept the studies and recognize the six additional months of pediatric exclusivity. *See id.* Indeed, the studies need not even be conclusive. *See id.*

FDA's Written Request for SENSIPAR

FDA first approved SENSIPAR in March 2004. Complaint ¶ 26. The product currently is approved for use in adult patients for treating (i) secondary HPT in patients with chronic kidney disease on dialysis; (ii) hypercalcemia (too much calcium in the blood) in patients with parathyroid carcinoma, a malignancy of the parathyroid glands; and (iii) severe hypercalcemia in patients with primary HPT who are unable to undergo parathyroidectomy – the surgical removal of one or more of the parathyroid glands. FDA, Approval Letter for NDA 21-688 (Mar. 8 2004); FDA, Supplemental Approval Letter for NDA 021588/S-015 (Feb. 25, 2011).[2]

There was and remains an unmet medical need to treat secondary HPT in children. Left untreated, secondary HPT in children can lead to bone fractures, bone pain, bone deformities, decreased bone mass, and overall retarded growth. Complaint ¶ 27. To that end, in May 2010, FDA issued a written request to Amgen for pediatric studies in these pediatric patients in May 2010. Ex. 3. Over the next five years – and as commonly occurs when the agency and a drug sponsor work together to gather pediatric study information[3] – FDA's written request was amended five times based on frequent exchanges of information about the ongoing clinical studies between Amgen and FDA. Ex. 4; Ex. 5; Ex. 6; Ex. 7; Ex. 8.

---

[2] Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-688_Sensipar.cfm; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021688s015ltr.pdf.

[3] Available at https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm049997.htm

As finally amended, FDA's written request asked Amgen to perform the following four pediatric studies:

Study 1: A single-dose pharmacokinetics/pharmacodynamics (PK/PD)[4] study in pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary HPT receiving dialysis.

Study 2: A 30-week, randomized, double-blind, placebo-controlled, safety and efficacy study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary HPT receiving dialysis.

Study 3: A 26-week or time-until-transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to < 6 years.

Study 4: A 20-week, randomized, open-label, controlled study in pediatric subjects between the ages of 6 and < 18 years, with secondary HPT and chronic kidney disease who are receiving either hemodialysis or peritoneal dialysis.

Ex. 8. FDA set November 25, 2016 as the deadline for Amgen to report the results of the studies. Ex. 6.

Amgen's Study Reports

Amgen not only responded to FDA's written request for pediatric studies by that date; it far exceeded the scope of FDA's request. Complaint ¶ 31. In total, Amgen performed *nine* studies over the span of roughly eleven years, together covering 103 pediatric patients who received at least one dose of SENSIPAR in interventional clinical trials, along with an additional 113 patients who received SENSIPAR in either a registry or chart review. Ex. 9 at 7–8, tbl. 2.

---

[4] Pharmacokinetics is the "branch of pharmacology that deals with the movement of drugs within the body," and in particular the "quantitative aspects of their absorption, distribution, metabolism, etc." *Pharmacokinetics*, Oxford English Dictionary (2017). Pharmacodynamics refers to the "branch of pharmacology that deals with the actions of drugs" and "the characteristics of the action of a particular drug." *Pharmacodynamics*, Oxford English Dictionary (2017). PK/PD data in children are important to making dosing decisions for pediatric patients.

As to the four studies enumerated in FDA's written request, Amgen successfully completed Study 1, Study 2, and Study 4 precisely according to the terms of the agency's written request, even over-enrolling one study as permitted. *See* Ex. 2.

Unfortunately, Amgen confronted insurmountable obstacles beyond the company's control in its efforts to enroll a sufficient number of patients able to complete Study 3. FDA's written request asked that Study 3 involve a minimum of 15 patients who would be treated for either 26 weeks or, if a patient received a kidney transplant during the study, 12 weeks prior to transplant. Ex. 8. Amgen enrolled 18 patients in the study. However, a December 2012 report of the death of a child in Study 2 led FDA in February 2013 to temporarily suspend further testing on pediatric patients with secondary HPT. Ex. 11. During that partial clinical hold, which lasted through April 2014, Amgen was prohibited from enrolling new patients, and already enrolled patients could not be dosed with the drug. FDA also made additional safety-related changes to the written request in force at the time. Ex. 6.

Even before the partial clinical hold, Amgen faced an almost impossible challenge with enrollment in Study 3. There are fewer than 300 patients under age six receiving dialysis in the entire *country*. Complaint ¶ 38. And pediatric patients – especially those under six years old, comprising Study 3's population – are routinely prioritized for kidney transplants. *Id.* Relatedly, many of these very young pediatric patients' parents focused their efforts on finding a donor rather than beginning the cumbersome process of enrollment in a clinical study, including the repeated blood draws associated therewith. *Id.* Recruitment was additionally challenging because general nephrologists will not treat pediatric patients, and there are few pediatric nephrologists. Ex. 12.

But the clinical hold made an *almost* impossible task *actually* impossible. Following the start of the clinical hold, during which enrolled patients were not receiving treatment, six of the eight then-enrolled patients left the study. Complaint ¶ 40. Four of those who discontinued treatment left as a result of the partial clinical hold, another received a kidney transplant, and the sixth patient withdrew on the day of enrollment without receiving a dose of cinacalcet. *Id.* And while Amgen was able to enroll another 10 patients after the hold was lifted, by the end of the study only three patients had stayed enrolled throughout the required 26-week treatment period and one other completed the minimum 12 weeks' treatment before receiving a kidney transplant. *Id.* At the end of the day, a total of 11 patients were enrolled for at least 12 weeks in the study, but only four enrollees ultimately met all completion criteria. Ex. 10.

Notwithstanding these challenges, Amgen made every effort to reach the target number of completing patients in Study 3. Amgen held the enrollment period open for more than three years (from January 2012 to June 2016, not counting the fourteen-month clinical hold). Complaint ¶ 41. The company also implemented a comprehensive recruitment and retention program that involved generating a large number of study sites, engaging site-management organizations, offering home healthcare services for the benefits of enrolled patients, providing extensive support services, collaborating with the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) organization, organizing additional investigator meetings, and simplifying the protocol in response to feedback from site personal. Ex. 9 at 5. But even with these Herculean efforts, the inherent challenges of pediatric studies combined with the clinical hold were simply too disruptive, and Amgen was unable to enroll sufficient completing patients to meet FDA's target.

Nevertheless, FDA continued to push Amgen to continue with the study program. In a September 2013 teleconference – during the clinical hold – Amgen asked whether FDA agreed with Amgen's recommendation to discontinue the studies altogether. FDA responded: "No we do not agree, we continue to believe that cinacalcet can be useful for the management of secondary [HPT] in the pediatric population and that the cinacalcet pediatric program should continue with enhanced titration and monitoring safeguards." Ex. 1 at 4. The official meeting minutes from that conference (prepared by FDA) also recount that: "FDA stated that this pediatric program was very important to understand how to use this drug in the pediatric population." *Id.* at 5. The agency noted: "We have learned a lot from the analysis of the clinical data collected during the pediatric program." *Id.* at 7.

After receiving the agency's instruction to continue, and for the next two and a half years, Amgen continued to pour resources into the pediatric studies. All told, Amgen invested approximately $10 million to $15 million over the space of eleven years in performing the pediatric studies requested by FDA. Complaint ¶ 43.

FDA's Refusal to Amend the Written Request for Study 3

In the fall of 2015, Amgen requested that FDA amend its written request to accommodate the effects of the clinical hold on Study 3 and meet with the company to discuss the rationale for the requested amendments. *Id.* Amgen approached the agency to inform FDA of the unique challenges the study (and the hold) raised and to seek corresponding modifications to completing patient enrollments. Ex. 14. FDA refused to even meet with Amgen to discuss the issue. Instead, the agency responded that "we will not have any more discussion on this" and directed Amgen to "use [its] discretion moving forward." Ex. 13. The agency then denied Amgen's requests without explanation. Ex. 15.

Without further direction from the agency, Amgen pressed ahead to complete all of the studies, doing everything it could to address the particularly daunting enrollment challenges associated with Study 3. Complaint ¶ 46. Amgen also supplemented the study data with two studies analyzing real-world treatment evidence from patients administered SENSIPAR. One was a retrospective study of 538 pediatric patients with end-stage renal failure, which described and analyzed the course of treatment, both among those who had used SENSIPAR and those who had not, as an additional source of data about the drug. *Id.*

Amgen's Request for Pediatric Exclusivity

On November 23, 2016 – two days before the deadline set by FDA – Amgen submitted reports of the results of the requested pediatric studies in line with FDA's filing requirements, via a supplement to the SENSIPAR NDA. *Id.* ¶ 47. Amgen's submission met every single requirement of the written request except for one criterion: the number of completers in Study 3. Amgen performed all necessary pharmacokinetic and clinical studies, and it even supplemented the requested materials with additional statistical analyses and retrospective studies of patients receiving the drug in clinical practice. Ex. 9. Amgen therefore requested pediatric exclusivity. Amgen also sought approval of a pediatric indication for SENSIPAR, which would provide information to prescribers about how to use the drug safely and effectively in pediatric patients. *Id.*

The data and information Amgen provided to FDA were useful to the agency – with respect to *all four* studies. *See* Ex. 1 at 5, 7 ("We have learned a lot from the analysis of the clinical data collected during the pediatric program."). In Study 3, for example, the primary safety goal was to determine the proportion of patients whose serum calcium levels were below a certain target (9.0 mg/dL for patients under 2 years and 8.4 mg/dL for patients 2-6 years).

Pooling data from Study 1 (N = 14 SENSIPAR-treated children < 6 years of age), Study 3 (N=17 SENSIPAR-treated children < 6 years of age), the retrospective chart review (N=23 SENSIPAR-treated children < 6 years of age), and the prospective cohort study (which included 9 SENSIPAR-treated children < 6 years of age), Amgen submitted safety data from 63 patients under age 6 who received SENSIPAR. Complaint ¶ 48. This was a remarkable accomplishment. There are fewer than 300 patients under age six receiving dialysis in the entire *country*, meaning that Amgen managed to painstakingly gather data from over 20 percent of the entire patient subpopulation. Ex. 9 at 1. And FDA has admitted that it "learned a lot" from the studies. Ex. 1 at 7.

FDA's Denial of Pediatric Exclusivity

In addition to the 180 day deadline for responding to a request for exclusivity, the BPCA also sets another deadline: FDA "shall not extend" an underlying patent or regulatory exclusivity period to reflect pediatric exclusivity "if the determination made under subsection (d)(3) is made later than 9 months prior to the expiration of" the underlying patent exclusivity. *Id.* §§ 355a(b)(2), (c)(2). Because a key patent covering SENSIPAR (the '068 Patent) is set to expire on March 8, 2018, that statutory deadline is June 8, 2017.

Monday, May 22, was the deadline for the agency to accept or reject Amgen's studies. 21 U.S.C. § 355a(d)(3). Late Monday evening, the agency denied Amgen's request for pediatric exclusivity. Ex. 2. The denial letter admitted that "Amgen has met the literal terms of the [written request] for Studies 1, 2, and 4." *Id.* at 7. The letter also conceded that Study 3 fell short by a single criterion. *Id.* at 10. The agency nevertheless concluded that because "this criterion was not met," Amgen "has failed to fairly respond" to the written request.

The agency's denial letter also made clear that FDA considered whether Amgen's studies were "sufficient" to demonstrate safety (or the absence thereof) as part of its pediatric exclusivity analysis. *Id.* at 2, 3, 10. According to FDA, Amgen's "failure to provide sufficient safety data" in the youngest pediatric group "*prevent[ed] FDA from drawing any conclusions about the safety of the product*" in that population. *Id.* at 10 (emphasis added). As the agency saw it, "[i]f the totality of safety information Amgen submitted had provided an appropriate safety assessment in younger children *and supported a label description*—even if the exact minimum number of patients had not been met [ ]—this element of the [written response] could have been adequately satisfied and Amgen's response could be considered a fair response." *Id.* (emphasis added). Thus, because the agency found insufficient "safety information" pertaining to the youngest group studied, Amgen "failed to fairly respond." *Id.*

The agency's decision violates the statute twice over: It wrongly held Amgen to a standard of "*full* response," when the statute requires only "fair response." And it wrongly imported a safety assessment into its analysis, when the statute contains no such requirement. Whether a drug is safe (or unsafe) for a pediatric population is a different inquiry, governed by a different statute, and gauged by different standards. FDA was flatly wrong to import that inquiry into this determination.

The agency's decision also represents a sharp departure from multiple instances in the past where FDA has granted exclusivity even where one, two, or more study criteria were unsatisfied. The agency also failed to justify its conclusion with adequate reasoning. And (because it departed from past practice) the agency also ran afoul of fundamental due-process principles when it failed to notify Amgen that it would hold the company to a "fully respond," not a "fairly respond," standard.

There is a dispute resolution process available to Amgen within FDA, and Amgen intends to pursue that avenue; but in the meantime, the June 8 statutory deadline is ticking down. And only this Court can grant relief that will maintain the status quo during the administrative appeals process: a TRO requiring FDA to accept Amgen's studies pending either a favorable outcome of the administrative appeal, or resolution by this Court of a preliminary-injunction or summary-judgment motion.

ARGUMENT

To secure a TRO or preliminary injunction, a movant must establish (1) "that he is likely to succeed on the merits," (2) "that he is likely to suffer irreparable harm in the absence of preliminary relief," (3) "that the balance of equities tips in his favor," and (4) "that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 21 (2008); *see also Council on Am.-Islamic Relations v. Gaubatz*, 667 F. Supp. 2d 67, 74 (D.D.C. 2009) ("The standard for obtaining injunctive relief through either a temporary restraining order or a preliminary injunction is well established."). These four factors all strongly favor granting the requested relief.

I. AMGEN IS LIKELY TO PREVAIL ON THE MERITS.

The Administrative Procedure Act (APA) requires a reviewing court to "hold unlawful and set aside agency action, findings, and conclusions" that are determined to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Judicial review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987). A reviewing court may defer to an agency's technical judgments to the extent they are consistent and reasonable – but the court need not defer to an agency's interpretation of a statute

that does not call upon the agency's special expertise, nor should a court give *any* deference to an agency's legal conclusions. *See King v. Burwell*, 135 S. Ct. 2480, 2489 (2015); *PDK Labs. Inc. v. DEA*, 362 F.3d 786, 797 (D.C. Cir. 2004) (to warrant deference, "it is incumbent upon the agency not to rest simply on its parsing of the statutory language. It must bring its experience and expertise to bear in light of competing interests at stake.").

Four important administrative procedure principles control this case. Agency action is routinely set aside as unlawful where it violates a statute, *see, e.g.*, *Bennett v. Donovan*, 4 F. Supp. 3d 5, 13 (D.D.C. 2013), because agencies must "stay[ ] within the bounds of their statutory authority." *Util. Air Regulatory Grp. v. EPA*, 134 S. Ct. 2427, 2439 (2014). Agency action is also arbitrary and capricious when it treats similarly situated parties differently without adequate explanation. *See, e.g.*, *Lone Mountain Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013). Agency conduct violates the APA where it defies logic and reflects a want of reasoned decisionmaking. *See, e.g.*, *Fox v. Clinton*, 684 F.3d 67, 80 (D.C. Cir. 2012). And agency action violates the APA when it is unconstitutional. *See, e.g.*, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 516 (2009).

FDA flunks *all* of the standard APA tests here, as we next explain.

A. FDA Violated the Plain Language of its Governing Statute By Effectively Requiring Perfect Compliance with the Written Requests.

1. The Statutory Bargain

In the BPCA, Congress created a statutory bargain: in exchange for conducting pediatric studies that "fairly respond" to a request by FDA, a drug sponsor is entitled to receive an additional six months of regulatory exclusivity, as well as a six-month extension on the preclusive effect of certain patents. 21 U.S.C. §§ 355a(b)(1), (c)(1). The statute makes clear that

the *response* to FDA – and not any substantive showing of safety or efficacy – is what matters: By the statute's own terms, FDA's "*only* responsibility" in deciding whether to accept the studies is to confirm (1) that the studies "have been conducted in accordance with commonly accepted scientific principles and protocols"; (2) that "the studies fairly respond to the written request"; and (3) that the study results "have been reported in accordance with the requirements of the Secretary for filing." 21 U.S.C. § 355a(d)(3) (emphasis added). Once the studies and reports meet those objective standards, FDA must accept the reports, and the six-month extension of exclusivity and patent protection automatically applies. *Id.* § 355a(b)(1), (c)(1).

FDA can take no issue with checklist items (1) and (3). But FDA rejected the study reports, having concluded that Amgen's studies did not "fairly respond" to the agency's written request. Ex. 2. That is an insupportable conclusion under the statute.

2. The Agency's Interpretation Fails At *Chevron* Step One.

FDA's denial letter leaves no mystery about the standard that the agency applied here. FDA admits that "Amgen has met the literal terms of the [written request] for Studies 1, 2, and 4." *Id.* at 7. It also admits that Study 3 fell short by only "one criterion." *Id.* at 10. And yet it denied exclusivity. To be quite clear on this: Amgen performed nine clinical studies. It gave 103 patients at least one dose of SENSIPAR in interventional clinical trials. It submitted thousands of pages of data and analysis to FDA. And it pressed forward (at FDA's behest) against substantial countervailing factors. Yet FDA found its response lacking because of that one requirement in one study. That is not a "fair[] respon[se]" standard; it is a "perfect compliance" standard, and it flatly contradicts the controlling statute.

a. The Text of the Statute is Clear.

The two steps of the standard *Chevron* analysis are old hat. "First, always, is the question whether Congress has directly spoken to the precise question at issue." *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984). To determine Congressional intent, a court is charged with "employing traditional tools of statutory construction," including evaluation of a statute's "text, structure, purpose and history." *Hearth, Patio & Barbecue Ass'n v. U.S. Dep't of Energy*, 706 F.3d 499, 503 (D.C. Cir. 2013). "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." *Chevron*, 467 U.S. at 842-843.

These principles are easy to apply in the present case: To find FDA's statutory interpretation unlawful, this Court need look no further than the controlling statutory text. *See Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 461-462 (2002) ("[C]ourts must presume that a legislature says in a statute what it means and means in a statute what it says there."). Congress deliberately made clear that, in determining whether to accept pediatric studies, FDA's "*only* responsibility" (along with the other ministerial acts of ensuring compliance with scientific protocols and filing requirements) was to determine whether the studies "fairly respond" to the written requests, in addition to the two ministerial factors. That phrase – "fairly respond" – is rare. Indeed, this appears to be the only place in the entire U.S. Code where it is used, outside of rules of court procedure.[5] But its meaning can be guided by fundamental legal principles, and further informed by context.

---

[5] The phrase appears twice in the Federal Rules of Civil Procedure, once in Rule 8 and again in Rule 36. In each instance, parties are instructed to "fairly respond" to the substance of the

"Fairly respond" means "fairly respond." It does not mean "comply to the letter." *See, e.g.*, Webster's II New College Dictionary (1995) (defining "fairly" to mean "moderately"). This court has already decided as much. In *Merck & Co. v. FDA*, 148 F. Supp. 2d 27, 30 (D.D.C. 2001), a drug sponsor challenged FDA's denial of its request for pediatric exclusivity for its drug Mevacor. FDA based its denial on the fact that in one study (of two requested), only five girls were treated with the subject drug for six months or more. The court rejected that rationale, noting that Section 355a(d)(3) "plainly does not require compliance with every single provision of a written request, but requires only that a pediatric study 'fairly respond' to a written request." *Id.* The court went on: "Nor would it be consistent with the statutory standard to deny pediatric exclusivity because of disappointment with data submitted by a manufacturer if the study *as a whole* is a fair response to the written request." *Id.* (emphasis added).

That analysis is sound. Congress chose the phrase "fairly respond" over other, more common formulations – say, "fully," "completely," or even "substantially" – to make clear that perfect compliance with the agency's request was not contemplated or required. *Compare, e.g.*, 21 U.S.C. § 355(j)(5)(B)(iv)(II)(cc) (regarding ANDA exclusivity) ("As used in this subsection, the term '*substantially complete application*' means an application . . . that on its face is sufficiently complete to permit a substantive review and contains all the information required.") (emphasis added); 21 U.S.C. § 355(b)(1)(A)-(D) (regarding NDA contents) (requiring, *inter alia*, "*full* reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; … a *full* list of the articles used as components of such drug; … a *full* statement of the composition of such drug; [and] a *full* description of the

---

allegation (in Rule 8(b)(2)) or the matter on which a request for admission is made (in Rule 36(a)(4)).

methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug") (emphases added); 21 U.S.C. § 346a(b)(2)(D) (regarding pesticide chemical residue tolerances or exemptions) (directing Administrator to consider the "validity, *completeness*, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue") (emphasis added). Congress intentionally chose the phrase "fairly respond" over these other formulations to make clear that drug sponsors were *not* required to meet all of the study parameters requested by FDA.

b. The Statute's Context Supports Amgen.

The statute's context and underlying purpose confirm the text's plain meaning. *See Deal v. United States*, 508 U.S. 129, 132 (1993) (observing that "the meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used"). At the heart of the bargain struck by Congress – indeed, the entire reason for pediatric exclusivity – is the undeniable reality that testing drugs in pediatric populations is a singularly daunting proposition, as Amgen's experiences with SENSIPAR confirm. Construing this facially limited "fairly respond" standard to require compliance with every component and sub-component of a multi-part request – thereby investing FDA with virtually unfettered discretion to change its mind after a drug sponsor has committed substantial resources to answer the request for pediatric studies – would radically undermine the terms of Congress's intended bargain and dampen (if not extinguish) sponsors' willingness to engage with the challenges associated with pediatric studies.

All of these statutory indicators – text, context, and purpose – point in the same direction: A drug sponsor must conduct studies that "fairly respond" to the request, no more. The thrust of § 355a is clear: A sponsor's obligation is to conduct studies that "fairly respond" to FDA's written request, and once the sponsor has done so, FDA is required to uphold its end of the

bargain. That is not what happened here. FDA instead held Amgen to a standard well beyond what the plain language of the statute requires. Accordingly, FDA's interpretation of the statute fails at *Chevron* Step One.

c. This Court's Previous Ruling Supports Amgen.

In addition to text, context, and purpose, Amgen also has precedent on its side. *See Merck*, 148 F. Supp. 2d at 30. As FDA explained in that case, its written request for Mevacor required Merck to study 35 girls for at least six months. In the end, however, just *five* girls – fourteen percent of the study requirement – passed the six-month timeline. *See* Def. Mem. in Opp. to Pl.'s Mot. for a TRO and Prelim. Inj. at 11, *Merck & Co. v. FDA*, Civ. No. 1:01-cv-01343 (D.D.C. June 19, 2001), ECF No. 14. Nevertheless, this Court concluded that Merck's studies "fairly respond[ed]" to the written request and that FDA had impermissibly denied pediatric exclusivity for "failure to meet a single term of the written request." 148 F. Supp. 2d at 30.

Compare that to this case. Here, the agency has forthrightly admitted that 3 of the 4 requested studies "met the literal terms of the [written request]." Ex. 2 at 7. It also has conceded that the last study – Study 3 – fell short by only one criterion. *Id.* at 10. And Amgen's shortfall was shorter than Merck's: The written request set a target of 15 completing patients for Study 3. Amgen was able to recruit 18 patients, study 11 of them for more than 12 weeks, and have 4 patients cross the completion threshold –meaning that despite huge challenges, Amgen delivered a higher percentage (27%) of completers than Merck was able to deliver in its Mercavor study (14%). FDA made the same error here that it made in Merck.

3. Even At *Chevron* Step Two, The Agency's Interpretation Fails.

It is only when the statute is ambiguous or leaves gaps for the agency to fill that a court moves on to *Chevron* Step Two, where the question becomes whether the agency's interpretation is "based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. A court defers to an agency's permissible interpretation under Step Two only "if the agency has offered a reasoned explanation for why it chose that interpretation." *Amarin Pharm. Ireland Ltd. v. F.D.A.*, 106 F. Supp. 3d 196, 217 (D.D.C. May 28, 2015). Even under Step Two, moreover, the reasonableness of an agency's preferred interpretation "depends on the construction's 'fit' within the statutory language as well as its conformity to statutory purposes." *Abbott Labs. v. Young*, 920 F.2d 984, 988 (D.C. Cir. 1990). *See also Council for Urological Interests v. Burwell*, 790 F.3d 212, 224 (D.C. Cir. 2015) (determining at the *Chevron* Step Two stage whether a challenged regulation was "rationally related to the goals of the Stark Law"); *Shays v. FEC*, 528 F.3d 914, 919 (D.C. Cir. 2008) (observing that courts "must reject administrative constructions of a statute that frustrate the policy that Congress sought to implement") (alterations and citation omitted). And as the Supreme Court recently explained, a court does *not* defer to an agency's interpretation, even under *Chevron* Step Two, if the matter is not one that Congress intended to leave to the agency. *See, e.g.*, *King*, 135 S. Ct. at 2489.

That last principle is particularly instructive here. For even if the Court were to decide that the phrase "fairly respond" was ambiguous (which it is not), no deference to the agency would be warranted. The words "fairly respond" reflect a purely legal judgment as to which FDA has no particular expertise. FDA can claim no more authority to assess a "fair response" than this Court. (Indeed, because the "fairly respond" standard is most common in rules of procedure, *see supra* at 18 & n.4, this Court has far *greater* experience interpreting and applying

the standard than the agency.) And there is nothing in the statute to suggest that Congress intended to grant FDA *any* interpretative role under 21 U.S.C. § 355a(d)(3). Far from it, in fact. Congress tightly circumscribed FDA's role, instructing that the statutory checklist – Did the studies conform with accepted scientific principles and filing requirements?; and Did the studies fairly respond to FDA's request? – is the agency's "only responsibility." Determining whether a submission "fairly responds" to the request requires the same basic legal judgment as deciding whether something is "reasonable." And it in no way implicates the agency's unique technical or scientific expertise. *See, e.g.*, *King*, 135 S. Ct. at 2489 (denying *Chevron* deference to IRS's interpretation of provision in Affordable Care Act).

Nor does FDA's decision reflect any of the other traditional hallmarks of an agency statement to which courts defer. FDA has not promulgated any regulation – nor even offered up informal guidance – as to what "fairly respond" means; the agency simply lacks an official position to which deference, even if it were warranted, could be given. *See Bowen*, 488 U.S. at 213 (1988) ("Deference to what appears to be nothing more than an agency's convenient litigating position would be entirely inappropriate."); *U.S. v. Mead Corp.*, 533 U.S. 218, 228 (2001) ("The fair measure of deference to an agency administering its own statute has been understood to vary with circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position").

Notably, moreover, this Court has *already* rejected the reading of the statute FDA offers here. The *Merck* decision discussed above made clear that "355a(d)(3) . . . plainly does not require compliance with every single provision of a written request, but requires only that a pediatric study 'fairly respond' to a written request." 148 F. Supp. 2d at 30-31. And yet FDA

has committed the exact same mistake here. In light of the effort undertaken and the results produced, there can be no doubt that the Amgen pediatric studies "fairly respond" to FDA's written request. That is so under any conceivable definition of "fairly respond," save for the "perfect compliance even if impossible" standard that FDA has tried to blue-pencil into § 355a(d)(3). Accordingly, Amgen is likely to prevail on the merits.

B. FDA Violated the Statute By Performing an Unlawful Assessment of the Sufficiency of Safety Data When Analyzing the "Fairly Responds" Requirement.

FDA also violated the statute by conflating its duty in making *exclusivity* determinations with its separate and distinguishable duty to make *safety labeling* determinations. By improperly coupling these two distinct obligations, FDA performed a "qualitatively different" – and therefore statutorily impermissible – "inquiry." *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000).

FDA's denial letter took the remarkable position that the pediatric exclusivity provision "attempts to ensure that when pediatric exclusivity is granted for studies, FDA *also* may approve labeling describing the results of the studies and providing adequate information for use of the drug in relevant pediatric populations." Ex. 2 at 2 (emphasis added). There is a reason why FDA resorts to citing a single item of legislative history (and an inconclusive one at that) to justify this assertion: The actual *statute* shows otherwise. In determining whether to accept a sponsoring company's study reports, FDA must simply confirm three things: (1) that the reported data "fairly responds" to the written request, (2) that the studies have been conducted in accordance with commonly accepted scientific principles and protocols, and (3) that the data has been filed in accordance with FDA's requirements. 21 U.S.C. § 355a(d)(3) (emphasis added). That is it. There is no safety assessment hidden underneath any of these three requirements.

And Congress quite consciously left no room for the agency to hide a "proven safety" elephant in the "fairly responds" mousehole. Indeed, Congress elsewhere directed FDA to "order the labeling" of a tested drug "to include information about the results of the [pediatric] study," whether the study "does or does not demonstrate that the drug ... is safe and effective, *including whether such study results are inconclusive*, in pediatric populations or subpopulations." *See* 21 U.S.C. § 355a(j) (emphasis added). In other words, the decision whether to include studies in the labeling is entirely separate from the decision to "accept" the studies in the first place; and inclusion in the labeling is expressly required *even where the study data was too inconclusive to either establish or refute safety.*

The statute thus categorically refutes FDA's statement. But the agency nevertheless doubled down on its "no exclusivity unless safety" interpretation in the very next page of its letter. There, it admitted that it considered, as part of its exclusivity analysis, whether the data generated by Amgen's studies was "sufficient" to demonstrate safety: "In determining whether a submission 'fairly responds' to a [written request], FDA considers whether the submission is sufficient to enable it to approve pediatric labeling (including negative pediatric labeling) for all of the age groups and indications requested based on the studies conducted." Ex. 2 at 3. If the agency decides that "the possibility of a health benefit (including meaningful pediatric labeling) from the studies conducted is not likely, the Board is likely to conclude that the submission does not 'fairly respond' to the [written request]." *Id.* FDA could not find any cite, not even in the legislative history, for this statement, and for good reason; it is flatly contrary to the statutory requirements.

There is more. At the close of its letter, FDA *tripled* down:

In summary, Amgen's failure to provide sufficient safety data in [Study 3]

> *prevents FDA from drawing any conclusions about the safety of the product* in patients <6 years of age when used as intended.
>
> If the totality of safety information Amgen submitted had provided an *appropriate safety assessment* in younger children *and supported a label description* – even if the exact minimum number of patients had not been met in study 3 – *this element of the WR could have been adequately satisfied* and Amgen's response could be considered a fair response to the WR as a whole.

Id. at 10 (emphases added). On that same page, FDA concluded: "Amgen's failure to meet an important element of the [written request] also resulted in *the lack of sufficient safety data* for pediatric patients < 6 years of age with secondary HPT and CKD receiving dialysis. The *lack of sufficient safety data in this population has led to the inability to clearly establish the safety profile* of the drug for pediatric patients in accordance with objectives of the amended WR. Accordingly, [pediatric exclusivity] is denied for cinacalcet." *Id.* (emphasis added).

Again: None of this is supported by, or permitted by, the plain language of the statute. FDA's "*only* responsibility" is to (1) confirm that the reported data "fairly responds" to the written request, (2) confirm that the studies have been conducted in accordance with commonly accepted scientific principles and protocols, and (3) confirm that the data has been filed in accordance with FDA's requirements. 21 U.S.C. § 355a(d)(3). Because FDA's importation of a safety inquiry into a "fair response" analysis violates the statute, its decision should be vacated and the agency directed to accept Amgen's studies.

C. FDA's Decision Treats Similarly Situated Entities Differently.

It is a fundamental rule of administrative law that "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so." *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27–28 (D.D.C. 1997). "Government is at its most arbitrary when it treats similarly situated people differently." *Id.* at 27. "The disparate treatment of

functionally indistinguishable products is the essence of the meaning of arbitrary and capricious." *PREVOR v. FDA*, 895 F. Supp. 2d 90, 99 (D.D.C. 2012); *see also Cnty. Of Los Angeles v. Shalala*, 192 F.3d 1005, 1022 (D.C. Cir. 1999) ("A long line of precedent has established that an agency action is arbitrary when the agency offer[s] insufficient reasons for treating similar situations differently." (internal quotation marks omitted)). In order to justify treating similarly situated entities differently, an agency must "do more than enumerate factual differences, if any, between [one case] and the other cases; it must explain the relevance of those differences to the purposes of the [underlying law]." *Melody Music, Inc. v. FCC*, 345 F.2d 730, 733 (D.C. Cir. 1965).

And yet that is exactly what FDA has done here – treat similarly situated entities differently without offering an adequate (or any) explanation for doing so. Amgen has been able to identify at least *three* other situations where FDA considered a sponsor's pediatric studies to "fairly respond" to a written request, and accepted the study reports (thus resulting in an award of pediatric exclusivity), notwithstanding significant deviations from the terms of the relevant written requests.

BMS's Orencia. For example, FDA very recently granted pediatric exclusivity to Orencia (abatacept) injection, despite the sponsor's conceded inability to enroll the study in compliance with the written request:

> In 2015, the PWR [pediatric written request] was amended to specify that the interim report should include information on 180 patients with JIA with ≥12 months of abatacept treatment. The current submission provides an interim report for Study IM101240 to fulfill that amended PWR. However, due *to lower than expected patient recruitment* into the Study IM101240 registry and a higher temporary discontinuation rate than expected, the Sponsor was *unable to provide data on the previously agreed 180 patients with ≥12 months of treatment.* Therefore, to comply fulfill the intent of with [*sic*] the PWR, the Sponsor utilized two other sources of data to supplement the data submitted in the IM101240

> interim report: Truven Health MarketScan and a Swedish Pediatric Registry of Rheumatology.

BLA125118, Addendum to Primary Clinical Review of Supplement 211 (March 24, 2017) (emphases added).[6]

AstraZeneca's Zomig. When called upon to assess pediatric studies performed by AstraZeneca with Zomig (zolmitriptan) tablets, FDA considered the studies to "fairly respond" to the written request, and accepted the study reports – and awarded pediatric exclusivity – despite *several* significant deviations from the terms of the written request. The written request specified four studies:

- an inpatient adolescent safety study if doses > 5 mg are proposed (Study 1);
- a study to compare the pharmacokinetics (PK) of Zomig Tablet in adults and adolescents with a history of migraine (Study 2);
- an acute safety and efficacy trial in adolescents (Study 3); and
- a long term safety study in adolescents (Study 4).

AstraZeneca submitted reports of studies that deviated from the written request in multiple ways, including enrollment criteria, duration, and number of subjects completing the trial. For example, Study 4 called for "[a] sufficient number of adolescent migraine patients to be able to characterize the long-term safety of [the drug] when used to treat multiple migraine attacks over one year. Each patient should treat, on average, 2 or more headaches per month. At a minimum, *300 to 600 patients, using the highest planned marketed dose, should be exposed for one year. .* ." *See* Original Pediatric Written Request, Clinical Review, NDA 020768 (March 26, 1999) at

---

[6] Available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM552563.pdf.

38.[7] But FDA's review notes that, in the end, "only 42 patients took Zomig 5 mg for at least 1 year (360 days), [and] 151 subjects took Zomig tablet 5 mg for at least 326 days." *Id.* at 33. Forty-two patients is 14 percent of the *low* end of FDA's target population. And the 151 subjects who were treated for less than a year represented just 64% of the requested study population.

In addition, AstraZeneca did not conduct a study that complied with the written request's Study 2. Instead, the sponsor submitted three PK studies, each of which had significant deviations from the written request with respect to enrollment criteria, patient population and safety measures. The written request specified that Study 2 should be an "Open label, single dose, parallel group inpatient pharmacokinetic study in adolescents and adults with history of migraine. Ideally, this study should be conducted during a migraine." Original Pediatric Written Request, Clinical Review, NDA 020768 (March 26, 1999) at 38. However, none of the three studies that AstraZeneca submitted met these terms. Study 2a enrolled patients without requiring a history of migraine; Study 2b was conducted only in adults; and Study 2c used a nasal spray product rather than the oral tablets required by the written request and did not include sufficient information for FDA to conclude that healthy migraineurs were enrolled. *Id.* at 9-14.

Ortho-McNeil's Ortho-Tricyclen. Finally, FDA considered the pediatric studies to "fairly respond" to the written request and accepted the study reports (thus conveying pediatric exclusivity) with regard to Ortho-Tricyclen (ethinyl estradiol; norgestimate) Tablets, even though the sponsor submitted a PK study that did not meet the terms of the written request – and indeed, was not even conducted "in a manner consistent with recognized protocol." Clinical

---

[7] Available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM400085.pdf.

Review, NDA 019697 (May 6, 2005) at 20.[8] As amended, the written request required the sponsor to conduct a "population PK study to evaluate ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in a subset of pediatric patients with anorexia nervosa" using a "single-trough sampling design."[9] FDA, NDA 021690, Clinical Pharmacology And Biopharmaceutics Review at 1(March 8, 2004).[10] However, the sponsor did not use an appropriate sampling technique, and as a result, "[o]nly 26 of the proposed 60 patients, and required 40 for this study, had trough concentrations that fell within [the relevant] time ranges, and very few had true trough concentrations." *Id.* Nevertheless, although the reviewer concluded that the "[r]esults of this study were confounding," and the sponsor proposed no labeling change to incorporate the results of this PK study, FDA awarded pediatric exclusivity. *Id.*

It is not surprising, given the constraints and impediments that commonly are present when performing pediatric studies, that companies regularly fall short of FDA's ideal study goals. And yet pediatric exclusivity has been awarded to all but 18 of the 239 drug products that were the subject of a written request and for which study reports were submitted – fully 93% of

---

[8] Available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM343856.pdf.

[9] Single-trough sampling refers to the process of drawing blood only once, right before the administration of each dose, to measure the minimum level of blood concentration, which is then used to assess how quickly a drug is cleared from the bloodstream. FDA, Guidance for Industry: Population Pharmacokinetics at 6–7 (Feb. 1999), available at https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf.

[10] Available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM343859.pdf.

the time, the studies were deemed to "fairly respond" to the request, and the study reports were accepted.[11]

Amgen's submission comports with those made in the three examples cited above. Indeed, Amgen's submission arguably was far *closer* to a fully complete response than any of these three. Yet FDA made no effort to distinguish any of these precedents here. That, too, was arbitrary and capricious. *See, e.g., Lone Mountain Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013) (holding agency action arbitrary and capricious when the agency "failed to even mention or discuss, let alone distinguish" prior orders); *Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012) (holding agency decision arbitrary and capricious because "it failed to explain its departure from the agency's own precedents"). Nor would it even be possible for the agency to come up with any reasonable distinction that somehow requires better compliance of Amgen but allows all of these *other* applicants to gain the benefit of pediatric exclusivity even though they also fell short of the requested study parameters. Such disparate treatment is the definition of arbitrary and capricious agency conduct.

D. FDA's Decision Lacks Any Rational Basis.

An agency decision is arbitrary and capricious if the agency "offered an explanation for its decision that runs counter to the evidence before the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); *see also Clark County, Nev. v. FAA*, 522 F.3d 437, 44142 (D.C. Cir. 2008). The same is true when an agency ignores evidence bearing on the issue before it. *Butte County, Cal. v. Hogen*, 613 F.3d 190 (D.C. Cir. 2010). To survive arbitrary and capricious review, "an agency action must be the product of reasoned

---

[11] *See* https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm.

decisionmaking." *Fox v. Clinton*, 684 F.3d 67, 75 (D.C. Cir. 2012). "[N]o deference is owed to an agency action that is based on an agency's 'purported expertise' where the agency's explanation for its action 'lacks any coherence.'" *Id.*

The agency's decision here lacked any rational basis, because it held Amgen to standards that bore no relationship to what was actually achievable. Amgen took all reasonable steps to try to achieve the requested number of completers in Study 3. But a combination of factors outside its control made that goal completely unreachable. Complaint ¶¶ 38–40. Indeed, Amgen suggested to FDA in September 2013 that the studies should be discontinued altogether. Ex. 1 at 4. FDA objected: "No we do not agree, we continue to believe that cinacalcet can be useful for the management of secondary [HPT] in the pediatric population and that the cinacalcet pediatric program should continue with enhanced titration and monitoring safeguards." *Id.* So Amgen pressed ahead, continuing to devote substantial resources to the pediatric studies requested by FDA. But the clinical hold had caused a number of patients to drop out, and it was difficult to secure the participation of sufficient additional patients to make up for the deficiency, though two subjects in Study 3 were able to complete the trial after the hold was lifted. Compl. ¶ 40.

FDA was well aware of the practical impossibility of its stated goals, because Amgen repeatedly asked the agency to amend its written request to adjust the requirement for completing patients in Study 3. Exs. 13, 14, 15. The agency repeatedly refused. And when Amgen asked for a meeting to discuss those requests, FDA shut down communication altogether, stating: "we will not have any more discussion on this." Ex. 13. FDA offered no explanation at all for its staunch refusal to even *consider* Amgen's requests for amendment to the written request on Study 3. *See Florida Mun. Power Agency v. FERC*, 411 F.3d 287, 288 (D.C. Cir. 2005) (agency's refusal to consider specific issue of physical impossibility as a proper basis for an

exception was arbitrary and capricious). Indeed, it appears the agency refused to amend the request merely because it was a time-consuming process and the request had been amended a few times previously. But it was not as if Amgen had by that time worn out its welcome; Amgen sought and received just five amendments over five years, and FDA regularly amends written requests six or more times, as part of the collaborative back-and-forth between the sponsor and the agency.[12]

It is arbitrary and capricious for an agency to require the impossible, and then to refuse to accommodate the merely possible. *All. for Cannabis Therapeutics v. DEA*, 930 F.2d 936, 940 (D.C. Cir. 1991) ("Impossible requirements imposed by an agency are perforce unreasonable"). *See also PPL Wallingford Energy LLC v. FERC*, 419 F.3d 1194, 1198 (D.C. Cir. 2005) ("We have stressed that 'unless the agency answers objections that on their face seem legitimate, its decision can hardly be classified as reasoned.'"). FDA's unattainable requirements set Amgen up for failure. And the agency maintained those requirements in full knowledge of the difficulties Amgen faced – a completely illogical posture. For all of these reasons, too, the agency's conduct was arbitrary, capricious, and an abuse of discretion.

E. FDA's Conduct Violates Due Process Principles.

Finally, FDA's conduct violates basic principles of procedural due process. The Due Process Clause of the Fifth Amendment to the United States Constitution "requires, at minimum, that the government provide notice and some kind of hearing before final deprivation of a property interest." *Henke v. Dep't of the Interior*, 842 F. Supp. 2d 54, 61 (D.D.C. 2012). And that property interest can take the form of a statutory entitlement. *See Mpras v. District of*

---

[12] Available at https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm049997.htm

Columbia, 74 F. Supp. 3d 265, 270 (D.D.C. 2014) ("For due process purposes, 'to have a property interest in a benefit, a person clearly must have more than an abstract need or desire' and 'more than a unilateral expectation of it; he must, instead, have a legitimate claim of entitlement to it.'" (quoting *Bd. of Regents of State Colls. v. Roth*, 408 U.S. 564, 577 (1972).

Here, while Amgen was pouring money and resources into the clinical studies, FDA gave *no* indication that it would be evaluating Amgen's submissions under a bespoke standard of compliance that Amgen could never hope to meet – one that failed to take into account the difficulties of enrolling patients in Study 3. Had the agency done so, Amgen would not have incurred the additional, potentially massive liability and unrecoupable costs of continued testing and regulatory proceedings, which Amgen undertook in reliance on the plain meaning of § 355a that FDA's actions had previously appeared to endorse. *Christopher v. SmithKline Beecham Corp.*, 132 S. Ct. 2156, 2167 (2012) ("To defer to the agency's interpretation in this circumstance would seriously undermine the principle that agencies should provide regulated parties 'fair warning of the conduct . . . prohibit[ed] or require[d].'"); *see also Satellite Broadcasting Co. v. FCC*, 824 F.2d 1, 3–4 (D.C. Cir. 1987) ("Traditional concepts of due process . . . preclude an agency from penalizing a private party for violating a rule without first providing adequate notice of the substance of the rule. . . . Otherwise the practice of administrative law would come to resemble 'Russian Roulette.'").

II. AMGEN WILL SUFFER IRREPARABLE HARM ABSENT A TRO.

Amgen will suffer irreparable harm absent immediate judicial intervention. The pediatric exclusivity statute states that FDA "shall not extend the [exclusivity] period … if the determination made under subsection (d)(3) is made later than 9 months prior to the expiration of such period." 21 U.S.C. §§ 355a(b)(2), (c)(2). The key patent covering SENSIPAR expires on

March 8, 2018; for that patent to be extended, the statute requires that Amgen's pediatric studies be accepted no later than June 8, 2017. Given that FDA did not deny pediatric exclusivity until very late in the evening of May 22, 2017, Amgen has no choice but to ask this Court to act urgently to maintain the status quo by requiring FDA to accept the study reports in advance of that critical statutory deadline, thus preserving Amgen's ability to have its pediatric exclusivity recognized for the key patent covering SENSIPAR.[13]

Absent such judicial intervention, Amgen may lose the most meaningful benefit of the pediatric exclusivity to which the company is entitled. The threatened loss of a statutory entitlement due to an impending statutory deadline can supply the irreparable harm needed for preliminary injunctive relief. *See* 11A Charles Alan Wright et al., Federal Practice & Procedure Civil § 2948.1 (3d ed. 2017); *E. Tenn. Nat. Gas Co. v. Sage*, 361 F.3d 808, 829 (4th Cir. 2004) (discussing irreparable harm that would be created by missing FERC deadlines absent a preliminary injunction authorizing construction); *Apotex, Inc. v. FDA*, No. CIV.A. 06-0627 JDB, 2006 WL 1030151, at *17 (D.D.C. Apr. 19, 2006) (loss of "a statutory entitlement ... is a harm that has been recognized as sufficiently irreparable"); *Kyne v. Leedom*, 148 F. Supp. 597, 601 (D.D.C 1956) (loss of a "statutory right" "works irreparable harm").

---

[13] FDA presumably will contend that there is no need for injunctive relief at this point. According to the agency, it is "an open question" whether FDA's determination to reject Amgen's study reports before June 8 would bar a *later* acceptance by the agency, deemed to relate back to the date of that original rejection determination – for example, if FDA later reversed its own determination or was ordered to do so by a court. Ex. 16. But when a statute sets a deadline for agency action, the D.C. Circuit has confirmed that a plaintiff seeking a TRO is not required to take a risk on whether agency action *might* still be available after that deadline. Instead, even mere "uncertainty in the law" on the agency's ability to act after the statutory deadline "establishe[s] a substantial risk of irreparable harm" supporting a TRO to compel the agency to take the requested action prior to the statutory deadline, pending resolution of the lawsuit. *Jacksonville Port Authority v. Adams*, 556. F.2d 52, 58 (D.C. Cir. 1977).

In *Jacksonville Port Authority v. Adams*, 556 F.2d 52, 58 (D.C. Cir. 1977), the D.C. Circuit reversed the denial of a TRO under circumstances very similar to those presented here finding the district court's refusal to issue the TRO was an abuse of discretion. As the D.C. Circuit noted, the "[p]assing of the statutory deadline" in that case – one that potentially cut off funding for an airport – "threatened irreparable injury given [the district court's view that recovery was impossible, and the case moot, thereafter." The D.C. Circuit also did not require that the statutory deadline cause irreparable harm with virtual certainty; the "uncertainty in the law concerning the effect of the expiration of the FAA's authority" was enough. *Id.*

If Amgen were to lose its statutory rights, that, in turn, would subject SENSIPAR to generic competition half a year earlier than it otherwise would have experienced. That harm is estimated to be in the hundreds of millions of dollars. And because that harm, while financial, is not recoverable, it is also irreparable. *See Philip Morris USA Inc. v. Scott,* 131 S. Ct. 1 (2010) (Scalia, J., in chambers) ("If expenditures cannot be recouped, the resulting loss may be irreparable."); *Bayer HealthCare, LLC v. U.S. Food and Drug Admin.*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013) (finding irreparable harm where the innovator drug company would "experience a decline in market share, price erosion, loss of customer good will, and loss of research and development funding as a result of [a generic's] entry into the market"); *Clarke v. Office of Fed. Hous. Enterprise Oversight,* 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) (economic losses constitute irreparable injury where they are unrecoverable due to government immunity); *Nat'l Med. Care, Inc. v. Shalala,* 1995 WL 465650, at *3 (D.D.C. June 6, 1995) ("[T]he policy considerations behind the judiciary's general reluctance to label economic injuries as 'irreparable' do not come into play in APA cases: even if the Plaintiffs ultimately prevail on the merits, they cannot bring an action to recover the costs of their compliance with the Defendant's

unlawful retroactive rule, and thus will not be able to alleviate their economic damage through subsequent litigation.").

A TRO is necessary in order to preserve the status quo, to ensure that Amgen's statutory right is not lost forever.

III. THE BALANCE OF EQUITIES FAVORS GRANTING A TRO.

The balance of equities also tips sharply in favor of the requested relief. We have explained one side of that balance already: Amgen's need for immediate relief is strong. Injunctive relief also would benefit FDA by keeping it within the bounds of the law. It would benefit any generic filers by giving both the nine-month notice required by the statute, so all parties can plan accordingly. And it will benefit the public by fulfilling the statutory scheme that Congress designed to serve the public interest.

In contrast, temporary injunctive relief would harm precisely *nobody*. The statute is asymmetrical; it requires FDA to make a determination to accept the studies necessary to result in the *grant* of exclusivity by June 8 in order to trigger pediatric exclusivity for the key patent, but does not require the agency to reject the studies in order to *deny* exclusivity by that date. As a result, FDA would suffer no consequence from a temporary injunction requiring it to accept the studies pending a resolution on the merits, as it has no stake in the matter other than complying with the law. And generic manufacturers who are subject to the critical patent at issue (and who therefore would be affected by the six-month extension of patent exclusivity) are *already* prohibited from entering the market until at least March 8, 2018 – the end of the patent's term.

What is more, because this is an APA case that can and should be decided within a matter of a few months based on the administrative record, perhaps by combining the PI hearing with one on the merits, by the time generic companies *are* eligible to enter the marketplace, this Court

will already have issued a final ruling. If that ruling comes out against pediatric exclusivity (which is unlikely), generic manufacturers would have suffered no harm during the short period of time that the TRO was in place. But while the harm to generic manufacturers is non-existent, the countervailing harm to Amgen is enormous, given the looming June 8 statutory deadline.

As in *Jacksonville Port Authority*: "Only a modest administrative burden would [be] involved in requiring the [agency] to take this preservative action, a burden devoid of expenditure and of impact on any other" regulated entity. 556 F.2d at 58.

IV. GRANTING A TRO WOULD ADVANCE THE PUBLIC INTEREST.

Finally, an injunction here would serve the public interest. The public has an unmistakable interest in seeing that laws are faithfully executed by public officials. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("there is a strong public interest in meticulous compliance with the law by public officials"). *See also, e.g., Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998) (affirming district court's conclusion that the public's interest in the "faithful application of the laws" tipped public- interest prong in favor of requested preliminary injunction. The public also has an interest in meaningful judicial review, which would be lost altogether in the absence of emergency relief.

An injunction also would serve the public interest by enforcing the incentives put in place by Congress to ensure that drugs are studied in pediatric populations when necessary. *See* S. Rep. No. 105-43, at 51 (1997); S. Rep. No. 107-79, at 3 (2001). Amgen more than fairly responded to FDA's written request. If FDA is permitted to create a scheme where companies that have expended significant resources in response to an agency request can be deprived of exclusivity, any rational actor would shrink from accepting any future FDA request for pediatric studies – significantly diminishing the incentives the pediatric exclusivity statute was intended to create,

and heightening the risk to the vulnerable pediatric population that Congress sought to minimize. In the absence of clinical studies testing drugs in pediatric populations, physicians will revert to guessing about whether and how to use drugs off-label, effectively winging it on critical issues like safety and dosing.

Having obtained the benefit of Amgen's considerable investment in research, FDA should not be permitted to deny it the benefit of the statutory incentives provided by Congress.

V. AMGEN HAS EXHAUSTED ITS ADMINISTRATIVE REMEDIES.

Finally, Amgen's suit is properly before this Court and appropriate for immediate adjudication. As a result of the unique time constraints on FDA's ability to make the determination required by Section 355a(d)(3), "irreparable injury would result unless immediate judicial review is permitted." *Randolph-Sheppard Vendors of Am. v. Weinberger*, 795 F.2d 90, 107 (D.C. Cir. 1986).

FDA has an internal dispute resolution procedure available to applicants denied pediatric exclusivity.[14] FDA's stated goal for resolving such appeals is 30 days.[15] Because FDA did not deny Amgen's request for pediatric exclusivity until May 22, however, Amgen cannot pursue that dispute resolution procedure and still hope to get a resolution by FDA before the June 8 statutory deadline – let alone in sufficient time to permit Amgen to seek judicial review of an adverse decision by that date.

---

[14] U.S. Food and Drug Administration, Formal Dispute Resolution: Appeals Level Guidance for Industry and Review Staff at 4–5 (Sept. 2015), *available at* https://www.fda.gov/downloads/drugs/guidances/ucm343101.pdf.

[15] U.S. Food and Drug Administration, *PDUFA Reauthorization Performance Goals and Procedures: Fiscal Years 2013 through 2017 at Part V.A.* (September 15, 2016), *available at* https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

Nonetheless, when it first became clear that FDA was poised to deny pediatric exclusivity, Amgen sought to invoke the administrative review process by submitting an administrative appeal to the agency on May 5th and requesting expedited review. Ex. 3. FDA rebuffed that request by letter dated May 19th, taking the position that Amgen could not even invoke the dispute resolution process until after FDA's May 22nd denial. Because the dispute resolution process takes 30 days, any such administrative review would be futile, as there is absolutely no reason to expect that FDA would accept Amgen's study reports by the statutory June 8 deadline. For this reason, exhaustion would be futile in these circumstances. *See Hillyer v. United States*, No. 4:CV-95-0709, 1995 WL 749553, at *1 (M.D. Pa. Oct. 13, 1995) ("the exhaustion requirement is excused if a statutory deadline is too imminent.").

Congress did not clearly mandate that a sponsor denied pediatric exclusivity exhaust all available administrative remedies before bringing suit to challenge that determination in federal court. *See* 21 U.S.C. § 355a. Therefore, whether to require exhaustion is left to this Court's discretion. *See* Lee Modjeska, Administrative Law Practice and Procedure § 6:8 (2016) ("Unless application of the exhaustion doctrine is statutorily mandated, its application is within the discretion of the courts."). The exhaustion doctrine serves a few purposes: "1) it ensures that persons do not flout legally established administrative processes; 2) it protects the autonomy of agency decisionmaking; 3) it aids judicial review by permitting factual development of issues relevant to the dispute; and 4) it serves judicial economy by avoiding repetitious administrative and judicial factfinding and by resolving some claims without judicial intervention." *Washington Legal Found. v. Kessler*, 880 F. Supp. 26, 33 (D.D.C. 1995). Requiring Amgen to exhaust its administrative remedies here undermines, rather than serves, those salutary purposes.

First, hearing this case would in no way encourage other litigants to "flout legally established administrative processes." *Id.* Quite the opposite. Amgen has worked closely and diligently with FDA in developing and responding to the agency's written request, and in pursuing whatever relief it could before the agency, at every turn availing itself of the proper agency channels. Indeed, Amgen even tried to file an administrative appeal shortly more than 30 days before June 8, to try to ensure that it could be resolved in advance of the statutory deadline. FDA rebuffed this request. Ex. 16. Amgen's actions demonstrate a deep respect for, and commitment to, FDA's legally established administrative processes. But in these circumstances, exhaustion is simply not possible in the time allotted.

Second, hearing this case now would not harm FDA's autonomy. Even with the unique time constraints at play, FDA has had sufficient time both to render its initial determination and, because of Amgen's advance notice, to engage the agency's internal review process. Indeed, in its letter to Amgen refusing its request for dispute resolution, the agency acknowledged that not less than 4 offices within its Center for Drug Evaluation and Research had been consulted on Amgen's request to engage in dispute resolution on the matter. Had the agency desired to complete its decisionmaking before this litigation became necessary, it could and should have done so.

Third, no further factual development is necessary, because the record already before FDA at the time of the initial denial was more than sufficient to support—indeed, the record *required*—acceptance of the studies and the resulting recognition of pediatric exclusivity.

And fourth, delaying resolution of this case will not advance judicial economy because FDA has given no indication that it plans to conclude administrative review by June 8. Any such delay would only spawn further uncertainties for the parties and this Court about the effect of

that fast-approaching statutory deadline. By contrast, a decision from this Court on the merits, which are straightforward, avoids those complications altogether.

Nonetheless, in an abundance of caution, Amgen is submitting a second dispute resolution request to FDA simultaneously with filing this lawsuit. Both the agency's own policies and the agency's response to Amgen's May 5 letter make clear, however, that FDA will not respond to that administrative appeal before June 8. Amgen therefore respectfully requests a TRO ordering the agency to accept the study reports pending either (a) a favorable decision in the administrative appeal; or (b) further order of this Court.

Amgen suggests that a hearing on June 2, 2017, would give FDA time to respond to Amgen's motion (and Amgen time to file a brief reply), while still permitting the Court some latitude of time to issue a decision on this motion before June 6. Amgen accordingly suggests the following schedule apply to briefing and argument on this TRO request: FDA opposition by noon on Wednesday, May 31; Amgen reply by end of day Thursday, June 1; hearing at any point during the day of Friday, June 2.

CONCLUSION

For the foregoing reasons, Amgen's motion for a TRO and/or preliminary injunction should be granted, and FDA ordered to accept Amgen's study reports, in order to preserve the status quo pending either a favorable decision from FDA or a final resolution on the merits.

Respectfully submitted,

Catherine E. Stetson (D.C. Bar # 453221)
Susan M. Cook (D.C. Bar # 462978)
HOGAN LOVELLS US LLP
555 Thirteenth Street, NW
Washington, DC 20004
Telephone: 202-637-5491
Fax: 202-637-5910
cate.stetson@hoganlovells.com
susan.cook@hoganlovells.com

Counsel for Plaintiff Amgen Inc.

Dated: May 25, 2017