UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ASTRAZENECA PHARMACEUTICALS LP 1800 Concord Pike Wilmington, Delaware 19850 and IPR PHARMACEUTICALS, INC. Road 188, Lot 17 San Isidro Industrial Park Canovanas, PR 00729 Plaintiffs, v. SYLVIA MATHEWS BURWELL, Secretary of Health and Human Services 200 Independence Avenue, S.W. Washington, D.C. 20201, and DR. ROBERT M. CALIFF, Commissioner of Food and Drugs Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, Maryland 20993, and U.S. FOOD AND DRUG ADMINISTRATION, 10903 New Hampshire Avenue Silver Spring, Maryland 20993, Defendants.	No. _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

NATURE OF THE ACTION

1. This is an action for declaratory and injunctive relief arising from the Defendants'

violation of: the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301–399f; the Food and Drug Administration's ("FDA") regulations and policies implementing the FDCA; and the Administrative Procedure Act ("APA"), 5 U.S.C. § 706. Specifically, this action challenges Defendants' interpretation of statutes and regulations that (i) prohibit a generic drug from being marketed unless it includes *all* pediatric information appearing on the corresponding brand-name drug label, and (ii) allow generic drug manufacturers to "carve out"—i.e., omit—certain labeling for which the brand-name drug manufacturer enjoys marketing exclusivity.

2. In 2015, FDA interpreted these statutes and regulations in a way that broadens generic drug manufacturers' ability to carve out pediatric labeling for which the brand-name manufacturer enjoys exclusive marketing rights. *See* Letter from John R. Peters, M.D., Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to Ralph S. Tyler, Counsel for Otsuka Pharmaceuticals, Co., at 10–14 (Apr. 28, 2015) ("Otsuka Letter"). A true and correct copy of the Otsuka Letter is attached as Exhibit A to this Complaint.

3. The policy set forth in the Otsuka Letter (the "2015 Interpretation") paves the way for FDA approval (and subsequent mass marketing) of generic drugs even when the brand-name manufacturer enjoys marketing exclusivity for one or more pediatric indications of use, and even though FDA regulations state that pediatric information *must* appear on the generic drug's label.

4. FDA's 2015 Interpretation is unlawful. FDA's pediatric-labeling regulations impose a categorical rule: A generic drug must include *all* pediatric labeling approved for the corresponding brand-name drug. Although Congress has enacted a handful of narrow and carefully targeted exceptions to that categorical rule, none of those exceptions (also known as "carve out" authorities) provides a valid basis for FDA's 2015 Interpretation.

5. Plaintiffs AstraZeneca Pharmaceuticals LP and iPR Pharmaceuticals, Inc.

(collectively, "AstraZeneca") face an imminent risk of concrete, particularized, and irreparable harm as a result of FDA's unlawful 2015 Interpretation. FDA has tentatively approved ten abbreviated new drug applications ("ANDAs") for generic versions of AstraZeneca's cholesterol-treatment drug Crestor (rosuvastatin calcium), and is expected on or about July 8, 2016, to grant final approval for several of those ANDAs based on the 2015 Interpretation.

6. AstraZeneca currently has orphan drug marketing exclusivity for Crestor with respect to treatment of a rare and serious pediatric "orphan" disease known as homozygous familial hypercholesterolemia ("HoFH") in pediatric patients ages 7 to 17. Under the correct interpretation of the FDCA and its implementing regulations, FDA may not grant final approval for applications to market generic rosuvastatin calcium until the expiration of AstraZeneca's pediatric HoFH orphan drug exclusivity period on May 27, 2023.

7. However, in the 2015 Interpretation, FDA improperly determined that it may approve ANDAs notwithstanding the existence of pediatric labeling protected by orphan drug exclusivity. FDA's final approval of the tentatively approved ANDAs will cause the market immediately to be flooded with generic rosuvastatin calcium, thereby eviscerating AstraZeneca's orphan drug exclusivity and undercutting Crestor's market share and price.

8. AstraZeneca would not sustain this imminent and irreparable harm but for FDA's unlawful 2015 Interpretation. AstraZeneca brings this suit to obtain relief from FDA's unlawful 2015 Interpretation.

PARTIES

9. Plaintiff iPR Pharmaceuticals, Inc. owns the New Drug Application ("NDA") for Crestor (No. 021366) and the supplemental NDA ("sNDA") for use of Crestor to treat pediatric patients 7 to 17 years of age with HoFH (No. 021366/S-033). Plaintiff iPR Pharmaceuticals is

located in Puerto Rico and is an affiliate of Plaintiff AstraZeneca Pharmaceuticals LP.

10. Plaintiff AstraZeneca Pharmaceuticals LP serves as the agent for Plaintiff iPR Pharmaceuticals, Inc. with respect to Crestor and in that capacity manufactures and markets Crestor tablets. Plaintiff AstraZeneca Pharmaceuticals LP is located in Delaware. Through their sale of Crestor, Plaintiffs conduct substantial business in the District of Columbia and throughout the United States.

11. Defendant Sylvia Mathews Burwell is Secretary of Health and Human Services. The U.S. Department of Health and Human Services ("HHS") is a cabinet-level agency of the Executive Branch of the United States Government. Secretary Burwell is charged with administering the FDCA, including the drug-approval provisions of 21 U.S.C. § 355. Defendant FDA is a major operating division of HHS. As Secretary of HHS, Secretary Burwell has supervisory responsibility for FDA. Secretary Burwell has delegated her authority under the FDCA to the Commissioner of Food and Drugs. Secretary Burwell is sued in her official capacity as Secretary of HHS.

12. Defendant Dr. Robert M. Califf is Commissioner of Food and Drugs. In that capacity, Dr. Califf has the authority and responsibility for administering FDA and the FDCA, including matters delegated by the Secretary of HHS relating to drug approvals as well as the statutes and regulations at issue in this case. Dr. Califf is sued in his official capacity as Commissioner of FDA.

13. Defendant FDA is the agency of the United States Government that administers the FDCA.

14. HHS and FDA are agencies within the meaning of the APA, 5 U.S.C. § 701(b)(1).

JURISDICTION AND VENUE

15. This action arises under federal law, specifically the FDCA, 21 U.S.C. § 301 *et seq.*, and the APA, 5 U.S.C. § 551 *et seq.* The declaratory, injunctive, and other relief requested by AstraZeneca is authorized by 5 U.S.C. §§ 702 and 706, and 28 U.S.C. §§ 1361, 1651, 2201–2202, and this Court's general equitable powers.

16. This Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1361.

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

18. Defendants' issuance of the 2015 Interpretation constitutes final agency action. AstraZeneca has exhausted its available administrative remedies by challenging the 2015 Interpretation before FDA. However, that challenge is futile because Defendants adopted their unlawful 2015 Interpretation in the nearly identical Otsuka adjudication, adhered to the 2015 Interpretation in federal district court, and prevailed in the federal suit based on the (erroneous) determination—not binding on this Court—that the 2015 Interpretation complies with the FDCA and APA. *See Otsuka Pharmaceutical Co. v. Burwell*, No. GJH-15-852, 2015 WL 1962240 (D. Md. Apr. 29, 2015) (*Otsuka I*); *Otsuka Pharm. Co. v. Burwell*, No. GJH-15-852, 2015 WL 3442013 (D. Md. May 27, 2015) (*Otsuka II*).

19. An actual and justiciable controversy exists between AstraZeneca and Defendants.

STATEMENT OF FACTS

A. Statutory And Regulatory Background

1. New Drug Applications, Supplemental New Drug Applications, And Orphan Drug Exclusivity

20. The FDCA prohibits the sale or distribution in interstate commerce of a "new

drug" unless it has been proven to be safe and effective. 21 U.S.C. § 355(a). The research and development necessary to secure approval of a new drug generally requires an extensive battery of analytical tests, animal studies, and human clinical safety and efficacy trials, takes many years, and is extremely costly. Based on its research and development efforts, the sponsor of a new drug submits an NDA consisting of manufacturing information and all analytical, preclinical, and clinical data to FDA for review and approval. 21 U.S.C. § 355(b).

21. To gain approval of a new indication for a previously approved drug, the drug sponsor must submit a sNDA. *See* 21 C.F.R. § 314.1 *et seq.* The approval requirements for a sNDA are the same as for a NDA. *See id.* §§ 314.1, 314.71(b).

22. A sNDA seeking approval for a new indication must include evidence of the drug's safety and effectiveness for the particular indication sought to be approved, with safety and effectiveness demonstrated by the sponsor's submission of "full reports of [all clinical] investigations which have been made to show whether . . . such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(5). FDA's approval of an indication for a drug is limited by the clinical data the manufacturer submits in its application in support of the use of the drug for that particular purpose. *See* 21 U.S.C. § 355(d)(1), (2), (5); *see also* 21 C.F.R. § 314.126(a) ("Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs.").

23. ANDAs for generic versions of a previously-approved brand-name drug avoid the costly and lengthy process applicable to new drugs and new indications for previously-approved drugs. Rather than investing the significant time and money that would be required to establish the safety and efficacy of a proposed generic drug, an ANDA applicant may rely on the safety

and efficacy data contained in the NDA and any sNDAs of the predicate brand-name drug (sometimes referred to as the "originator," "pioneer," or "reference listed" drug). An ANDA applicant need only show that the generic product has the same active ingredient, strength, dosage form, and route of administration, has the same labeling (including indications of use), and is "bioequivalent" to the brand-name drug. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(v).

24. To incentivize the exceedingly risky and uncertain investment of substantial time and sums of money involved in research and development of pioneering new drugs and the ensuing submission of NDAs and sNDAs, Congress has enacted a statutory framework in the FDCA that protects innovators' patent rights and provides non-patent statutory exclusivity periods that collectively are designed to ensure that, for a fixed period of time, innovators will have the exclusive right to market their drugs following FDA approval.

25. The very first type of non-patent exclusivity enacted by Congress to incentivize development of new drugs and drug treatments was orphan drug exclusivity granted by the Orphan Drug Act 1983, Pub. L. 97-414, 96 Stat. 2049 ("ODA"). The ODA provides drug manufacturers with incentives to develop drugs for the treatment of rare (also known as "orphan") diseases or disorders—diseases which, by definition, affect only a small patient population. Ordinarily, when FDA approves a drug for treatment of an orphan disease, it grants the sponsor seven years of orphan drug marketing exclusivity. Pursuant to this exclusivity, FDA may not approve a subsequent application for "the same drug for the same use or indication" until after the seven-year exclusivity period expires. 21 U.S.C. § 360cc(a); 21 C.F.R. § 316.3(b)(12). Without this incentive, sponsors would be far less likely to develop treatments for rare diseases or disorders because the small size of the potential patient population would not justify a sponsor's risk and investment.

2. The Pediatric-Labeling And Same-Labeling Requirements For Prescription Drugs

26. A drug's labeling includes "all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article." 21 U.S.C. § 321(m)(1)–(2).

27. A prescription drug's labeling must "contain [a]dequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented." 21 C.F.R. § 201.100(d)(1).

28. In 1994, FDA promulgated regulations that set out specific requirements regarding the inclusion of pediatric information on drug labeling. *See* 59 Fed. Reg. 64,240 (1994).

29. The "Full Prescribing Information" portion of the drug's label must include an "Indications and Usage" section that "state[s] that the drug is indicated for the treatment, prevention, mitigation, cure or diagnosis of a recognized disease or condition." 21 C.F.R. § 201.57(c)(2). "If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., . . . *patients in a special age group*) . . . a succinct description of the limitations or usefulness of the drug and any uncertainty about anticipated clinical benefits" must be included. *Id.* § 201.57(c)(2)(i)(B) (emphasis added). The regulations also provide that, "[i]f there is a specific pediatric indication

different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the 'Indications and Usage' section." *Id.* § 201.57(c)(9)(iv)(B).

30. The "Dosage and Administration" section "must state the recommended dose," including "[d]osages for each indication and *subpopulation*." *Id.* § 201.57(c)(3)(C) (emphasis added). This section must include appropriate pediatric dosage information "[i]f there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population." *Id.* § 201.57(c)(9)(iv)(B).

31. FDA's pediatric-labeling regulations require that other specific pediatric information also be included. Where a specific pediatric indication has been demonstrated by adequate and well-controlled studies, the pediatric use section "must cite any limitations on the pediatric indication," among other things. 21 C.F.R. § 201.57(c)(9)(iv)(B). "If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well- controlled studies in the pediatric population, they must be summarized in the 'Pediatric use' subsection." *Id.* § 201.57(c)(9)(iv)(C).

32. Generally, generic drugs must contain the same information on their labels as the corresponding brand-name predicate drug. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). This rule is known as the "same-labeling" requirement.

33. The FDCA prohibits the marketing and sale of misbranded drugs. 21 U.S.C. § 352(f). A branded or generic "drug product that is not in compliance with" the pediatric-labeling rules set forth above is "considered misbranded and an unapproved new drug under the [FDCA]." 59 Fed. Reg. 64,240, 64,247 (1994).

34. Collectively, these statutes and regulations establish a categorical rule: Generic

drugs must contain *all* the pediatric information included on the corresponding brand-name drug's label.

3. Targeted Statutory Exceptions To The Same-Labeling And Pediatric-Labeling Rules

35. Congress has enacted a small handful of exceptions to the categorical rule described in Paragraph 34 above.

36. The FDCA provides that a generic drug's label may differ from the corresponding brand-name drug's label if "changes [are] required because of differences approved under a petition filed under [21 U.S.C. § 355(j)(2)(C)] or because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v); *see also id.* § 355(j)(2)(C).

37. In 1992, FDA promulgated a series of "general" carve-out regulations based on the statutory provisions described in Paragraph 36 above. *See* 57 Fed. Reg. 17,950, 17,984–86, 17,992 (1992). These regulations empower FDA to approve a generic drug even when its label differs from the brand-name drug in specified ways. For example, the regulations provide that a generic drug label may differ from the brand-name drug's label by the "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FDCA]" so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7).

38. In 2002, Congress enacted section 505A(*o*) of the FDCA to address a perceived "loophole" involving drugs protected only by patent or three-year Hatch-Waxman exclusivity, 21 U.S.C. § 355(j)(5)(F)(iii)–(iv). Specifically, Bristol Myers Squibb, a brand-name drug

manufacturer, obtained three-year Hatch-Waxman exclusivity for a pediatric indication for its drug Glucophage (metformin), and argued that this exclusivity, when considered together with FDA's pediatric-labeling rules, resulted in a "de facto exclusivity for use of the drug in all populations." Otsuka Letter, Ex. A, at 10 n.27. FDA agreed with this assessment and accordingly refused to approve ANDAs for generic metformin. *See, e.g.*, 147 Cong. Rec. H8551 (Nov. 28, 2001) (statement of Rep. Pallone) ("the only obstacle" to approval of generic metformin was a "loophole in the Waxman-Hatch [Act]" that granted the brand-name manufacturer a "monopoly" and made "FDA's Office of Generic Drugs" "unable to allow . . . generics onto the market").

39. Section 505A(*o*) addressed this issue by creating a new exception to FDA's categorical pediatric-labeling rules. The exception allows generic applicants to carve out specific types of pediatric indications or other information from their product labels, and also authorizes FDA to require generic drugs to include certain disclaimers on generic-drug labeling. *See* 21 U.S.C. § 355a(*o*). Section 505A(*o*) provides in relevant part (emphasis added):

> (1) General rule.—A drug for which an application has been submitted or approved under section 355(j) of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use *when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title*.
>
> (2) Labeling.—Notwithstanding clauses (iii) and (iv) of section 355(j)(5)(F) of this title, the Secretary may require that the labeling of a drug approved under section 355(j) of this title that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include—
>
> (A) a statement that, because of marketing exclusivity for a manufacturer—
>
> (i) the drug is not labeled for pediatric use; or
>
> (ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not

> labeled for the pediatric use under paragraph (1); and
>
> (B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.

40. In short, section 505A(*o*) expressly allows pediatric indications and information to be carved out from the labeling of generic products, and a substitute disclaimer added, if such information is protected by patent or three-year exclusivity under 21 U.S.C. § 355(j)(5)(F)(iii) or (iv), but provides no such authorization where other protections apply to the innovator labeling or product.[1]

B. FDA's Initial And Correct Interpretation Of Its Pediatric-Labeling And Carve Out Authorities

41. The pediatric-labeling and same-labeling rules create a barrier to approval of a generic drug when (i) the brand-name drug is approved for one or more pediatric indications and (ii) at least one of those pediatric indications is protected by patent, Hatch-Waxman, or some other form of exclusivity. In the absence of an applicable carve-out provision, FDA generally is foreclosed from approving generic drug applications: The pediatric-labeling rules require the generic manufacturer to include the pediatric labeling, *see* 21 C.F.R. §§ 201.57(a), (c)(9)(iv)(B), but that labeling is protected and thus unavailable. If FDA carved the protected labeling out, the generic drug would be considered misbranded under the pediatric-labeling rules. *See* 59 Fed. Reg. at 64,247.

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[1] Under 21 U.S.C. § 355(j)(5)(F)(iii), three-year Hatch-Waxman exclusivity is given to an drug that includes an active ingredient that has been approved in another application, is approved after September 24, 1984, and the "application contains reports of new clinical investigations . . . essential to the approval of the application and conducted or sponsored by the applicant." Under 21 U.S.C. § 355(j)(5)(F)(iv), a sNDA approved after September 24, 1984, containing "reports of new clinical investigations . . . essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement" is entitled to three-year exclusivity for "a change approved in the supplement." *See also* 21 C.F.R. § 314.108(b)(4)–(5).

42. FDA faced this barrier in 2001 when Bristol Myers Squibb obtained three-year Hatch-Waxman exclusivity for a new pediatric indication for Glucophage (metformin). *See* 147 Cong. Rec. H8551 (Nov. 28, 2001) (statement of Rep. Pallone). Bristol Myers Squibb argued that FDA could not approve generic metformin for *any* population, adult or pediatric, or for *any* indication—whether protected by exclusivity or not—because its three-year Hatch-Waxman exclusivity pertained to a pediatric indication, and FDA regulations categorically required all pediatric information to appear on generic drug labels. Generic drugs could not lawfully comply with that requirement—and thus could not lawfully be sold—because the required information was owned exclusively by Bristol Myers Squibb for the duration of its three-year Hatch Waxman exclusivity period. *See* 147 Cong. Rec. H10209 (Dec. 18, 2001).

43. Although FDA's general carve-out regulations were on the books in 2001, FDA correctly concluded that those authorities could not be used to carve out Bristol Myers Squibb's protected pediatric labeling given the categorical and later-adopted pediatric-labeling rules. Thus, FDA declined to approve applications to market generic metformin. *See* 147 Cong. Rec. H8551 (Nov. 28, 2001) (statement of Rep. Pallone); *see also id*. at H8105 (Nov. 13, 2001) (statement of Rep. Dingell).

44. FDA reversed course and approved the Glucophage (metformin) ANDAs, but did so only after Congress enacted section 505A(*o*), which gave FDA express authority to carve out Bristol Myers Squibb's protected pediatric labeling. *See* 21 U.S.C. § 355A(*o*)(1) (ANDA "shall not be considered ineligible for approval . . . on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use *when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title*" (emphasis added)).

45. The text of section 505A(*o*) makes clear that its carve-out authority extends to pediatric labeling protected only "by patent or by [Hatch-Waxman] exclusivity." *Id.*

46. Critically, section 505A(*o*) does not allow a generic sponsor to carve out pediatric labeling protected by other forms of exclusivity, such as orphan drug exclusivity granted pursuant to section 527 of the FDCA, 21 U.S.C. § 360cc(a).

47. FDA's general carve-out authorities likewise do not allow a generic sponsor to carve out pediatric labeling protected by orphan drug exclusivity. This conclusion follows from FDA's interpretation of those authorities in adjudicating the Glucophage ANDAs. It is also supported by the categorical language of FDA's pediatric-labeling regulations; FDA's promulgation of those regulations in 1994, after its adoption of the general carve-out regulations; the text, structure, purposes, and history of the FDCA; and Congress's decision not to include orphan drug exclusivity in section 505A(*o*).

48. Therefore, the barrier to generic entry created by FDA's categorical pediatric-labeling regulations and acknowledged by FDA in its adjudication of the Glucophage ANDAs remains in place with respect to pediatric labeling protected by orphan drug exclusivity. That barrier prevents FDA from approving a generic drug for *any* population or use so long as the corresponding brand-name drug has an active period of orphan drug exclusivity for treatment of pediatric patients.

C. FDA's Revised And Unlawful 2015 Interpretation Of Its Pediatric Labeling And Carve Out Authorities

49. In 2015, FDA abandoned its initial and correct interpretation of its pediatric-labeling and carve-out authorities and adopted in its place a new and unlawful interpretation that is the focus of this suit.

50. FDA adopted the 2015 Interpretation in the course of adjudicating a claim made by Otsuka Pharmaceutical Co. ("Otsuka"), a brand-name drug manufacturer, that FDA lacked authority to approve ANDAs for its Abilify (aripiprazole) drug.

51. FDA first approved Abilify in 2002 and subsequently approved its use to treat schizophrenia, depression, bipolar disorder, and other conditions. Otsuka filed a sNDA seeking approval of Abilify for treatment of pediatric patients ages 6 to 18 with Tourette's Syndrome. FDA approved this sNDA in December 2014 and granted Otsuka three years of Hatch-Waxman exclusivity and seven years of orphan drug exclusivity with respect to the newly approved pediatric indication.

52. After Otsuka obtained those exclusivities, several manufacturers filed ANDAs seeking permission to market generic versions of Abilify. Otsuka sent a letter to FDA, contending that FDA lacked authority to approve the Abilify ANDAs for the same reason that FDA initially was unable to approve the Glucophage ANDAs: the brand-name manufacturer held an exclusive right to certain pediatric labeling, such that no generic manufacturer could comply with the requirement to include *all* pediatric labeling. *See* Otsuka Letter, Ex. A, at 1.

53. FDA rejected Otsuka's argument and approved the Abilify ANDAs. *See id.* at 2–3, 15.

54. In the Otsuka Letter, FDA concluded that its general-carve-out authorities "allow carve-outs of labeling protected by [orphan drug exclusivity] . . . as long as FDA determines that the drug with the information carved out remains safe and effective for the remaining non-protected conditions of use." *Id.* at 13–14. Under this interpretation, a generic drug may be approved *unless* (i) the corresponding brand-name drug "is approved in adults and pediatric patients for the same indication"; (ii) "the pediatric information is protected by exclusivity and is

significantly different from the information regarding use in adults for the same indication"; and (iii) "a carve-out of [the] pediatric information while the adult information is retained in the ANDA labeling may result in a potential safety risk to pediatric patients." *Id.* at 10. FDA concluded that the Abilify ANDAs could be approved under this framework because omitting Otsuka's protected Tourette's Syndrome labeling would not present a safety risk to pediatric patients. *Id.* at 14.

55. In the Otsuka Letter, FDA also recast its position with respect to the Glucophage ANDAs as focused solely on safety risk for pediatric patients. FDA explained that it initially declined to approve the metformin ANDAs for any indication during Bristol Myers Squibb's three-year exclusivity period because Glucophage "was approved for the same indication in adults" and pediatric patients, and "the protected pediatric information was necessary for the safe use of the drug and therefore could not be carved out." *Id.* at 10 n.27.

56. FDA's Otsuka Letter thus adopted a new interpretation of FDA's pediatric-labeling and carve-out authorities that bears directly on this case. Under that interpretation—referred to throughout this Complaint as the 2015 Interpretation—a generic manufacturer may carve out *any* protected pediatric labeling (including labeling protected by orphan drug exclusivity) so long as the carve out will not pose a safety risk.

57. Otsuka sought judicial review of FDA's 2015 Interpretation in the United States District Court for the District of Maryland. *See Otsuka I*, 2015 WL 1962240, at *1. The court granted an accelerated briefing schedule and heard oral argument on Otsuka's request for a preliminary injunction less than two hours after FDA approved the Abilify ANDAs. *Id.* Ultimately, however, the court sided with FDA, denied the preliminary injunction, and granted summary judgment in FDA's favor. *See id.* at *13; *see also Otsuka II*, 2015 WL 3442013, at

*15. Throughout the *Otsuka* litigation, FDA adhered to its view that its pediatric-labeling and carve-out authorities permit generic manufacturers to omit pediatric labeling whenever doing so would not present a safety risk.

58. That interpretation is incorrect, and it marks a sharp and unexplained departure from the categorical rule FDA applied in its adjudication of the Glucophage ANDAs: That, absent clear statutory authority (as provided in section 505A(*o*)), a generic drug label may *never* carve out protected pediatric labeling.

59. The error in FDA's 2015 Interpretation is particularly apparent from the lack of contemporaneous support offered by FDA for its newfound safety-based approach. The 2015 Interpretation does not cite agency memoranda, regulations, or guidance documents in support its characterization of the Glucophage decision. Instead, FDA relies solely on a memorandum placed in the *Congressional Record* during the floor debate on section 505A(*o*). *See* Otsuka Letter at 10 n.27 (citing 147 Cong. Rec. H10209). That memorandum undermines, rather than supports, FDA's safety-based rationale. Specifically, the memorandum states that "[u]nder existing law and regulations" prior to section 505A(*o*)'s enactment, a "grant of labeling exclusivity" for a pediatric indication "amounted to a grant of marketing exclusivity for . . . all users, not simply children, *because all prescription drugs (including generics) were required by FDA regulations promulgated in 1994 to include pediatric information in their labels*." 147 Cong. Rec. H10209 (Dec. 18, 2001) (emphasis added).

D. AstraZeneca's Pediatric HoFH Orphan Drug Exclusivity

60. AstraZeneca is the owner of the valuable and medically useful prescription drug rosuvastatin calcium, which AstraZeneca markets under the Crestor brand name.

61. Among other things, Crestor helps patients reduce cholesterol levels. In the

United States, Crestor first was approved by FDA for use in adult patients with dyslipidemia on August 12, 2003 (NDA No. 021366). FDA has since approved rosuvastatin calcium for other indications.

62. HoFH—homozygous familial hypercholesterolemia—is an extremely serious condition. If left untreated, HoFH causes substantially elevated plasma cholesterol levels, which in turn lead to cardiovascular disease, myocardial infarction (heart attacks), and premature death.

63. HoFH is extremely rare and affects approximately one in one million people. *See* George Yuan, Jian Wang, & Robert A. Hegele, Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease, Canadian Medical Ass'n J. (Apr. 11, 2006), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1421462/.

64. Heterozygous Familial Hypercholesterolemia ("HeFH") is related to HoFH and presents some of the same symptoms, but is significantly less serious and more treatable than HoFH. HeFH is more common than HoFH; approximately one in five hundred people has HeFH. *Id.*

65. HoFH is generally more resistant to statin treatment than HeFH, and the risk of an early cardiac event is considerably higher in pediatric HoFH patients than in HeFH patients. For those reasons, physicians generally prescribe statin therapy much earlier and more aggressively in pediatric HoFH patients than pediatric HeFH patients. The recommended dosing for Crestor also differs between pediatric HoFH and HeFH patients ages 7 to 17. Whereas 20 mg once daily is the recommended dose for pediatric HoFH patients, the recommended dose is 5-10 mg once daily for HeFH patients ages 8 to less than 10, and 5 to 20 mg once daily for HeFH patients ages 10 to 17. Physicians typically treat pediatric HeFH patients by titrating upwards from the recommended 5 mg starting dose. Some pediatric HeFH patients achieve treatment goals at

doses below 20 mg, in which case the 20 mg dose of Crestor is not administered.

66. FDA's Office of Orphan Products Development ("OOPD") granted AstraZeneca Orphan Drug Designation for the use of rosuvastatin calcium in the treatment of pediatric HoFH on February 14, 2014.

67. After consultation with FDA, in 2014 AstraZeneca initiated clinical trials evaluating the safety and efficacy of the use of rosuvastatin calcium in the pediatric HoFH population (the "Pediatric HoFH Study").

68. The Pediatric HoFH Study (also known as the "HYDRA study") concluded in 2015 and established that Crestor 20 mg is a safe and effective means of treatment for pediatric HoFH patients ages 7 to 17.

69. Based on the Pediatric HoFH Study and other data, AstraZeneca submitted a sNDA on July 27, 2015, in which AstraZeneca sought FDA approval for rosuvastatin calcium for the treatment of pediatric HoFH patients (the "Pediatric HoFH sNDA").

70. AstraZeneca attempted to expedite FDA's consideration and approval of the Pediatric HoFH sNDA in several ways, including by filing a request for priority review that met all FDA required criteria. FDA denied that request for priority review, as well as a subsequent request for reconsideration or in the alternative for expedited consideration through the standard review process. FDA's refusal to expedite processing of the Pediatric HoFH sNDA was inconsistent with the agency's processing of AstraZeneca's sNDA regarding use of Crestor to treat pediatric HeFH patients. Although HeFH is a less serious disease than HoFH, on April 22, 2009, FDA granted priority review of the HeFH sNDA.

71. On May 27, 2016, FDA approved the Pediatric HoFH sNDA and informed AstraZeneca that rosuvastatin calcium was approved for use in the treatment of pediatric patients

7 to 17 years old with HoFH. This approval resulted in substantial modifications to the label of AstraZeneca's rosuvastatin calcium product, including modifications that add new dosing, warnings, and "Use in Specific Populations" labeling focused on pediatric HoFH patients.

72. On June 3, 2016, FDA granted AstraZeneca seven years of orphan drug marketing exclusivity with respect to treatment of pediatric HoFH patients ages 7 to 17. This exclusivity became effective May 27, 2016, and expires on May 27, 2023. This exclusivity is limited to the pediatric HoFH population, as indicated on the revised Crestor label and in FDA's letter confirming the grant of orphan drug exclusivity.

73. The FDA-approved Crestor label contains a substantial amount of pediatric HoFH information protected by orphan drug exclusivity. In the "Highlights of Prescribing Information," for example, the "Dosage and Administration" section lists a recommended dose of "20 mg/day" for "[p]ediatric patients with HoFH" ages 7 to 17. More detailed information is provided regarding treatment of pediatric HoFH patients in the "Full Prescribing Information" portion of the approved label. These references include information regarding "Indications and Usage" (§ 1.2); "Pediatric Dosing" (§ 2.2); "Pediatric Use" (§ 8.4); and "Clinical Studies" concerning "Pediatric Patients with Homozygous Familial Hypercholesterolemia" (§ 14.6).

74. Separate and apart from the orphan drug exclusivity described in Paragraph 72 above, AstraZeneca currently enjoys patent and other exclusivities with respect to Crestor. These protections include a six-month period pediatric exclusivity under 21 U.S.C. § 355a(c), based on a prior pediatric study (known as the "PLUTO" study) conducted by AstraZeneca. This six-month pediatric exclusivity expires on July 8, 2016. Prior to that date, no other drug maker may sell rosuvastatin calcium for any indication or population without first obtaining a license from AstraZeneca. There is no relationship or connection between this six-month pediatric

exclusivity and the pediatric HoFH orphan drug exclusivity at issue in this suit.

75. In 2013, in connection with resolution of an unrelated patent-infringement dispute, AstraZeneca executed an agreement with Watson Laboratories, Inc. ("Watson"), that allowed Watson to market generic rosuvastatin calcium beginning on May 2, 2016, notwithstanding AstraZeneca's patent and exclusivity rights with respect to Crestor. Watson obtained final FDA approval of a generic rosuvastatin calcium product on April 29, 2016, began marketing that product on or about May 2, 2016, and has continued to market that product through the date of this Complaint. The status of Watson's generic rosuvastatin calcium product is not at issue in this suit.

E. The Imminent And Irreparable Threat Posed By Application Of FDA's 2015 Interpretation To Crestor

76. According to FDA's Drugs@FDA online database, FDA has tentatively approved at least ten ANDAs for generic rosuvastatin calcium. A tentative approval signifies that, with the exception of the potential need for a final site inspection, an ANDA satisfies all the requirements needed for FDA approval and is eligible for immediate approval once any applicable brand-name exclusivities expire.

77. Under FDA's unlawful 2015 Interpretation of its pediatric-labeling and carve-out authorities, several of the tentatively approved rosuvastatin calcium ANDAs could be approved by FDA on or about July 8, 2016, when the six-month period of pediatric exclusivity identified in Paragraph 74 above expires.

78. In contrast, the tentatively approved rosuvastatin calcium ANDAs could not be approved during the pendency of AstraZeneca's pediatric HoFH orphan drug exclusivity period—i.e., until May 27, 2023—if FDA applied the categorical rule it adopted when

adjudicating the Glucophage ANDAs. That rule is correct and should be applied in this case.

79. If FDA applies the 2015 Interpretation to grant final approval to the tentatively approved rosuvastatin calcium ANDAs, additional generic manufacturers would immediately flood the market with low-cost rosuvastatin calcium—thereby dramatically eroding Crestor's market share and causing AstraZeneca to sustain substantial and immediate revenue losses. Because manufacturers typically ship several months' worth of generic drugs immediately upon FDA approval, AstraZeneca would be unable to recoup its market position and lost revenues even if it ultimately prevails in this litigation.

80. AstraZeneca would also suffer other irreparable injuries as a direct result of Defendants' action if FDA applied its 2015 Interpretation to the tentatively approved rosuvastatin calcium ANDAs.

81. These imminent and irreparable injuries are redressable by an order enjoining FDA from applying its unlawful 2015 Interpretation to current or future applications to market generic rosuvastatin calcium.

82. AstraZeneca is concurrently providing FDA and the United States Department of Justice with a copy of this Complaint and will promptly confer to see if Defendants will agree to an expedited briefing schedule that would enable this Court to resolve this case before FDA approves the generic Crestor ANDAs on or about July 8, 2016. If, however, Defendants are not willing to agree, or are unwilling to agree at a minimum to providing AstraZeneca with at least one business day's notice prior to any ANDA approval, then AstraZeneca will have no choice but to file an application for a temporary restraining order to preserve the status quo pending resolution of the merits of AstraZeneca's claims.

F. AstraZeneca's Challenge To The 2015 Interpretation Is Ripe For Immediate Judicial Review

83. On May 31, 2016, two business days after FDA's approval of the Pediatric HoFH sNDA, AstraZeneca submitted a citizen petition to FDA setting forth its position that the pediatric-labeling regulations preclude FDA from approving generic rosuvastatin calcium products until after the expiration of AstraZeneca's statutory seven-year period of orphan drug exclusivity. A true and correct copy of AstraZeneca's citizen petition is attached as Exhibit B to this Complaint.

84. AstraZeneca's citizen petition also makes a separate argument—not raised in this Complaint—that carving out AstraZeneca's protected pediatric HoFH labeling will give rise to serious safety and efficacy risks for pediatric HoFH patients, and that a carve out is therefore improper even under the 2015 Interpretation. AstraZeneca intends to bring this separate safety claim before the Court as soon as it is ripe for review.

85. As of the date of this filing, FDA has not ruled on AstraZeneca's citizen petition.

86. The Court need not wait for FDA to rule on AstraZeneca's challenge to the 2015 Interpretation, because FDA's response to that claim is a foregone conclusion. FDA demonstrated in the Otsuka proceedings that it has made a final determination regarding the meaning and application of its pediatric-labeling and carve-out authorities. The propriety of that determination is a pure question of law and is fit for immediate adjudication by this Court. AstraZeneca will suffer significant hardship, including significant unrecoverable economic losses, if the Court postpones review. *See generally Teva Pharms. v. Sebelius*, 595 F.3d 1307–15 (D.C. Cir. 2010).

FIRST CLAIM FOR RELIEF

Unlawful, Arbitrary, And Capricious FDA Action

87. AstraZeneca adopts and incorporates by reference Paragraphs 1–86 of this Complaint as if fully set forth herein.

88. FDA is an agency subject to the requirements of the APA. 5 U.S.C. § 701(b)(1). "[A]gency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" shall be held "unlawful and set aside." *Id.* § 706(2)(A).

89. The 2015 Interpretation is arbitrary, capricious, and contrary to law, in violation of 5 U.S.C. § 706(2), because it conflicts with the interpretation of the pediatric-labeling regulations FDA adopted in adjudicating the Glucophage ANDAs; the categorical language of FDA's pediatric-labeling regulations; and the text, structure, purposes, and history of the FDCA, as amended by the ODA and section 505A(*o*).

SECOND CLAIM FOR RELIEF

Unexplained Departure From Past Agency Practice

90. AstraZeneca adopts and incorporates by reference Paragraphs 1–89 of this Complaint as if fully set forth herein.

91. Federal agencies "are free to change course . . . but when they do so they must provide a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored." *Ramaprakash v. FAA*, 346 F.3d 1121, 1124–25 (D.C. Cir. 2003).

92. Agency action is arbitrary and capricious, and violates the APA, when an agency departs from its past practice without acknowledging or providing a reasoned explanation for the

change. *Ramaprakash*, 346 F.3d at 1124–25; *see also CBS Corp. v. FCC*, 785 F.3d 699, 708–09 (D.C. Cir. 2015).

93. The 2015 Interpretation is arbitrary and capricious, and violates the APA, because it departed without explanation from the categorical rule applied by FDA to the Glucophage ANDAs and set forth in FDA's pediatric-labeling regulations.

PRAYER FOR RELIEF

WHEREFORE, plaintiff AstraZeneca respectfully requests that this Court:

a) expedite proceedings in this matter;

b) pending the final determination of this matter on the merits, the Court grant all necessary temporary, preliminary, or interim relief to preserve the status quo, including a preliminary injunction barring FDA from approving ANDAs for generic rosuvastatin calcium products pending expedited resolution of this suit;

c) enter a declaratory judgment that FDA's 2015 Interpretation is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law;

d) vacate and set aside FDA's 2015 Interpretation;

e) permanently enjoin FDA from granting approval of any ANDA or other application for a rosuvastatin calcium product prior to expiration of AstraZeneca's seven-year orphan drug exclusivity period on May 27, 2023 (absent a license from AstraZeneca); and

f) grant AstraZeneca any and all other, further, and additional relief as the nature of the Court may deem just and proper, including all necessary and appropriate declarations of rights and injunctive relief.

Respectfully submitted,

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