DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Silver Spring, MD 20993

Joseph A. Cash, Jr.
AstraZeneca Pharmaceuticals
FOP 3-131
1800 Concord Pike
Wilmington, DE 19850

JUL 19 2016

Re: Docket No. FDA-2016-P-1485

Dear Mr. Cash:

This letter responds to the citizen petition you submitted pursuant to section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)) and 21 CFR 10.30 on behalf of AstraZeneca Pharmaceuticals LP and its affiliate iPR Pharmaceuticals, Inc. (collectively "AstraZeneca") on May 31, 2016 (Petition).[1] You request that FDA not approve any abbreviated new drug application (ANDA) or section 505(b)(2)[2] new drug application (NDA) referencing Crestor (rosuvastatin calcium) tablets (NDA 21366) until the expiration of Crestor's orphan drug exclusivity for the treatment of pediatric homozygous familial hypercholesterolemia (HoFH) (Petition at 1).

More specifically, your Petition requests that FDA:

1. Determine that the labeling for any rosuvastatin calcium product must include the pediatric orphan HoFH indication and prescribing information, including all data and information derived from AstraZeneca's pediatric HoFH study supporting approval of the Crestor pediatric orphan drug [supplemental new drug application (sNDA)], to ensure the safe and effective use of the product in pediatric HoFH patients, and

2. Refrain from approving any ANDA or section 505(b)(2) NDA referencing Crestor on or before May 27, 2023, if the labeling of the proposed product omits the pediatric orphan HoFH labeling, including all data and information derived from the pediatric HoFH study supporting approval of the Crestor pediatric orphan drug sNDA, which is protected by orphan exclusivity.

(Petition at 2-3).

For the reasons explained below, your Petition is denied.

[1] AstraZeneca submitted an updated version of its Petition on June 21, 2016, to add certain required contact information. That Petition is otherwise identical to the Petition submitted on May 31, 2016.

[2] Section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)).

I. BACKGROUND

A. Crestor

AstraZeneca holds approved NDA 21366 for Crestor (rosuvastatin calcium) tablets, 5, 10, 20, and 40 milligrams (mg). FDA approved NDA 21366 on August 12, 2003.[3] Crestor is a lipid and cholesterol lowering synthetic drug for oral administration.

Eight indications currently appear in Crestor's FDA-approved labeling. Most recently, FDA approved revised labeling for Crestor on May 27, 2016, based on AstraZeneca's sNDA 21366/S-033, which supported the addition of information regarding use of Crestor in pediatric patients with HoFH (see labeling approved on May 27, 2016).[4] As indicated in FDA's publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), the pediatric HoFH indication is protected by both orphan drug exclusivity and 3-year Hatch-Waxman exclusivity.[5]

Of relevance to your Petition, Crestor's labeling includes the following information:

	Adult indication and corresponding dosage information[6]	Pediatric indication and corresponding dosage information
HoFH	Adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB Adult HoFH: Starting dose 20 mg/day	Pediatric patients 7 to 17 years of age with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, nonHDL-C and ApoB as an adjunct to diet, either alone or with other lipid-lowering treatments Pediatric patients with HoFH: 20 mg/day for patients 7 to 17 years of age

[3] The 2003 Crestor approval letter is available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[4] This labeling is available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[5] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[6] Key to abbreviations included in this table:
LDL-C = low density lipoprotein cholesterol
Total-C = total cholesterol
nonHDL-C = non high density lipoprotein cholesterol
ApoB = Apolipoprotein B

Crestor's labeling also includes the following general recommendations:

- "The maximum CRESTOR dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose [see *Warnings and Precautions (5.1)*]."

- "When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly."

B. Homozygous Familial Hypercholesterolemia

HoFH is a form of familial hypercholesterolemia.[7] HoFH is a rare genetic disease most often caused by mutations in the gene encoding the low density lipoprotein (LDL) receptor, which either attenuate or eliminate its function. This defect precludes the ability of the liver to scavenge LDL particles from the blood, leading to markedly elevated LDL-cholesterol (LDL-C) blood levels and resultant premature atherosclerosis and elevated risk of cardiovascular events. The majority of HoFH patients present with xanthomas (cholesterol-rich lipid deposits under the skin) during the first decade of life. Given that severely elevated LDL-C levels lead to premature atherosclerosis and early-onset cardiovascular disease, the primary goal of treatment in pediatric patients with HoFH, in addition to encouraging healthy diet and lifestyle, is to reduce LDL-C. Lipid-lowering therapy is recommended to begin as early as possible for these patients.

In 2011, the National Lipid Association (NLA) Expert Panel on Familial Hypercholesterolemia published clinical guidance regarding the screening, diagnosis, and management of patients with familial hypercholesterolemia, including considerations for pediatric patients.[8] The panel recommended LDL-C reduction of ≥50% or a target LDL-C less than 130 mg/deciliter in children with familial hypercholesterolemia (including both HoFH and HeFH). According to clinical guidance, statin drugs are considered the first-line pharmacologic treatment after initiation of diet and physical activity management for treatment of familial hypercholesterolemia. Initiation of statin treatment at the age of 8 years or older for children with familial hypercholesterolemia is recommended, although earlier treatment may be needed in "special cases" such as HoFH. Regarding pediatric HoFH specifically, the panel stated that "[i]nitiation of therapy early in life and ongoing monitoring of [HoFH] is vital."[9]

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[7] Heterozygous familial hypercholesterolemia (HeFH) is another form of familial hypercholesterolemia. HeFH is a more prevalent and typically a less severe form of familial hypercholesterolemia than HoFH.

[8] Daniels SR, et al. Pediatric aspects of familial hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipid* 2011; 5: S30-S37.

[9] Id. at S31.

Statins lower LDL-C by increasing the number of LDL receptors on the surface of liver cells. These LDL receptors remove LDL particles from the blood. In HoFH, however, these receptors are defective or absent; therefore, the response to statins among patients with HoFH is variable. Thus, it is standard of care to measure LDL-C levels after initiating or titrating therapy.[10] Furthermore, the European Atherosclerosis Society (EAS) notes,

> [c]hildren with suspected HoFH should be referred promptly to specialized centres due to the aggressive nature of this condition.... A very aggressive cholesterol-lowering approach should be initiated as soon as possible to prevent or delay the development of CHD [coronary heart disease]. Treatment with a statin and ezetimibe must be started at diagnosis.[11]

For additional LDL-C reduction in pediatric HoFH, specialized health care providers may consider certain non-statin therapies. Repatha (evolocumab) injection was approved in 2015 "as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C." The labeling for Repatha states that its safety and effectiveness in adolescents with HoFH were established based on data from a 12-week, placebo-controlled trial that included 10 adolescents (ages 13 to 17 years).[12]

Despite treatment with lipid-lowering drugs such as statins, however, the NLA expert panel noted that the majority of HoFH patients will require LDL apheresis, an extracorporeal procedure that removes LDL particles from plasma. Patients typically undergo this procedure every 1 to 2 weeks. A recent position paper about HoFH by the EAS recommends that LDL apheresis be considered in patients with HoFH, initiating therapy by age 5 and no later than age 8.[13] Liver transplantation may also be considered, because it replaces dysfunctional LDL receptors in the liver and markedly improves LDL-C levels, but this option has several disadvantages, including the need for liver transplant patients to receive chronic immunosuppressive therapy.

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[10] Crestor's labeling reflects this standard of care in stating "[a]fter initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly" under heading 2.1, *General Dosing Information.*

[11] Wiegman A, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015; 36:2425-2437.

[12] See Repatha approval letter and Repatha labeling available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

[13] Cuchel M, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014; 35:2146-2157.

C. Legal and Regulatory Background

1. Drug Approval Pathways Under the Federal Food, Drug, and Cosmetic Act

Section 505 of the FD&C Act (21 U.S.C. 355) establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) applications (ANDAs).

a. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an NDA contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[14] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

b. 505(b)(2) Applications

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[15] amended the FD&C Act to add section 505(b)(2) and 505(j), as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[16] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[17]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act, is approved under section 505(c) of the FD&C Act, and must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a 505(b)(1) NDA. Unlike a stand-alone NDA, however, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations (1)

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[14] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include a full list of the articles used as components of such drug described in the NDA; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments (see section 505(b)(1) of the FD&C Act).

[15] Public Law 98-417 (1984).

[16] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[17] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-1134 (Fed. Cir. 1995).

"not conducted by or for the applicant" and (2) "for which the applicant has not obtained a right of reference or use." Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as its own studies, published reports of studies to which the applicant has no right of reference, the Agency's findings of safety and/or effectiveness for one or more previously approved drugs, or a combination of these sources to support approval.

c. ANDAs

To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product. Instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[18] is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug is bioequivalent to the RLD. In addition, a drug product described in an ANDA generally must contain the same active ingredient;[19] conditions of use;[20] route of administration, dosage form, strength;[21] and (with certain permissible differences) labeling as the RLD, unless a petition for certain changes is approved by the Secretary (section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act).

2. Exclusivity

a. Three-Year Hatch-Waxman Exclusivity

Under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and § 314.108(b)(4) (21 CFR 314.108(b)(4)), a 3-year period of exclusivity attaches to a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application. During this 3-year period, the Agency will not make effective the approval of a 505(b)(2) NDA or an ANDA for the conditions of approval of the original application.

Three-year Hatch-Waxman exclusivity also attaches when a supplement to an NDA is approved and the supplement contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the supplement. When a supplement meets the criteria set forth in these provisions, FDA "may not make the approval of an application . . . for a change approved in the supplement effective before

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[18] An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in the Orange Book.

[19] See, e.g., § 314.94(a)(5) (21 CFR 314.94(a)(5)).

[20] See, e.g., § 314.94(a)(4).

[21] See, e.g., § 314.94(a)(6).

the expiration of three years . . . ." (see sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act and § 314.108(b)(5) (21 CFR 314.108(b)(5))).

b. Orphan Drug Exclusivity

The Orphan Drug Act (Public Law 97-414) was enacted in 1983 and added sections 525 to 528 to the FD&C Act. In enacting the Orphan Drug Act, Congress sought to promote the development of drugs for rare diseases and conditions that would not otherwise be developed and approved, including drugs that are potentially safer or more effective than already approved drugs. Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is generally so limited that drug developers expected them to be unprofitable and had little incentive to invest in their development.[22] Accordingly, as amended, the Orphan Drug Act provides various incentives, including tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, formal protocol assistance to sponsors of drugs for rare diseases, and a 7-year exclusivity period during which FDA may not approve another sponsor's application "for such drug for such disease or condition," subject to certain conditions.[23] The scope of orphan drug exclusivity "protects only the approved indication or use of a designated drug."[24] FDA has issued regulations implementing its Orphan Drug Act authority.[25]

To be eligible for 7-year orphan drug exclusivity, a sponsor must participate in a two-step process that includes designation and approval. A sponsor must first submit a request for designation of its drug for a rare disease or condition that includes, among other things, a scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition identified.[26] To obtain orphan drug exclusivity, the sponsor must then obtain approval of the drug for the rare disease or condition for which orphan designation was granted. Orphan drug exclusivity begins on the date that the marketing application is approved and precludes approval for 7 years of the same drug (same active moiety) for the same orphan indication for which the drug has been designated and approved, i.e., for "such drug for such disease or condition."[27] Orphan drug exclusivity is limited in its scope and protects against

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[22] See Orphan Drug Regulations, Notice of Proposed Rulemaking, Docket No. 85N-0483, 56 FR 3338 (January 29, 1991).

[23] See sections 525 to 528 of the FD&C Act and section 227 of the Public Health Service Act (42 U.S.C. 236); see also part 316 (21 CFR part 316).

[24] 21 CFR 316.31(b).

[25] See 21 CFR part 316.

[26] See section 526 of the FD&C Act (21 U.S.C. 360bb); see also § 316.20.

[27] See section 527(a) of the FD&C Act (21 U.S.C. 360cc) (providing that FDA "may not approve another application . . . for such drug *for such disease or condition* . . . until the expiration of seven years") (emphasis added); § 316.31(b) ("Orphan-drug exclusive approval protects only the approved indication or use of a designated

approval only of the same drug for the same indication. It does not preclude approval of the same drug for which orphan drug exclusivity was granted for a different, non-protected indication.

3. *"Same Labeling" Requirement for Products Approved in ANDAs and Permissible Carve-Outs*

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Also, section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain:

> information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers."[28]

A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[29]

Although the requirements set forth in section 505(j)(2)(A)(v) and 505(j)(4)(G) are known as the "same labeling" requirements, they do not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect, among other things, Congress's intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling without requiring that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the Hatch-Waxman Amendments, Congress explicitly acknowledged that "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved."[30]

In interpreting the statutory exception to the same labeling requirement, which allows certain labeling differences due to the fact that the proposed ANDA and the listed drug are "produced or

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drug."). The regulation also describes certain situations not relevant here when an application for the same drug for the same indication can be approved during the period of orphan drug exclusivity (see § 316.31(a)).

[28] See also 21 CFR 314.92(a)(1), 314.94(a)(4)(i), 314.94(a)(8)(iv), 314.127(a)(2), and 314.127(a)(7).

[29] Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[30] H.R. Rep. No. 98-857, pt.1, at 2; see also id. at 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.").

distributed by different manufacturers," among other things, the regulations at § 314.92(a)(1) (21 CFR 314.92(a)(1)) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted *because of exclusivity* or an existing patent may be omitted" (emphasis added). Section 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) sets forth some examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:

> [D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent or accorded exclusivity* under section 505(j)(5)(F) of the act.[31]

The regulations at § 314.127(a)(7) (21 CFR 314.127(a)(7)) further provide that, to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent, or by exclusivity*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (emphasis added). These provisions thus specifically affirm that ANDA applicants may carve out from their proposed labeling any patent- or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use as long as the ANDA remains safe and effective for the remaining non-protected conditions of use.

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol-Myers Squibb Co. v. Shalala,* 91 F.3d 1493 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference."[32] Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out

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[31] (emphasis added). We note that although the regulation provides removal of an aspect of labeling protected by exclusivity under section 505(j)(5)(F) of the FD&C Act as an example of a permissible difference due to difference in manufacturer, FDA has never interpreted this example as the only permissible exclusivity-based carve-out. On the contrary, FDA has consistently permitted labeling carve-outs based on orphan drug exclusivity protection as well. See, e.g., ANDA labeling approvals for levoleucovorin (carving out labeling protected by both Hatch-Waxman exclusivity and orphan drug exclusivity), temozolomide (carving out labeling protected by both Hatch-Waxman exclusivity and orphan drug exclusivity), tacrolimus (carving out labeling protected by orphan drug exclusivity), and aripiprazole (carving out labeling protected by both Hatch-Waxman exclusivity and orphan drug exclusivity).

[32] *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). See also *Spectrum Pharm., Inc. v. Burwell*, --- F.3d ----, 2016 WL 3126834, at *3 (D.C. Cir. June 3, 2016) (explaining that D.C. Circuit has "approved FDA's general approach to labeling carve-outs as an acceptable interpretation of the [FDCA]" and upholding FDA's approval of a generic drug with an indication protected by orphan exclusivity carved out).

an indication protected by orphan drug exclusivity as a permissible difference due to a difference in manufacturer.[33] Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) argued that FDA was obligated to look beyond the labeling an ANDA applicant proposed to use in determining whether a generic drug would violate an innovator's orphan drug exclusivity. The court observed that orphan exclusivity is "disease-specific, not drug-specific," and noted that if FDA adopted Sigma-Tau's argument this could mean that once the Agency approves an orphan drug for a protected indication, "generic competitors might be prohibited from entering the market for almost any use."[34] The court further stated that Sigma-Tau's argument would extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses."[35] The court reasoned that "[Sigma-Tau's theory] to bar the approval of generic drugs, even for unprotected indications. . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive."[36] Accordingly, the court rejected Sigma-Tau's argument and concluded that the statutory scheme permitted an ANDA applicant to carve out the orphan-protected indication at issue.

As your Petition acknowledges, the U.S. District Court for the District of Maryland issued a 2015 opinion in *Otsuka Pharmaceutical Co., Ltd. v. Burwell*, No. GJH-15-852, 2015 WL 3442013 (D. Md. May 27, 2015) affirming FDA's interpretation of the FD&C Act and the applicable regulations as permitting approval of an ANDA with labeling that carves out a pediatric indication protected by orphan drug exclusivity. The court concluded that:

> [T]he FDCA, its legislative history, the case law, and FDA's regulations all support the FDA's construction of the statute that allows it to carve out an indication or other information from ANDA labeling when that indication or information is protected by orphan drug exclusivity as long as the ANDA with that carved out label remains safe and effective for the remaining non-protected conditions of use. To be sure, Otsuka's reading of section 355a(o) would nullify the limitation expressly written into section 360cc – that the exclusivity is given to a drug "for [the orphan] disease or condition" – and instead treat the orphan drug exclusivity as extending to the drug for any and all diseases and conditions, directly contradicting that provision's text and the Fourth Circuit's holding in *Sigma-Tau*.[37]

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity, including orphan drug exclusivity, as an acceptable difference between the proposed generic drug and the RLD that are produced or distributed by different manufacturers if the omission does not render the

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[33] *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002).

[34] Id. at 147.

[35] Id. (citations omitted).

[36] Id.

[37] *Otsuka* at 27 (bracketed alteration in original).

proposed generic drug less safe or effective than the RLD for the non-protected conditions of use that remain in the labeling.

4. Pediatric Labeling, Carve-Outs, and Disclaimers

When a product is approved for use in adults for an indication that also occurs in pediatric populations, FDA generally presumes, based on experience, that the product will be used in the pediatric population for that adult-approved indication regardless of whether the product is labeled for that use. It is this experience that led to the Pediatric Research Equity Act (PREA), which in certain circumstances requires studies of drugs in pediatric populations for indications that have been approved in adults.[38]

Because pediatric patients and adults may metabolize some drugs differently, may be susceptible to different safety risks, and may require different dosing instructions, Congress recognized the need for pediatric studies in certain circumstances. Specifically, Congress gave FDA explicit authority to require studies in pediatric populations when an applicant is making certain changes (new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration) and seeks approval for adults for an indication that occurs in pediatric patients but its labeling does not include adequate information regarding the use of the drug in pediatric populations for that approved indication.[39]

When FDA's concern about adequate labeling for the use of a drug in pediatric populations is implicated by the labeling carve-out scheme in section 505(j) of the FD&C Act, additional considerations regarding potential labeling carve-outs may apply. In some such cases, where a drug is approved in adults and pediatric patients for the same indication but the pediatric information is protected by exclusivity and is significantly different from the information regarding use in adults for the same indication, a carve-out of pediatric information – while adult information is retained in the ANDA labeling – may result in a potential safety risk to pediatric patients. The risk arises because pediatric patients may be given the drug without adequate safety or dosing information and with the unsubstantiated expectation that the drug will behave in the same way in pediatric patients as it does in adults. We therefore consider whether there is a safety risk to the protected pediatric population as part of our analysis regarding whether the drug without the pediatric information in its labeling is safe and effective for the remaining non-protected conditions of use. In some cases, even though a drug is otherwise subject to a carve-out under section 505(j)(2)(A)(v) of the FD&C Act, and §§ 314.92(a)(1), 314.94(a)(8)(iv), and 314.127(a)(7), the drug with the labeling carved out might not be considered safe and effective for the remaining non-protected conditions of use because the remaining adult indication could

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[38] Public Law 108-155. See section 505B of the FD&C Act (21 U.S.C. 355c); see also 21 CFR 201.57(c)(9)(iv)(C) ("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").

[39] See section 505B(a)(2)(A)(i) of the FD&C Act (requiring submission of pediatric studies "for the claimed indications in all relevant pediatric subpopulations").

result in a safety risk to pediatric patients who use the drug for the carved out, protected pediatric indication. In such a case, FDA might not approve the generic drug for the adult indication with the corresponding pediatric information omitted.

To ensure that ANDA approval is not delayed in cases where a listed drug is approved in adults and pediatric patients for the same indication but the pediatric indication is protected by patent or 3-year Hatch-Waxman exclusivity and certain pediatric labeling information is essential to the safe use of the product, Congress added section 505A(o) to the FD&C Act (21 U.S.C. 355a(o)) in the Best Pharmaceuticals for Children Act (BPCA).[40] Section 505A(o), entitled "Prompt Approval of Drugs under Section 505(j) When Pediatric Information Is Added To Labeling," gave FDA additional tools to ensure that ANDAs are adequately labeled and not unnecessarily blocked in cases where pediatric labeling is protected, and the absence of this information from the labeling of an ANDA would have safety implications and the potential to misbrand the product. This provision does not limit FDA's authority to carve out pediatric labeling where a carve-out would otherwise be appropriate, nor does it restrict in any way FDA's ability to approve an otherwise approvable ANDA; instead it provides FDA with additional authority to retain certain protected pediatric information in ANDA labeling where such information is necessary for safe use of the product, thus ensuring "Prompt Approval of Drugs under Section 505(j) When Pediatric Information Is Added To Labeling."

Specifically, for pediatric labeling protected by 3-year Hatch-Waxman exclusivity, section 505A(o)(1) of the FD&C Act provides that an ANDA "shall not be considered ineligible for approval under [section 505(j)] or misbranded under section 502 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 . . . exclusivity under clause (iii) or (iv) of section 505(j)(5)(F)."

Section 505A(o)(2) further provides that notwithstanding any patent or 3-year Hatch-Waxman exclusivity, the Secretary may require a drug that omits pediatric labeling protected by such exclusivity to 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 with some pediatric labeling included but other pediatric labeling carved out due to patent or Hatch-Waxman exclusivity] the drug is not labeled for the protected pediatric use [due to patent or Hatch-Waxman exclusivity]; and/or (B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use."

These provisions evidence Congress's intent that approval should not be withheld from ANDAs for unprotected indications based on the inability to retain certain essential pediatric safety information in labeling once certain pediatric use information protected by patent or 3-year

[40] Public Law 107-109.

Hatch-Waxman exclusivity is carved out.[41] The language of section 505A(o) allows certain information to remain in ANDA labeling even when it relates to a pediatric use that is protected by patent or 3-year Hatch-Waxman exclusivity if removing that information would otherwise misbrand the drug by rendering it unsafe or ineffective for the remaining non-protected conditions of use. Section 505A(o) was not intended to speak directly to, and leaves unchanged, other situations where carve-outs are permissible and would not misbrand the drug. Section 505A(o)(3)(D) expressly states that "except as expressly provided in [section 505A(o)(1) and (2)]" section 505A(o) does not affect "the operation of section 505."

Accordingly, section 505A(o) does not limit but, in fact, is complementary to FDA's longstanding approach to labeling carve-outs under section 505(j). As noted above in section I.C.3 of this response, under that longstanding approach, "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." 21 CFR 314.92(a)(1). Under section 505(j) and FDA regulations, FDA has long carved out from ANDA labeling information protected by orphan drug exclusivity, consistent with the Orphan Drug Act and FDA's implementing regulations which, as described above in section I.C.2.b of this response, provide that orphan drug exclusivity protects only against approval of the same drug *for the same indication or use*. As the court made clear in *Sigma-Tau*, a carve-out of an orphan-protected indication is permissible provided that the drug that omits the protected indication will remain safe and effective for the remaining, non-protected conditions of use.

II. DISCUSSION

Your Petition presents two lines of argument in support of its requested actions. First, you contend that carving out AstraZeneca's protected pediatric HoFH labeling from the labeling of a product marketed under an ANDA or a 505(b)(2) application would "present substantial safety and efficacy risks" (Petition at 1 and 11-17). Second, you contend that FDA lacks legal authority to carve out pediatric labeling protected by orphan drug exclusivity (Petition at 2 and 17-26). We address each of these arguments below.[42]

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[41] See BPCA House Report 107-277 (Nov. 9, 2001) at 30 ("[505A(o)]would require prompt approval of a generic drug that otherwise meets all other applicable requirements even when its labeling omits pediatric information that is protected by patent or other market exclusivity provisions"); id. at 38 ("[505A(o)] does make clear that if a manufacturer does claim supplemental exclusivity under section 505(j), the terms of that exclusivity will not prevent generic competition for the indications or aspects of labeling which are not protected."). See also Letter from Janet Woodcock to Terry G. Mahn (May 21, 2003), Docket No. FDA-2002-P-0289 (Original Docket No. 02P-0469/CP1, changed as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008) at 12 (noting that section 11 of BPCA codified at 505A(o) was entitled "Prompt Approval of Drugs under Section 505(j) When Pediatric Information is Added to Labeling" and was designed to ensure that protection of pediatric labeling for an RLD will not block generics from entering the market); *Otsuka* at 16 ("[S]ection 355a(o) merely tells FDA it may not *disapprove* an ANDA based on the omission of pediatric indications that is the result of patent or three-year new clinical study exclusivity with no language to indicate that it intended to restrict FDA's ability to *approve* ANDAs not covered by those two categories." (emphasis in original)).

[42] Your Petition requests that FDA not approve a 505(b)(2) application or an ANDA that references Crestor until the expiry of the orphan drug exclusivity for the pediatric HoFH indication. The scientific analysis in this response regarding the safety of rosuvastatin with the pediatric HoFH indication carved out of its labeling applies equally to

A. A Carve-Out of the Protected Pediatric HoFH Indication Does Not Render Rosuvastatin Less Safe or Effective for the Remaining Non-Protected Conditions of Use

Your Petition asserts that FDA may not carve out the orphan-protected pediatric HoFH labeling because doing so may present "serious safety and efficacy risks."[43] In support of this assertion, you refer to a letter from John R. Peters, M.D., Acting Director of the Office of Generic Drugs in FDA's Center for Drug Evaluation and Research to Ralph S. Tyler, Venable LLP, dated April 28, 2015 ("Otsuka letter").[44] This letter concerned the approvability of an ANDA referencing Abilify (aripiprazole) with pediatric information protected by orphan drug exclusivity carved out of the generic product's labeling.

The Otsuka letter states:

> [W]here a drug is approved in adults and pediatric patients for the same indication but the pediatric information is protected by exclusivity and is significantly different from the information regarding use in adults for the same indication, a carve-out of pediatric information while adult information is retained in the ANDA labeling may result in a potential safety risk to pediatric patients. The risk arises because pediatric patients may be given the drug without adequate safety or dosing information and with the unsubstantiated expectation that it will behave the same way it does in adults. In such cases, even though a drug is otherwise subject to a carve out under section 505(j)(2)(A)(v) of the FD&C Act, and 21 CFR 314.92(a)(1), 314.94(a)(8)(iv) and 314.127(a)(7), the drug with the labeling carved out might not be considered safe and effective for the remaining non-protected conditions of use.[45]

Your Petition suggests that FDA should apply the same analysis presented in that letter to your requested actions. FDA agrees that the general analysis reflected in the Otsuka letter regarding FDA's carve-out inquiry applies here. Crestor is approved for both adult and pediatric patients with HoFH, but only the pediatric indication is protected by exclusivity. The Agency disagrees, however, that this analysis leads to a conclusion that a drug product that carves out the protected pediatric HoFH indication is not approvable. On the contrary, and for the reasons described below, FDA does not believe that carving out the orphan-protected pediatric HoFH indication

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any 505(b)(2) applicants who choose not to seek approval for the pediatric HoFH indication (and who will therefore not include the pediatric HoFH indication in their labeling) as it does to ANDAs for rosuvastatin that carve out the pediatric HoFH indication during the pendency of the orphan drug exclusivity period. The legal analysis in this response focuses primarily on ANDAs because ANDAs, unlike 505(b)(2) applications, are subject to the same labeling requirements in section 505(j) of the FD&C Act.

[43] We note that although you state that a carve-out of the protected pediatric HoFH indication may present "serious safety and efficacy risks," your Petition focuses only on safety.

[44] Your Petition refers to this letter as being dated April 27, 2015.

[45] Otsuka letter at 10.

would present a safety risk to pediatric patients with HoFH and concludes that a 505(b)(2) NDA or ANDA referencing Crestor that does not include the orphan-protected information in its labeling is safe and effective for the remaining non-protected conditions of use.

1. Adult HoFH Labeling Information Is Not "Significantly Different" from Pediatric HoFH Labeling Information

As a scientific matter, FDA concludes that Crestor's labeling information for adults with HoFH is not "significantly different" from its labeling information for pediatric patients with HoFH. The DOSAGE AND ADMINISTRATION section of Crestor's labeling, under Full Prescribing Information, includes these statements:

> "The usual starting dose in adult patients with [HoFH] is 20 mg once daily." (Heading 2.1, *General Dosing Information*), and
>
> "In [HoFH], the recommended dose is 20 mg orally once daily in patients 7 to 17 years of age." (Heading 2.2, *Pediatric Dosing*).

The general, non-indication-specific portion of the Crestor labeling also states that the overall dose range for Crestor is 5 to 40 mg once daily in adults and advises physicians to use the 40-mg dose only for patients not reaching their LDL-C goal with 20 mg (see the DOSAGE AND ADMINISTRATION section under the Highlights of Prescribing Information and also the DOSAGE AND ADMINISTRATION section under the Full Prescribing Information).

Additional general dosing information states:

> When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy.
>
> After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

Practitioners following the labeled recommendations reflected above would initiate therapy with 20 mg daily for both adults and pediatric patients with HoFH. In addition, Crestor's labeling makes clear that for all indications, including pediatric and adult HoFH, the "starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy." Given that (1) the 20-mg pediatric HoFH dose is stated as a "recommended" dose; (2) the approved starting dose for adult HoFH is also 20 mg, the same as the recommended pediatric dose; (3) there are no dosing instructions in the labeling to avoid doses exceeding 20 mg daily in pediatric patients with HoFH; and (4) there is a general dosing recommendation, which is not limited to certain indications, that dosing may be titrated to 40 mg daily for patients not reaching their LDL-C goal with 20 mg, we conclude that the information for pediatric HoFH is not significantly different from the information for adult HoFH, and thus an ANDA with the

protected pediatric labeling carved out would not present a safety risk to pediatric patients with HoFH and will remain safe and effective for the remaining non-protected conditions of use.

2. *The Scenarios Raised in Your Petition Would Not Result in a Safety Risk to Pediatric HoFH Patients*

Your Petition presents four specific scenarios under which you believe a pediatric HoFH carve-out may result in a potential safety risk to pediatric patients (Petition at 13-15). Although FDA has concluded that a carve-out of the protected pediatric HoFH indication would not present a safety risk to pediatric patients because the protected pediatric information is not significantly different from the adult information and, thus, the scenarios you present should not occur, for purposes of argument, the Agency has considered your scenarios. For the reasons described below, we do not believe that your scenarios indicate that a carve-out of the pediatric HoFH indication would result in a safety risk to pediatric patients with HoFH.

As an initial matter, we note that the adult HoFH indication (which, as noted above, recommends a usual starting dose of 20 mg, the same as the pediatric dose) has been included in Crestor's label since the drug was first approved in 2003.[46] For approximately 13 years, Crestor's labeling has included adult HoFH information without the pediatric HoFH indication. To the extent that Crestor was used in pediatric patients with HoFH before the pediatric HoFH indication was added to Crestor's labeling in May 2016, there have been no reports to the FDA Adverse Event Reporting System (FAERS) to indicate there is any new or increased severity of any safety issue with the use of Crestor by pediatric patients. As the Crestor clinical reviewer noted in reviewing the pediatric HoFH supplement, "[t]he safety profile of Crestor is well-characterized in numerous populations, and no new safety concerns were identified in [the] small trial of pediatric patients with HoFH."[47]

With respect to the first scenario in your petition, you assert that specialists relying on labeling that does not include pediatric HoFH information may over treat pediatric HoFH patients by prescribing the 40-mg dose instead of the 20-mg dose. Assuming *arguendo* that specialists may prescribe the 40-mg dose instead of the recommended 20-mg dose for pediatric HoFH in the absence of labeling regarding pediatric HoFH, we do not believe that this presents a safety risk to pediatric HoFH patients. Crestor's labeling states that 20 mg is the recommended pediatric HoFH dose because that is the single dose AstraZeneca elected to study against placebo in its HYDRA trial.[48] Before the HYDRA trial began, FDA requested that AstraZeneca provide a

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[46] The 2003 approved labeling is available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[47] Clinical Review, sNDA 021366 S-033, Julie Golden, MD, April 19, 2016 at 9. See Crestor labeling under section 8.4, "Pediatric Use" ("In general, the safety profile in [the pediatric HoFH] trial was consistent with that of the previously established safety profile in adults.").

[48] HYDRA is the short-hand name for the clinical trial supporting approval of Crestor's pediatric HoFH indication. Its full title is "A Randomized, Double-blind, Placebo-controlled, Multi-center, Cross-over Study of Rosuvastatin in Children and Adolescents (Aged 6 to <18 Years) With Homozygous Familial Hypercholesterolemia (HoFH)."

rationale for excluding the 40-mg dose from the trial.[49] AstraZeneca explained that its decision to study only the 20-mg dose was based in part on the observation that there was only a small incremental LDL-C lowering beyond that achieved with the 20-mg dose in an earlier study in HoFH.[50] AstraZeneca did not cite a safety concern as a basis for not studying the 40-mg dose in the HYDRA trial. Further, AstraZeneca's protocol for a long-term extension study for pediatric HoFH patients completing the HYDRA trial permits patients to titrate up to 40 mg as necessary.[51]

In addition, existing pharmacokinetic data support the conclusion that a 505(b)(2) application or ANDA with the pediatric HoFH information carved out is not expected to present a safety risk if used in pediatric HoFH patients. Pharmacokinetic data for children ages 6 to 18 were reviewed as part of a recent supplemental NDA to extend the indication for HeFH, the related but less severe form of familial hypercholesterolemia, from age 10 to a younger age. According to the clinical pharmacology review for this supplement sNDA 21366/S-031, "rosuvastatin exposure of HeFH patients 6 - <10 and 10 - <18 years of age appears comparable or lower than rosuvastatin exposure in adult patients" (doses up to 20 mg were evaluated).[52] In addition, in the NDA supporting Crestor's initial approval, another pharmacokinetic study in pediatric subjects with HeFH (ages 10 to 17 years) found no difference in Cmax or AUC[53] between pediatric patients and adult subjects for 10-, 40-, and 80-mg doses.[54] Given that we would not anticipate the number of genetic mutations carried by a patient (i.e., patients with HoFH versus HeFH) to modify rosuvastatin's pharmacokinetic profile, we do not have a basis to believe that exposure in children with HoFH would be higher than that observed in adults at any marketed dose, including 40 mg. Thus, the expected risk of adverse events in pediatric patients taking rosuvastatin would be expected to be similar to what has been observed in the adult population at those doses. This conclusion is supported by the fact that, to date, the safety of Crestor in studies involving pediatric patients has been consistent with that observed for adult patients.[55]

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[49] Clinical Review, sNDA 021366 S-033, Julie Golden, MD, April 19, 2016 at 14.

[50] See id. at 14-15. AstraZeneca also cited the fact that the majority of pediatric patients are prescribed doses less than 40 mg as a basis for not including the 40 mg dose in the HYDRA trial. See id.

[51] Id. The long-term extension study is described at https://clinicaltrials.gov/ct2/show/NCT02434497?term=crestor+long+term+extension&rank=2.

[52] Clinical Pharmacology Review, sNDA 21366/S-031, S.W. Johnny Lau, November 18, 2015 at 7-8.

[53] Cmax and AUC are pharmacokinetic parameters. *Cmax* is the maximum drug concentration, usually measured in an accessible biological fluid, such as blood plasma in this case. *AUC* refers to area under the plasma concentration versus time curve and represents total exposure of the drug over a defined time period.

[54] Clinical Pharmacology Review, NDA 21366, Sang Chung, July 21, 2003 at section 2.2.

[55] In addition to clinical trial data involving patients with familial hypercholesterolemia, a search of the FAERS database, which contains spontaneous post-marketing reports of adverse events submitted to the FDA, supports the conclusion that FDA is not aware of any new safety concerns or those of increased severity with pediatric patients taking Crestor. Although FAERS data are supportive of our conclusion, we make a general note that FAERS data

In addition, the labeling for rosuvastatin products that may be approved for ANDAs or, where appropriate, 505(b)(2) applications, will retain the Warnings and Precautions associated with Crestor, including warnings regarding risks of skeletal muscle effects and rhabdomyolysis. Crestor's labeling states (and ANDA labeling will also state) that these risks can occur at any dose level but are increased at the highest dose (40 mg). We have no reason to anticipate a difference in risk between the pediatric and adult populations and believe that – should the 40-mg dose be prescribed in pediatric HoFH patients – physicians and caregivers will be sufficiently informed to guide management and mitigation of risk even with the pediatric HoFH information carved out of the ANDA labeling.

We also note that Crestor has been studied to a more limited extent in pediatric patients at doses above 20 mg without adverse effects noted. Your Petition references on page 9 AstraZeneca's "Study 54," which was submitted in the original NDA for Crestor. Study 54 was an open-label trial of 36 adult and 8 pediatric patients with HoFH (ages 8 to 17 years). The rosuvastatin doses studied included 20 and 40 mg. There were no adverse events leading to discontinuation of study treatment including when pediatric patients were treated with 40 mg Crestor daily.[56]

Based on all of the foregoing, we do not agree that the first scenario described in your Petition – which you refer to as overtreatment of pediatric HoFH patients with the 40-mg dose – presents a safety risk to pediatric patients such that generic rosuvastatin with the pediatric HoFH indication carved out would be unsafe for this population.

Your petition's second and third scenarios both allege a potential for under-treatment of pediatric HoFH patients. You assert that a pediatric HoFH carve-out may cause doctors with limited experience treating HoFH to under treat pediatric HoFH patients with the lower dose range labeled for pediatric HeFH. Further, you assert that pediatric HoFH patients in the 7 to 9 age group would be at risk of under-treatment "because the Crestor label recommends titrating upwards from a 5 mg starting dose to a 10 mg starting dose for HeFH patients ages 8 to less than 10, and titrating upwards from a 5 mg starting dose to a maximum dose of 20 mg for HeFH patients ages 10-17." (Petition at 14). In support of this scenario, you also note "the HeFH labeling includes no information at all about the treatment of 7-year olds" (Id).

FDA does not agree. First, given the labeled general dosing information that Crestor should be titrated according to the patient's response and individual goal of therapy (general dosing

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have numerous limitations (e.g., missing information, under-reporting, lack of information about drug dechallenge and rechallenge, and lack of exposure data).

[56] See Clinical Review, sNDA 021366 S-033, Julie Golden, MD, April 19, 2016 at 53. This limited information does not provide a sufficient basis to evaluate the safety and effectiveness of 40 mg Crestor in pediatric patients to support approval of that dose as safe and effective, but the results from this study support the conclusion that the totality of data for Crestor suggest that use of Crestor 40 mg in pediatric patients with HoFH is unlikely to be associated with an adverse event profile that is not otherwise described in portions of the labeling that would be retained if the protected pediatric HoFH information is carved out.

information that will be retained in ANDA labeling), healthcare providers would be expected to assess the patient's LDL-C response and titrate Crestor, assuming *arguendo* that the provider had initiated treatment at a dose below 20 mg daily.

Further, treatment guidelines recommend that pediatric patients with HoFH be treated by specialists with specialized training and knowledge of the disease and not by doctors with limited experience treating these patients. For example, the NLA Expert Panel on Familial Hypercholesterolemia recommends, "[a] pediatric patient with homozygous FH should always be managed by a lipid specialist. Pediatric lipid specialists include pediatric cardiologists, endocrinologists, or other health care providers with specialized lipidology training."[57] Similarly, an EAS Consensus Panel stated that "[c]hildren with suspected HoFH should be referred promptly to specialized centres due to the aggressive nature of this condition."[58] A provider caring for patients with this rare disease would be accustomed to monitoring patients' responses to the addition of LDL-C-lowering therapies and titrating, as appropriate.[59]

Finally, your Petition asserts as a fourth scenario that a disclaimer of the type permitted by section 505A(o) of the FD&C Act, discussed in section I.C.4 of this response, would not cure the risks described in your Petition. As described below, we conclude that the pediatric HoFH indication is protected by both 3-year Hatch-Waxman exclusivity and orphan drug exclusivity. We therefore conclude that inclusion of a disclaimer in ANDA labeling during the pendency of the 3-year Hatch-Waxman exclusivity is permissible and appropriate. Although this disclaimer will be included in ANDA labeling pursuant to section 505A(o) and consistent with general agency practice, we conclude that the disclaimer is not necessary for the safe and effective use of the product because, as discussed above, the pediatric HoFH indication can be carved out in its entirety without presenting a safety risk to pediatric patients with HoFH.[60]

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[57] Daniels SR, et al. Pediatric aspects of Familial Hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipid* 2011; 5: S30-S37.

[58] Wiegman A, et al. for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015; 36:2425-2437.

[59] Additionally, providers reading the ANDA labeling to guide treatment would not be expected to use doses below 20 mg daily on the basis of labeled recommendations for pediatric HeFH because labeling for pediatric HeFH will remain carved out of ANDA labeling due to existing 3-year Hatch-Waxman exclusivity and patent protection for that use, the latter of which does not expire until June 17, 2022.

[60] Your Petition quotes a disclaimer appearing in the labeling of a generic rosuvastatin calcium product approved under ANDA 79167 held by Watson Laboratories, Inc. (Watson). As your Petition points out, that disclaimer is based on Crestor's pediatric HeFH labeling and pre-dates the May 27, 2016 approval of the pediatric HoFH indication. That disclaimer therefore does not reflect any updates that might be included in the disclaimer language for a generic product that carves out the pediatric HoFH indication approved for Crestor on May 27, 2016.

For all of these reasons, we conclude that an ANDA with the protected pediatric HoFH information carved out will not present a safety risk to the pediatric HoFH population and will remain safe and effective for the remaining non-protected conditions of use.

B. FDA Has the Authority to Carve Out the Protected Pediatric HoFH Indication

In addition to the scientific arguments you make, your Petition presents three arguments concerning FDA's legal authority to approve an ANDA or 505(b)(2) application with a pediatric indication protected by orphan drug exclusivity carved out. First, you contend that FDA's regulations pertaining to pediatric information in drug labeling do not accommodate such carve-outs (Petition at 17-19). Second, you contend that section 505A(o) of the FD&C Act (captioned "Prompt Approval of Drugs Under Section 505(j) When Pediatric Information is Added to Labeling") does not permit approval of an ANDA with labeling from which a pediatric indication protected by orphan drug exclusivity has been carved out (Petition at 19-20). Third, you contend that FDA's general carve-out regulations also do not provide authority for approval of such a product (Petition at 20-26). We address each of these arguments below, although not in the order you present the issues in your petition.

1. FDA's General Carve-Out Authority Enables FDA to Carve Out the Protected Pediatric HoFH Indication

FDA's general carve-out authority permits the Agency to carve out the pediatric HoFH indication in this case.[61] FDA has long interpreted the *differences due to differences in manufacturer* exception to the "same labeling" requirement in section 505(j)(2)(A)(v) of the FD&C Act and §§ 314.92(a)(1), 314.94(a)(8)(iv), and 314.127(a)(7) to allow carve-outs of labeling (including pediatric 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. As discussed in section I.C.3 of this response, courts have repeatedly upheld FDA's ability to carve out indications protected by orphan drug exclusivity.[62]

In conducting our carve-out analysis under our general carve-out authority to determine whether an ANDA that carves out the pediatric HoFH indication would be safe and effective for the remaining non-protected conditions of use, we consider both the information that will be carved out and the information that will remain in the labeling once the carve-out is implemented. As described in section I.C.4 of this response, FDA has determined in certain instances that ANDA

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[61] As described in SectionII.B.2.a of this response, the pediatric HoFH indication is protected by both orphan drug and 3-year Hatch-Waxman exclusivity.

[62] See, e.g., *Otsuka*, No. GJH-15-852, 2015 WL 3442013, at 24-25 (D. Md. May 27, 2015) (discussing that both the Hatch-Waxman Amendments and the Orphan Drug Act confirm FDA's ability to carve out indications protected by orphan drug exclusivity and that the result Otsuka seeks "is directly contrary to FDA's prior decisions on orphan drug exclusivity carve-outs where that exclusivity incorporated pediatric information"); *Sigma-Tau*, 288 F.3d 141 (4th Cir. 2002).

applicants need to retain certain pediatric information related to a pediatric indication protected by exclusivity where carving it out would present a safety risk to pediatric patients using the drug based on its approved (non-protected) adult indication.[63] As further described in section I.C.4 of this response, protected pediatric information is required to be retained in ANDA labeling only when the indication for which pediatric information is protected is one that is also approved for adults and where the remaining adult information and carved out pediatric information are sufficiently different such that a pediatric patient using the drug according to the adult labeling would be at risk.

As reflected in section II.A of this response, FDA has determined as a scientific matter in this case that given the nature of the pediatric HoFH information that was added in sNDA 21366/S-033, it is not necessary to retain in the labeling for rosuvastatin any protected pediatric HoFH information to assure safe use (including safe use in pediatric patients with HoFH who use the product based on its approval for HoFH in adults). FDA has also determined that rosuvastatin with the protected pediatric HoFH information carved out remains safe and effective for the remaining non-protected conditions of use. Accordingly, a carve-out of pediatric information is permissible in this case.

2. *Section 505A(o) of the FD&C Act Does Not Abrogate FDA's Authority to Approve ANDAs that Carve Out Orphan-Protected Indications*

As described above, FDA's general carve-out authority permits the Agency to carve out the protected pediatric HoFH indication. Section 505A(o) does not limit that authority.

a. The Pediatric HoFH Indication Is Protected by Hatch-Waxman Exclusivity

As an initial matter, we note that the pediatric HoFH indication is protected by both orphan drug exclusivity and 3-year Hatch-Waxman exclusivity. On June 15, 2016, AstraZeneca wrote to the Division of Metabolism and Endocrinology Products (DMEP) in FDA's Center for Drug Evaluation and Research disputing the notation in the Orange Book that 3-year Hatch-Waxman exclusivity has attached to Crestor's pediatric HoFH indication.[64] AstraZeneca argued, in relevant part, that because it had not requested 3-year Hatch-Waxman exclusivity, no such exclusivity can attach.

As set forth in section I.C.2.a of this response, a 3-year period of Hatch-Waxman exclusivity attaches to a drug product that contains an active moiety that has been previously approved, when an NDA or supplemental NDA for that drug product contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that

[63] See, e.g., ANDA labeling approvals for sildenafil tablets and zolpidem tablets.

[64] AstraZeneca submitted this letter to Docket No. FDA-2016-P-1485 as a supplement to the Petition on June 24, 2016. AstraZeneca submitted an updated version of the supplement on June 30, 2016, to conform to certain verification requirements in section 505(q). The June 30, 2016 supplement is otherwise identical to the June 24, 2016 supplement.

were essential to approval of the application or supplemental application.[65] The sections of the FD&C Act governing 3-year Hatch-Waxman exclusivity expressly state that if the criteria for 3-year Hatch-Waxman exclusivity are met, FDA "may not make the approval of an application . . . for a change approved in the supplement effective before the expiration of three years . . . ." (see sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act). Consistent with these statutory provisions, FDA's regulations state that "the agency will not make effective for a period of 3 years after the date of approval" an application to which 3-year Hatch-Waxman exclusivity attaches (see §§ 314.108(b)(4) and 314.108(b)(5)).

The prohibition on FDA approval for certain changes during the pendency of the 3-year exclusivity period is not discretionary and is not predicated on the NDA or supplemental NDA sponsor's having requested 3-year Hatch-Waxman exclusivity. On the contrary, attachment of 3-year Hatch-Waxman exclusivity is automatic for NDAs and supplemental NDAs that meet the statutory criteria for such exclusivity.[66] Supplement sNDA 21366/S-033 to your Crestor NDA met all of the qualifying criteria for the attachment of 3-year Hatch-Waxman exclusivity. It contained new clinical investigations (other than bioavailability studies) conducted by or on behalf of AstraZeneca that were essential to approval of the supplement. Accordingly, AstraZeneca's failure to request 3-year Hatch-Waxman exclusivity notwithstanding, the Orange Book accurately reflects this exclusivity.

As such, the relevant pediatric HoFH indication is protected by both orphan drug exclusivity and 3-year Hatch-Waxman exclusivity, so it expressly falls within the contours of section 505A(o). Thus, if FDA had concluded that certain information relating to the HoFH indication (e.g., certain warnings or adverse event information) in pediatric patients was essential to assure safe use of the product, under section 505A(o) FDA would have been permitted to allow that information to remain in the ANDA labeling despite 3-year Hatch-Waxman exclusivity for pediatric HoFH. (In this case, as reflected above, FDA determined that such information was not necessary to assure safe use of the product and that the pediatric HoFH indication could be carved out in its entirety).

b. Section 505A(o) of the FD&C Act Does Not Preclude FDA from Carving Out the Protected Pediatric HoFH Indication

Your Petition contends that section 505A(o) limits the availability of a carve-out such that ANDA applicants can carve out only pediatric information protected by patent or 3-year Hatch-Waxman exclusivity, and not information protected by orphan drug exclusivity. Your Petition

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[65] See 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and § 314.108(b)(4) (21 CFR 314.108(b)(4)) (new drug applications); see sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act and § 314.108(b)(5) (21 CFR 314.108(b)(5)) (supplemental new drug applications).

[66] Sponsors may voluntarily choose to waive exclusivity as to one or more applicants, but this has no effect on the fact that exclusivity attaches by statute in the first instance. *See* Orange Book Preface (36th ed., 2016) at xxi-xxii (noting that an NDA holder may waive its exclusivity as to any or all 505(b)(2) and ANDA applicants, and that an NDA for which the holder has waived its exclusivity as to all 505(b)(2) and ANDA applications will be coded with a "W" in the Patent and Exclusivity Section of the Orange Book).

also asserts that section 505A(o) provided essential authority for FDA to approve generic drugs with pediatric information carved out and that prior to enactment of this provision, carve-outs of pediatric information (including presumably pediatric information protected by patent and 3-year Hatch-Waxman exclusivity) were not permitted under any circumstances. Accordingly, you argue, because orphan drug exclusivity is not expressly enumerated under section 505A(o)(1), ANDAs referencing Crestor must await the expiration of Crestor's orphan drug exclusivity for the pediatric HoFH indication before they will be eligible for approval even for the multiple unprotected indications and conditions of use for which Crestor is approved.

FDA rejects these arguments, as we did in the Otsuka letter your Petition references regarding approval of generic versions of Abilify, approvals that were upheld by the United States District Court for the District of Maryland in *Otsuka Pharmaceutical Co., Ltd. v. Burwell*, No. GJH-15-852, 2015 WL 3442013 (D. Md. May 27, 2015).

As Otsuka unsuccessfully attempted previously, AstraZeneca seeks to use a provision designed to ensure that ANDA approvals would not be delayed in certain circumstances to support its arguments to delay approval for any ANDA referencing Crestor, including those ANDAs seeking approval only for the non-protected indications. This argument turns 505A(o) on its head. As indicated by the title of section 505A(o) (captioned "Prompt Approval of Drugs Under Section 505(j) When Pediatric Information Is Added To Labeling"), Congress intended section 505A(o) to remove an obstacle to the timely approval of generic drugs, not to create one.

As discussed above, FDA's general carve-out authority permits a carve-out of orphan-protected indications, such as the pediatric HoFH indication here; FDA has been implementing that authority since passage of the Hatch-Waxman Amendments and courts have repeatedly upheld this authority. Nothing that AstraZeneca points to in section 505A(o) or in the circumstances surrounding the enactment of section 505A(o) takes away that authority.

The language of section 505A(o)(1) reads, in relevant part:

> [An ANDA] shall not be considered ineligible for approval . . . or misbranded . . . on the basis that the labeling of the drug omits a pediatric indication . . . when the omitted indication . . . is protected by patent or by exclusivity under clause (iii) or (iv) [referring to 3-year Hatch-Waxman exclusivity for new applications and supplements respectively] of section 505(j)(5)(F).

AstraZeneca contends that because section 505A(o) mentions only patent and Hatch-Waxman exclusivity-protected information, FDA has no authority to carve out pediatric information protected by orphan drug exclusivity in any circumstance, "regardless of a factual inquiry into whether the omitted labeling raises a safety issue" (Petition at 17). But as described above, AstraZeneca ignores FDA's general carve-out authority under section 505(j) to carve out orphan-protected indications and other protected conditions of use, which authority remained unchanged by section 505A(o). Congress explicitly stated in section 505A(o)(3) that the addition of that provision was not intended to affect "the operation of section 505." This language encompasses the provisions under section 505(j) that otherwise allow for labeling carve-outs where the labeling retained would result in a drug product that is safe and effective for the remaining non-

protected conditions of use. Thus, FDA's interpretations of the same labeling requirement and of the scope of the *difference due to difference in manufacturer* exception remain unchanged after enactment of section 505A(o). The words of section 505A(o), when viewed in the context of the statute as a whole, do not bear the weight that your Petition ascribes to them.

Further, like Otsuka, AstraZeneca "ignores the critical fact that [section 505A(o)] sets forth circumstances where FDA cannot *deny* approval for a labeling carve-out; it does not… address situations where FDA can or cannot *grant* approval."[67] Section 505A(o), among other things, gave FDA authority to *include* certain information in the labeling of an ANDA drug product with pediatric use information carved out to facilitate prompt ANDA approvals. Specifically, section 505A(o)(2) allows FDA to approve an ANDA with labeling that includes, for example, (1) a statement that due to marketing exclusivity for a manufacturer, the drug is not labeled for pediatric use; or (2) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information FDA considers necessary to assure safe use.

You have cited no evidence that with the adoption of section 505A(o), Congress intended to negate FDA's pre-existing authority to carve out pediatric information protected by orphan drug exclusivity in any circumstance. Your Petition asserts that because Congress was considering orphan drug legislation at the same time it was considering the language of section 505A(o), Congress intended that section 505A(o)(1) was worded in a way that intentionally and purposefully omitted orphan drug exclusivity. We do not find this argument persuasive, nor did the *Otsuka* court.[68] FDA instead properly interprets section 505A(o) in light of its stated purpose, to allow for prompt approval of ANDAs when pediatric information is included in RLD labeling, and in light of the larger statutory scheme, which has long allowed for the approval of ANDAs with patent- or exclusivity-protected information omitted from labeling (including omission of labeling protected by orphan exclusivity). The *Otsuka* court expressly rejected the outcome AstraZeneca urges here. It held that reading section 505A(o) to "treat the orphan drug exclusivity [(which protects *only* the orphan indication)] as extending to the drug for any and all diseases and conditions" would "directly contradict[] that provision's text and the Fourth Circuit's holding in *Sigma-Tau*."[69]

Your Petition also contends that FDA's approval of generic versions of Glucophage is further support for your conclusion that FDA does not have authority to carve out pediatric orphan-protected indications. You state that FDA delayed the approval of generic Glucophage products until after the adoption of section 505A(o), contending that FDA relied on section 505A(o)(1) for pediatric carve-out authority that had been lacking previously. Even if FDA accepts your Petition's characterization of the Glucophage precedent (which we do not), your characterization does not preclude a carve-out here. Given the facts and circumstances of this case and the

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[67] No. GJH-15-852, 2015 WL 3442013 (D. Md. May 27, 2015) at 16, quoting the court's previous decision in *Otsuka Pharm. Co.*, No. GJH-15-852, 2015 WL 1962240 (D. Md. Apr. 29, 2015) at 7 (emphasis in original).

[68] *Otsuka* at 18.

[69] Id. at 27 (emphasis added).

current labeling carve-out scheme, FDA has concluded that all information related to the pediatric HoFH indication can be carved out without the need to retain any information related to that indication to assure safe use of rosuvastatin.

Your Petition also presents arguments that section 505A(o) addresses pediatric labeling carve-outs more specifically than other statutory provisions, such as the *difference due to difference in manufacturer* exception to the same labeling requirement, and it therefore controls. Again, we do not find this argument persuasive. You state that "Congress acts with knowledge of existing law, and . . . absent a clear manifestation of contrary intent, a newly-enacted or revised statute is presumed to be harmonious with existing law and its judicial construction" (Petition at 22, quoting from *United States v. Langley*, 62 F.3d 602 (4th Cir. 1995)). FDA's interpretation of section 505A(o) assigns meaning and intent to the entire provision, recognizing its purpose, its explicit statement that it does not change the operation of section 505, and its harmonious place in the broader statutory and regulatory scheme created by the Hatch-Waxman Amendments. AstraZeneca's interpretation, which the *Otsuka* court rejected, does precisely the opposite: "Given the context, it would defy logic to believe that in enacting a measure to prevent three-year exclusivity from becoming a 'fundamental abuse of the system' that harmed consumers, Congress nonetheless intended to permit the seven-year exclusivity Otsuka seeks here."[70]

Your Petition also argues that the incentives for orphan drug development provided in the Orphan Drug Act apply with special force to a pediatric orphan disease or condition (Petition at 24). You also assert that Congress considered the BPCA, including section 505A(o), in parallel with a bill entitled "Rare Diseases Act of 2001," and you argue that this suggests Congress intentionally omitted orphan drug exclusivity from section 505A(o)(1).

We find these arguments unpersuasive for the reasons discussed above and the *Otsuka* court also expressly rejected them. As the *Otsuka* court stated, "[s]imply showing that some members of the Congress that enacted section 355a(o) were generally aware of the Orphan Drug Act or orphan drug issues hardly suggests that by not mentioning orphan drugs in section 355a(o) Congress intended, by negative implication, to limit FDA's existing carve-out authority under 21 U.S.C. § 355(j) and 360cc."[71] FDA understands the importance of incentivizing the development of drugs to treat rare conditions and incentivizing drug studies in pediatric patients. The law provides AstraZeneca with 7 years of orphan drug exclusivity for Crestor's pediatric HoFH indication, and FDA's decision here does not abrogate that protection. AstraZeneca has the exclusive right to obtain approval for and to market Crestor for pediatric HoFH for 7 years, and no NDA or ANDA labeling will include that protected pediatric orphan indication without AstraZeneca's permission during that time period.[72]

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[70] Id. at 21.

[71] See id. at 18.

[72] We note further that the position you advocate in your Petition would potentially allow sequential periods of orphan exclusivity that would block approvals of ANDAs for Crestor (even for unprotected indications) indefinitely should new pediatric orphan indications be added to labeling in serial fashion.

C. FDA's Labeling Regulations Do Not Preclude a Carve-Out of the Pediatric HoFH Indication

Your Petition refers to a combination of requirements in FDA's labeling regulations (codified in relevant part at 21 CFR 201.56 and 201.57),[73] which govern labeling for certain drugs, and which you argue preclude carve-out of the pediatric HoFH indication. For example, you cite § 201.57(a) (21 CFR 201.57(a)) (captioned "Highlights of prescribing information") as stating that certain information "must appear in all prescription drug labeling." You point out that this statement is followed by § 201.57(a)(6) (requiring a concise statement of each of a product's indications along with major limitations of use, such as lack of effect in particular population subsets), § 201.57(a)(7) (requiring a concise summary of dosage and administration information, including critical differences among populations subsets), and § 201.57(a)(13) (requiring a concise summary of information concerning use in specific populations including use in pediatric patients). You also reference § 201.57(c)(2)(i)(B), which requires a succinct description of the limitations of usefulness of a drug, where appropriate, including, for example, evidence that the drug is safe and effective only in selected subgroups of the population, such as patients in special age groups. You further reference § 201.57(c)(3)(i)(H), which requires that the DOSAGE AND ADMINISTRATION section of prescription drug labeling include any modification of dosage needed in special patient populations, including children.

Your Petition also references § 201.57(c)(9)(iv)(B), which requires, among other things, 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, and appropriate pediatric dosage information must be given under the 'Dosage and Administration section'" of labeling. You also cite 21 CFR 201.57(c)(9)(iv)(C), which requires, among other things, that "[i]f 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 and discussed in more detail, if appropriate, under the 'Clinical Pharmacology' and 'Clinical Studies' sections. Appropriate pediatric dosage must be given under the 'Dosage and Administration section'" of labeling.

Your Petition argues that these labeling provisions, which require the inclusion of certain pediatric use information in drug labels, create a barrier to approval of generic drugs where "(i) the reference-listed drug is approved for one or more pediatric indications and (ii) at least one of these pediatric indications is protected by patent, Hatch-Waxman, or some other form of exclusivity" (Petition at 18). To support this argument, you cite a statement FDA made in describing the Agency's legal authority to issue a 1994 regulation concerning pediatric labeling of prescription drug products, that drug products not in compliance with those requirements would be misbranded (Petition at 18 citing 59 FR 64240 at 64247 (Dec. 13, 1994)).

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[73] Your Petition refers to these requirements as FDA's pediatric-labeling regulations.

We disagree with your interpretation of these regulations. To be clear, the 1994 preamble you quote was a preamble to a regulation requiring manufacturers of marketed drugs to survey existing data to determine whether those data were sufficient to support adding pediatric use information to the drug's labeling, and if so, submit an sNDA to seek approval for a labeling change to include that pediatric use information.[74] The 1994 regulation did not require a categorical inclusion of specific pediatric information in drug labeling, and as such, did not need to address whether such non-required information could be carved out of generic drug labeling. After issuance of the 1994 rule, product labeling "frequently continued to fail to provide directions for safe and effective pediatric use."[75]

Accordingly, FDA and Congress undertook additional actions to address the continued lack of pediatric use information in drug labeling. These actions included Congress's enactment of section 505A of the FD&C Act, FDA's issuance of the 1998 "Pediatric Rule,"[76] and Congress's later enactment of PREA in section 505B of the FD&C Act, which codified many of the provisions of FDA's 1998 Pediatric Rule. In light of the purpose of the 1994 rule in the first instance, and superseding statutory requirements that have been enacted since 1994, the 1994 regulation cannot bear the meaning you attribute to it, and does not reflect the current legal requirements regarding pediatric labeling.

In addition, contrary to AstraZeneca's argument, current pediatric labeling regulations do not establish a categorical rule that binds FDA to find labeling that excludes a pediatric indication misbranded. In fact, the regulations that you cite, some of which were promulgated as part of the 2006 Physician Labeling Rule, expressly recognize that FDA has discretion *not to require* any specific labeling statement. Section 201.57(c)(9)(iv) expressly permits FDA to approve labeling *without* the statements required by § 201.57(c)(9)(iv)(B) (and without other statements specified under subsection 201.57(c)(9)(iv)), if FDA determines that the statements are not "appropriate or relevant to the drug's labeling" and the alternative statements are "accurate and appropriate." 21 CFR 201.57(c)(9)(iv)(G).

Further, FDA's decision to carve out the pediatric HoFH indication here tracks the explanation that the Agency gave when adding § 201.57 to its regulations in 2006. There, FDA expressly noted: "[t]his final rule does not change the requirement to exclude any condition of use or indication from the labeling of a generic product when necessary (e.g., when the reference listed drug has patent protection or market exclusivity for an indication), nor does it prevent, as

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[74] 59 Fed. Reg. 64240 (Dec. 13, 1994).

[75] FDA July 2016 Status Report to Congress, Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, at 2 (FDA July 2016 Status Report), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf.

[76] See 63 Fed. Reg. 66632 (Dec. 2, 1998).

described in § 314.127(a)(7), approval of an ANDA when the reference listed drug has protected labeling." (71 FR 3922 at 3963 (Jan. 24, 2006)).[77]

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[77] The *Otsuka* court reached the same conclusion: "This case, however, is not about the general requirements for pediatric information in labeling; rather, this case is about FDA's statutory authority to approve ANDAs that carve out an entire protected orphan pediatric indication, a permissible practice which the Physician Labeling Rule does not change." *Otsuka* at 26.