

May 31, 2016
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By Electronic Filing

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**RE: Crestor[®] (rosuvastatin calcium) Pediatric Orphan Drug Exclusivity For
Treatment Of Pediatric Homozygous Familial Hypercholesterolemia**

Dear Sir or Madam:

CITIZEN PETITION

AstraZeneca Pharmaceuticals LP and its affiliate iPR Pharmaceuticals, Inc. (collectively, “AstraZeneca”) hereby submit this Citizen Petition pursuant to 21 U.S.C. § 355(q) and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs not approve any abbreviated new drug application (“ANDA”) or section 505(b)(2) new drug application (“NDA”) referencing Crestor[®] (rosuvastatin calcium) until the expiration of the orphan drug exclusivity for use of Crestor[®] in the treatment of pediatric patients ages 7 to 17 with homozygous familial hypercholesterolemia (“HoFH”).

Pediatric HoFH is a rare and extremely serious condition. If left untreated, HoFH causes substantially elevated plasma cholesterol levels, which in turn lead to cardiovascular disease, myocardial infarction, and premature death. As demonstrated in AstraZeneca’s Pediatric HoFH Study (also known as HYDRA) and supplemental NDA (“sNDA”), No. 21-366/S-033, Crestor[®] offers a safe and effective means for treating HoFH in pediatric patients. Crestor[®] statin therapy helps reduce patients’ cholesterol levels, thereby helping prevent or delay the adverse cardiovascular effects caused by HoFH. The Pediatric HoFH Study provides critical new information on appropriate treatment for HoFH in children. On May 27, 2016, FDA approved Crestor[®] “for treatment of pediatric patients 7 to 17 years of age with [HoFH] to reduce LDL-C, total C, nonHDL-C and ApoB as an adjunct to diet, either alone or with other lipid-lowering treatments.” Previously, on February 14, 2014, FDA’s Office of Orphan Products Development granted AstraZeneca Orphan Drug Designation for Crestor[®] in the treatment of pediatric HoFH.

The Commissioner should grant this Citizen Petition for two principal reasons. *First*, carving out AstraZeneca’s protected pediatric HoFH labeling from the labeling of a product marketed under an ANDA or section 505(b)(2) NDA would present substantial safety and efficacy risks. Although FDA may in some instances approve ANDAs that omit protected pediatric labeling, FDA has made clear that a carve out is inappropriate when, as here, the

protected pediatric labeling is “necessary for the safe use of the drug.”¹ Crestor[®] is labeled for treatment of HoFH in adult and pediatric patients, and for treatment of heterozygous familial hypercholesterolemia (“HeFH”), a related but far less severe condition. In many instances, the recommended dosage and course of treatment differ between adult HoFH and pediatric HoFH patients, and likewise between HeFH and HoFH patients. Given these differences, there are substantial risks that doctors would over- or under-treat pediatric HoFH patients if generic or other rosuvastatin calcium omitted AstraZeneca’s protected pediatric HoFH labeling.

Second, irrespective of whether a carve out would present a safety risk, FDA lacks legal authority to carve out pediatric labeling protected by orphan drug exclusivity. Together, the Hatch-Waxman Act’s same-labeling requirement and FDA’s pediatric-labeling regulations impose a categorical rule: pediatric labeling information subject to orphan drug exclusivity may not be omitted from generic-drug labeling. The Best Pharmaceuticals for Children Act, 21 U.S.C. § 505A(o), permits the carve out of labeling protected only by patent and Hatch-Waxman exclusivity—and therefore provides no basis for carving out labeling protected by orphan drug exclusivity. FDA also possesses several other “general” carve-out authorities, *see* 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7), but those authorities are inapposite in light of FDA’s subsequently adopted pediatric-labeling rules and Congress’s enactment of section 505A(o). Indeed, prior to the passage of section 505A(o), FDA concluded that it lacked authority to carve out protected pediatric labeling in circumstances nearly identical to those presented here. FDA and the United States District Court for the District of Maryland concluded in the *Otsuka* litigation that FDA has authority to carve out pediatric labeling protected by orphan drug exclusivity. However, that conclusion is incorrect for the reasons given above and in Part II.B of this Citizen Petition.

ACTIONS REQUESTED

AstraZeneca respectfully requests that the Commissioner:

- (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 sNDA, to ensure the safe and effective use of the product in pediatric HoFH patients; and

¹ Letter from John R. Peters, M.D., Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to Ralph S. Tyler, Venable LLP, at 10 n.27 (Apr. 27, 2015) (“Otsuka Letter”); *see also id.* at 14 (labeling must be included “where carving it out would present a safety risk to pediatric patients using the drug for its approved (non-protected adult) indication”).

- (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.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Background On The Development Of Rosuvastatin

Rosuvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (“HMG CoA”) reductase inhibitor and a member of the statin class of lipid-lowering agents. Rosuvastatin is a selective, potent, and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol. Rosuvastatin produces its lipid-modifying effects in two ways: (i) it increases the number of hepatic cell surface low-density lipoprotein (“LDL”) receptors, enhancing uptake and catabolism of LDL; and (ii) it inhibits the hepatic synthesis of very low-density lipoproteins (“VLDL”), thereby reducing both VLDL and LDL. In an extensive clinical study program involving over 60,000 subjects, more than 35,000 subjects received rosuvastatin and nearly 400 of these (not including the recent Pediatric HoFH Study) subjects were children or adolescents. The clinical study program demonstrated that rosuvastatin is a highly efficacious statin and favorably modifies plasma levels of lipids, lipoproteins, and their ratios in adults and in pediatric patients with HeFH—a related, but more common and far less serious condition—ages 6 to 17.

Crestor[®] (rosuvastatin calcium) was first approved for marketing in the Netherlands on November 6, 2002. In the United States, Crestor[®] was approved for use in adult patients with dyslipidemia, including HoFH, on August 12, 2003 (NDA 21-366). On October 15, 2009, based on the results of Study D3561C00087 (also known as PLUTO), Crestor[®] was approved for the treatment of HeFH in adolescent boys and postmenarchal girls, ages 10 to 17, to reduce total cholesterol (“TC”), LDL-C, and Apolipoprotein B (“ApoB”) with a recommended dosing range of 5 to 20 mg once daily. Based on the results of Study D3561C00002 (also known as CHARON), AstraZeneca submitted a sNDA, No. 21-366/S-031, to support an expansion of the age range for the HeFH indication to pediatric patients ages 8 to 17, with a recommended dosing range of 5 to 10 mg once daily in patients 8 to less than 10 years old and 5 to 20 mg once daily in patients 10 to 17 years old. In Europe, the dossier supporting the expanded age range of 6 to 17 years for the HeFH indication received approval from the Committee for Medicinal Products for Human Use in April 2014, and the approval was adopted by the European Commission in June 2014. In the United States, FDA approved AstraZeneca’s sNDA 21-366/S-031 on November 20, 2015.

In markets where Crestor[®] was approved prior to approval of the pediatric orphan drug HoFH sNDA, it is indicated for one or more of the following indications: treatment of patients with primary hypercholesterolemia (heterozygous familial and nonfamilial), mixed dyslipidemia, primary dysbetalipoproteinemia, and isolated hypertriglyceridemia, as an adjunct to diet when response to diet and exercise is inadequate. Crestor[®] also is indicated for the treatment of adult patients with HoFH, either alone or as an adjunct to diet and other lipid-lowering treatments (e.g., LDL-apheresis), and to reduce TC, LDL-C, and ApoB in children and adolescents ages 8 to 17 with HeFH. In some markets, rosuvastatin is approved to slow progression of atherosclerosis and/or reduce the risk of major cardiovascular events.

In 2013, AstraZeneca executed a settlement agreement with Watson Laboratories, Inc. (“Watson”) that granted Watson the ability to market generic rosuvastatin beginning on May 2, 2016. Watson began marketing its generic rosuvastatin product on or about May 2, 2016, and has continued to market that product through the date of this Citizen Petition. As required under the terms of the March 2013 settlement agreement, AstraZeneca has granted Watson a patent license and a selective waiver of all periods of exclusivity applicable to FDA’s May 27, 2016, approval of the pediatric HoFH indication and labeling with respect to Watson’s marketing of its generic rosuvastatin product.²

B. Background On Homozygous Familial Hypercholesterolemia (HoFH)

HoFH adversely affects day-to-day functioning, morbidity, and mortality.³ If left untreated, HoFH progresses from a serious condition to a severe condition and eventually leads to premature death. Typically, children with HoFH have substantially elevated plasma cholesterol levels and are predisposed to premature and progressive atherosclerotic cardiovascular disease (Cuchel, et. al 2014⁴). In the pediatric HoFH patient population, the accumulation of cholesterol begins at birth and produces increasingly severe clinical manifestations. Angina pectoris, myocardial infarction, and death in early childhood have been reported, although the first major cardiovascular events usually occur during adolescence (Wiegman, et. al 2015⁵). Pediatric HoFH patients often develop accumulation of cholesterol in

² See Exhibit A, Declaration of Sarah Walters ¶¶ 3–7 (“Walters Decl.”).

³ See Exhibit B, Declaration of Gregory F. Keenan, MD ¶¶ 4–6 (“Keenan Decl.”).

⁴ Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al.; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. *Eur. Heart J.* 2014 Aug 21; 35(32):2146-2157.

⁵ Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur. Heart J.* 2015 May 25 (Epub ahead of print). doi:10.1093/eurheartj/ehv157.

other parts of the body leading to cutaneous xanthomas within the first four years of life, commonly serving as the first clue for diagnosis. Cholesterol retention in the arterial wall and foam cell formation within the intima of arteries typically progresses to occlusive atherosclerosis with angina pectoris and/or plaque rupture resulting in thrombotic occlusion of the coronary artery (*i.e.*, myocardial infarction). As a result, patients develop clinically significant cardiovascular disease in early childhood, often leading to premature coronary death before the patient turns 30 years old in untreated individuals (Nordestgaard et al 2013;⁶ Wierzbicki 2013⁷). The figure below depicts the concept of cumulative cholesterol burden in this pediatric orphan population:

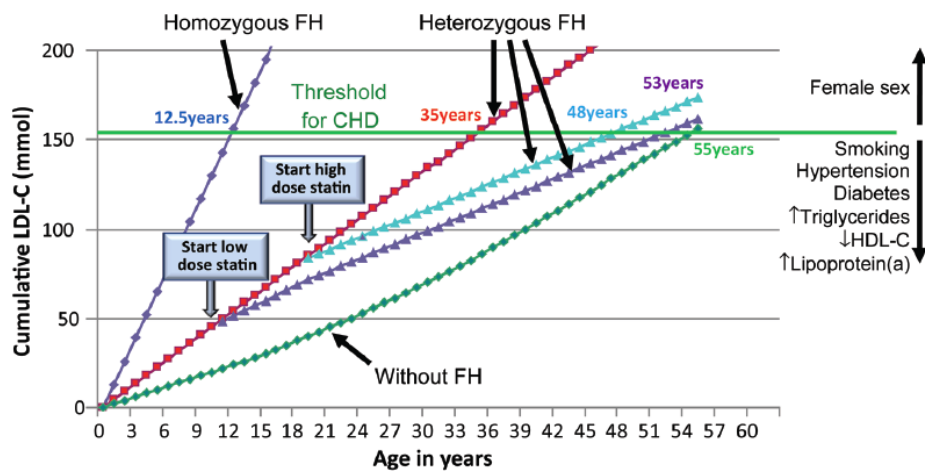


Fig. 1: LDL-C burden in individuals with or without familial hypercholesterolemia as a function of the age of initiation of statin therapy. Data derived from Huijgen et al. and Starr et al. Abbreviations: LDL, low-density lipoprotein; LDL-C, LDL cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; FH, familial hypercholesterolemia.

Compared to healthy children, the day-to-day functioning of children with HoFH is significantly impaired. Cholesterol deposits in the tendons and joints may lead to tendinitis and joint pain, which impairs patients' quality of life (Cuchel et al. 2014). Non-pharmacological intervention includes lipoprotein apheresis, beginning at an early age.⁸ Typically lipoprotein apheresis treatments take two to four hours and must be repeated every one to two weeks. The children participating in the Pediatric HoFH Study who were treated with apheresis were all

⁶ Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur. Heart J.* 2013; 34 (45):3478-90a.

⁷ Wierzbicki AS. Homozygous Familial Hypercholesterolemia. *Clin. Lipidology.* 2013;8(4):407-409.

⁸ See Keenan Decl. ¶ 8.

scheduled to be on weekly apheresis treatments. Another non-pharmacological approach to treatment of HoFH is liver transplantation (Goldberg et al 2011⁹), which requires a suitable donor organ and carries with it the complications of transplant surgery and recovery.

Recent guidance from the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia focused on early diagnosis and treatment of patients with HoFH (Cuchel et al 2014). The Panel recommended lifestyle intervention and maximal statin therapy as the mainstays of treatment starting in the first year after a patient is diagnosed with HoFH. The Panel also supported the addition of ezetimibe and recommended lipoprotein apheresis starting by age 5, although, other than Crestor[®], neither statin nor ezetimibe therapies are approved for the treatment of pediatric patients with HoFH.

HoFH is related to HeFH, a more common and less serious form of familial hypercholesterolemia.¹⁰ In contrast to HoFH, which arises when a patient inherits altered hypercholesterolemia-causing genes from both parents, HeFH arises when a patient inherits an altered hypercholesterolemia-causing gene from only one parent.¹¹ HeFH is characterized by elevated LDL-C levels that cause atherosclerotic plaque deposition in arteries and an increased risk of coronary artery disease. Treatment for HeFH consists largely of dietary modification and statin therapy—often in conjunction with ezetimibe, gemfibrozil, fenofibrate, or similar drugs. Reflecting the substantial difference in disease severity, a lower daily dosage is recommended for some patients with HeFH than patients of the same age with HoFH. For example, Crestor[®]'s label indicates that the dosage range for HeFH patients ages 8 to less than 10 is 5 to 10 mg once daily, whereas the dosage for HoFH patients in the same age range is 20 mg once daily.¹² Larger doses of rosuvastatin may be required for pediatric HoFH patients because these patients tend to show 50 percent less response on LDL-C and are at a much greater risk of a cardiac event early in life than patients with HeFH.¹³

⁹ Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol* 2011;5:133–140.

¹⁰ See Keenan Decl. ¶¶ 8–10.

¹¹ Whereas HeFH affects approximately one in 500 people, HoFH is “extremely rare” and affects only 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/>.

¹² See Keenan Decl. ¶¶ 9, 17. A copy of the current FDA-approved Crestor[®] label is attached as Exhibit 1 to the Keenan Declaration.

¹³ See *id.* ¶ 25.

C. Background On The Development Of Rosuvastatin For Use In The Treatment Of The Pediatric Orphan HoFH Population

In 2014, AstraZeneca initiated a trial of rosuvastatin in pediatric patients with HoFH ages 6 to 17 to address unmet medical needs of pediatric HoFH patients. Among other things, the study focused on the greater degree of LDL-C reduction demonstrated with rosuvastatin compared to some of the other approved statins in previous clinical studies of adults. This study, No. D3561C00004, is referred to herein as the HYDRA study or the Pediatric HoFH Study, and is formally entitled “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).”

A critical question in designing the Pediatric HoFH Study concerned the appropriate dosing regimen to study for pediatric HoFH patients, taking into account both the need for adequate dosing to achieve efficacy and the potential safety risks to pediatric patients associated with increased dosages. When AstraZeneca discussed the Pediatric HoFH Study design with drug review personnel in the Division of Metabolism and Endocrinology Protections of FDA’s Center for Drug Evaluation and Research, the FDA personnel inquired whether the Pediatric HoFH Study should include doses of up to 40 mg. In response, AstraZeneca presented its views that 20 mg was an appropriate dose for pediatric HoFH patients, and that there was insufficient safety data on higher doses (including the 40 mg dose) to justify a change in study design. Following further discussions of this issue, the Pediatric HoFH Study proceeded and evaluated the 20 mg dose.¹⁴

In the Pediatric HoFH Study, rosuvastatin was studied in a randomized, double-blind, placebo-controlled, multicenter, cross-over study with 20 mg once daily versus placebo (once daily) in 14 children and adolescents (ages 6 to 17) with HoFH. The study design included an active 4-week dietary lead-in phase during which all patients were treated with rosuvastatin 10 or 20 mg, a cross-over phase that included a six-week treatment period with rosuvastatin 20 mg preceded or followed by a six-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy were permitted to continue the treatment throughout the study.¹⁵

The Pediatric HoFH Study met its primary objective. In particular, the study identified a clinically meaningful reduction in LDL-C among patients in the study group. The LS mean relative difference in LDL-C after six weeks of treatment with rosuvastatin 20 mg compared to placebo was -22.3 percent (absolute difference: -85.4 mg/dL; -2.2 mmol/L) in pediatric HoFH

¹⁴ See *id.* ¶¶ 15–16.

¹⁵ See *id.* ¶ 17.

patients. This treatment effect was statistically significant ($p=0.005$). In treating HoFH, LDL cholesterol is the primary target of therapy. The reduction in both cardiovascular and total mortality is proportional to the degree of LDL cholesterol reduction (based on meta analysis of the results of large, lipid lowering outcome studies in the general population), with every 1 mmol/L reduction being associated with a corresponding 22 percent reduction in cardiovascular mortality and a 12 percent reduction in total mortality over five years. (Baigent et al 2010,¹⁶ Nordestgaard et al 2013,¹⁷ CTT Collaborators 2005,¹⁸ CTT Collaborators 2010,¹⁹ CTT Collaborators 2012.²⁰) Therefore, the magnitude of effect observed in the Pediatric HoFH Study represents a clinically meaningful reduction in LDL-C among pediatric HoFH patients.

The levels of LDL-C observed after six weeks of treatment with rosuvastatin 20 mg were maintained over a 12- to 18-week period. A positive treatment effect was seen across both of the analyzed subgroups: males and females, and patients treated and not treated with apheresis. The treatment effect on LDL-C was similar for males (-24.2%) and females (-20.1%). The treatment effect was greater in patients not being treated with apheresis (-26.3%) than in those who were treated with apheresis (-18.7%).

The Pediatric HoFH Study also met each of its key secondary objectives. Statistically significant ($p<0.05$) LS mean relative differences in TC (-20.1%), non-HDL-C (-22.9%), and ApoB (-17.1%) were observed in pediatric HoFH patients following six weeks of treatment with rosuvastatin 20 mg versus placebo.

Positive treatment effects were also seen for HDL-C, TG, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, Apolipoprotein A-1 (“ApoA-1”), and ApoB/ApoA-1 following six weeks of treatment with rosuvastatin 20 mg versus placebo in pediatric HoFH patients, with nominally

¹⁶ Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.

¹⁷ Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur. Heart. J.* 2013;34 (45):3478-90a.

¹⁸ Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-1278.

¹⁹ Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.

²⁰ Cholesterol Treatment Trialists' Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380:581-590.

significant differences for all parameters except HDL-C and ApoA-1. These levels also were maintained over a 12- to 18-week period of treatment with rosuvastatin.

In addition, as detailed in AstraZeneca's pediatric orphan drug HoFH sNDA, in the eight children and adolescents patients (ages 8 to 17) from the forced-titration open label study (Study 54) with HoFH, the reduction in LDL-C (21%), TC (18.6%), and non-HDL-C (20.2%) from baseline following six weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the Pediatric HoFH Study.

D. AstraZeneca Diligently Pursued The Pediatric Orphan Drug HoFH Development Program And Approval Of The Crestor® Pediatric Orphan Drug HoFH sNDA

AstraZeneca diligently pursued each of the clinical and regulatory processes that provide the basis for this Citizen Petition.²¹

1. The Orphan Drug HoFH sNDA. AstraZeneca filed its Crestor® pediatric orphan drug HoFH sNDA on July 27, 2015—shortly after completion of the successful Pediatric HoFH Study. To expedite the approval process, AstraZeneca filed a request for priority review of its sNDA that fully met all FDA required criteria. *See* NDA 21-366/S-033 § 1.2.1. That request showed that the Pediatric HoFH Study and its results meet the criteria for priority review set forth in FDA's Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014). Nevertheless, FDA informed AstraZeneca on October 9, 2015, that the sNDA would receive standard, rather than expedited, review.²²

AstraZeneca sought reconsideration of FDA's decision not to grant priority review, and requested in the alternative that FDA consider reviewing the application on an expedited basis through the standard review process.²³ In support of this request, AstraZeneca:

- highlighted the policies and procedures for review of NDAs outlined in FDA's Manual of Policies and Procedures (MAPP 6020.3 Rev. 2), noting that supplemental applications that propose labeling changes in accordance with a final pediatric study report will automatically receive a priority review designation;
- indicated that the pediatric orphan drug HoFH sNDA falls within a broad class of pediatric applications for which the MAPP strongly encourages priority review; and

²¹ *See* Keenan Decl. ¶¶ 18–19.

²² *See id.* ¶ 19.

²³ *See id.*

- showed that, following approval of REPATHA (evolocumab), approval of rosuvastatin would address the significant treatment gap that still remained for pediatric HoFH patients ages 6 to 12, as well as providing alternative and/or effective combination treatment for pediatric HoFH patients ages 13 to 17.

Despite these arguments, FDA did not reconsider its initial review classification decision and kept AstraZeneca's pediatric orphan drug HoFH sNDA on a standard review track.²⁴

FDA approved AstraZeneca's pediatric orphan drug sNDA on May 27, 2016.²⁵ This approval will enable a significant improvement in the treatment of an orphan population for which no statin therapy was previously approved. Indeed, even following the approval in 2015 of REPATHA as an adjunct to diet and other LDL-lowering therapies (*e.g.*, statins, ezetimibe, LDL apheresis) for the treatment of patients with HoFH who require additional lowering of LDL-C, there were no approved statins for treatment of pediatric HoFH patients under age 13 prior to FDA's approval of AstraZeneca's pediatric orphan drug sNDA in 2016.²⁶

2. Crestor[®] Pediatric HoFH Labeling. AstraZeneca submitted a draft revised Crestor[®] label with its sNDA, reflecting the pediatric HoFH indication being sought. In an additional effort to accelerate the approval process, AstraZeneca followed up with FDA on May 2, 2016, May 5, 2016, and on other occasions. On May 12, 2016, FDA forwarded a revised draft of the Crestor label to AstraZeneca. AstraZeneca responded with a further revised draft Crestor[®] label five days later, on May 17, 2016, and remained in regular contact with FDA through approval of the label on May 27, 2016.²⁷

3. Orphan Designation and Exclusivity. AstraZeneca applied for orphan designation for Crestor[®] for the treatment of pediatric HoFH in November 2013. FDA granted that designation on February 14, 2014. FDA's approval of the pediatric HoFH sNDA thus triggers a grant of seven years of orphan exclusivity to the new labeling, extending from May 27, 2016, to May 27, 2023.

* * *

In view of these efforts, AstraZeneca requests that FDA expedite its consideration of this Citizen Petition and ensure that the issues raised herein are fully considered *before* FDA issues a final approval determination with respect to ANDAs or section 505(b)(2) NDAs that reference Crestor[®].

²⁴ See *id.*

²⁵ See *id.* ¶ 17.

²⁶ See *id.* ¶ 7.

²⁷ See *id.* ¶ 19.

II. ARGUMENT

A. FDA May Not Carve Out AstraZeneca's Protected Labeling Because Doing So May Present Serious Safety and Efficacy Risks

FDA has adopted a safety and efficacy policy (the "Policy") that squarely applies to AstraZeneca's protected pediatric HoFH labeling. Under the Policy, a generic drug is "misbranded" and "will not [be] approve[d]" where

1. the reference-listed drug "is approved in adults and pediatric patients for the same indication";
2. "the pediatric information is protected by exclusivity and is significantly different from the information regarding use in adults for the same indication"; and
3. "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."

Otsuka Letter at 10.²⁸

FDA highlighted three key aspects of the Policy last year in response to a citizen petition filed by Otsuka Pharmaceutical.²⁹ FDA first reasoned that generic applications may not be approved so long as a carve out "*may result in a potential safety risk.*" *Id.* (emphases added). This language errs on the side of safety and makes clear that certainty is not required. Rather, the proper question is whether there is a meaningful prospect that a carve out would give rise to a safety or efficacy risk.

The Otsuka Letter also notes that the Policy operates independently of the Agency's general carve-out regulations. Hence, a generic drug is not "considered safe and effective" if the three criteria set forth above are met "*even though* the drug is otherwise subject to a carve out under section 505(j)(2)(A)(v) of the [FDCA], and 21 CFR 314.92(a)(1), 314.94(a)(8)(iv) and 314.12(a)(7)." *Id.* at 10 (emphasis added).

Finally, the third criterion focuses on whether, when considering "both the information that will be carved out and the information that will remain in the labeling once the carve out is implemented," the resulting label "would present a safety risk to pediatric patients using the drug for its approved (non-protected adult) indication." *Id.* at 14.³⁰ According to the Otsuka Letter,

²⁸ These same considerations should apply to a section 505(b)(2) product.

²⁹ Otsuka's citizen petition concerned Abilify (aripiprazole), a drug approved for treatment of Tourette's Disorder in pediatric patients, and for which Otsuka had obtained both Hatch-Waxman and orphan drug exclusivity for the pediatric treatment data. *See* Otsuka Letter at 1, 13–15.

³⁰ FDA also applies a comparative analysis, under which a carve out is impermissible if it "render[s] the

“[t]he Glucophage precedent” illustrates how this comparison test works in practice. *Id.* at 10 n.27. Bristol Myers Squibb (“BMS”), Glucophage’s sponsor, conducted pediatric studies for an indication for which Glucophage had already been approved in adults. These studies earned BMS three years of Hatch-Waxman exclusivity for the resulting pediatric labeling. FDA contends that it declined to

approve an ANDA for Glucophage even for the adult indication until the expiry of the three-year exclusivity resulting from the pediatric studies because the agency concluded that, given that the drug was approved for the same indication in adults, the pediatric information was necessary for the safe use of the drug and therefore could not be carved out.

Id. “As a result, the exclusivity awarded for the pediatric information provided a de facto exclusivity for use of the drug in all populations.” *Id.*³¹ In contrast, Otsuka was not entitled to the same “de facto exclusivity” because the label for its drug, Abilify (aripiprazole), “include[d] no dosing information for Tourette’s Disorder in adults” and therefore failed the first of the Policy’s three criteria. *Id.* at 14. In other words, once Abilify’s pediatric labeling was carved out, there was no risk that a doctor would rely on adult dosing information when prescribing generic aripiprazole to pediatric patients.

Unlike Abilify, Crestor[®] meets all three of the Policy’s criteria and is therefore entitled to de facto exclusivity for the duration of AstraZeneca’s seven-year period of orphan drug exclusivity.

Crestor[®] satisfies the Policy’s first criterion because it is approved for treatment of HoFH in adults and pediatric patients ages 7 to 17. This approval distinguishes Crestor[®] from Abilify and places Crestor[®] in the same position as Glucophage.

Crestor[®] meets the Policy’s second criterion because its labeling for treatment of pediatric HoFH is protected by seven-year orphan drug exclusivity. This pediatric HoFH labeling is significantly different from the labeling regarding treatment of HoFH in adult patients, as illustrated in the table below. Whereas the dose range for adult HoFH patients “is 5 to 40 mg orally once daily” and the “usual *starting* dose in adult patients . . . is 20 mg once daily,” Label § 2.1 (emphasis added), the *only* approved dose for pediatric HoFH patients “is 20 mg orally once daily,” *id.* § 2.2. Moreover, Crestor[®]’s label states that the 40 mg dose may be used “for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose,” and

proposed drug product *less safe or effective than the listed drug* for all remaining, nonprotected conditions of use.” 21 C.F.R. § 314.27(a)(7) (emphasis added).

³¹ Notably, the Otsuka Letter fails to cite agency memoranda to support this account of its reasoning regarding the Glucophage precedent. Instead, the Otsuka Letter points to a single page of the *Congressional Record* as support for FDA’s interpretation of the Policy.

that “[a]bout one third of the patients” in a prior study “benefited from increasing their dose from 20 mg to 40 mg, with further [cholesterol] lowering of greater than 6%.” Label §§ 2.1, 14.5

	HoFH - Adults	HoFH - Pediatrics	HeFH - Adults	HeFH - Pediatrics
Dosage	20 mg daily recommended starting dose; 40 mg dose recommended for patients who have not achieved their LDL-C goal utilizing the 20 mg dose	20 mg daily recommended dose for patients 7 to 17 years old	5 to 40 mg daily (based on general dosing)	5 to 10 mg daily for patients 8 to less than 10 years old; 5 to 20 mg daily for patients 10 to 17 years old
Other Information	About one third of patients in prior study benefitted from increasing their dose from 20 mg to 40 mg			Patients should be titrated upwards from starting 5 mg dose to a maximum dosage of 20 mg once daily

Fig. 2: Summary table of Crestor® current labeling information. Shaded material subject to seven-year orphan drug protection. Source: Label §§ 2.1–2.2, 14.5.

As to the third criterion, there is strong evidence that carving out AstraZeneca’s protected pediatric HoFH labeling “may result in a potential safety risk to pediatric patients.” Otsuka Letter at 10. The attached declaration of Gregory Keenan, MD, a clinician familiar with the Pediatric HoFH Study and with expertise in treatment of pediatric patients and pharmaceutical development, bears this out in four principal ways.³²

First, a carve out may lead specialists to over-treat pediatric HoFH patients. For example, without access to AstraZeneca’s protected pediatric HoFH labeling, a specialist might prescribe rosuvastatin doses in excess of 20 mg (the amount recommended in the protected labeling) based on the adult HoFH indication, which ranges up to 40 mg. This risk is particularly acute because Crestor®’s unprotected labeling states that the recommended “starting dose” for adult patients is 20 mg and that an increased 40 mg dose may be used for patients who have not achieved their LDL-C goal utilizing the 20 mg dose. Label § 2.1 (emphasis added). Physicians might also over-treat pediatric HoFH patients based on the unprotected label’s statement that

³² See Keenan Decl. ¶¶ 21–28.

“[a]bout one third of the patients” in a recent study “benefited from increasing their dose from 20 mg to 40 mg, with further [cholesterol] lowering of greater than 6%.” Label § 14.5.³³

Specialists may also be prone to over-treat pediatric HoFH patients by adjusting upward from the dose for pediatric HeFH—a related but much less serious condition—recited in Crestor[®]’s labeling.³⁴ Specialists may take this course based on the knowledge that HoFH patients are 50 percent less responsive to statin treatment than HeFH patients, and that pediatric HoFH patients are at a much greater risk of a cardiac event early in life than HeFH patients.³⁵

Second, a carve out may cause generalist doctors with limited experience in treating HoFH to under-treat their pediatric patients. For example, a generalist might prescribe below the protected 20 mg dosage based on the lower dose ranges for pediatric HeFH in Crestor[®]’s labeling.³⁶

Third, there is a risk that children ages 7 to 9 will be undertreated if AstraZeneca’s protected pediatric HoFH data is carved out, because the Crestor[®] label recommends titrating upwards from a 5 mg starting dose to a 10 mg 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 to 17.³⁷ In comparison, the protected pediatric labeling states that the recommended dose for pediatric HoFH patients ages 7 to 17 is 20 mg. *See* Label § 2.2. Indeed, while the protected labeling includes information on treatment of 7-year old HoFH patients, the HeFH labeling includes no information at all about the treatment of 7-year olds.

Fourth, if the Pediatric HoFH Study information is omitted from the labeling for rosuvastatin products other than Crestor[®], the resulting safety risk would not be cured by a general disclaimer referring to the existence of pediatric-use information in Crestor[®]’s labeling. Such a disclaimer currently appears on the labeling for a licensed generic rosuvastatin product marketed by Watson. Specifically, the Watson disclaimer states that

Pediatric use information for patients ages 8 to less than 10 years is approved for AstraZeneca’s CRESTOR (rosuvastatin calcium) tablets. However, due to

³³ Crestor[®]’s unprotected labeling states that 20 percent (8 of 40) of the patients in this study were ages 8 to 17, thus providing a further risk that specialists may over-treat by prescribing 40 mg for pediatric HoFH patients.

³⁴ Crestor[®]’s label recommends a dose of 5 to 10 mg once daily for pediatric HeFH patients age 8 to less than 10, and a dose of 5 to 20 mg once daily for pediatric HeFH patients age 10 to 17. In comparison, the protected labeling recommends a dose of 20 mg once daily for all pediatric HoFH patients. Label § 2.2.

³⁵ *See* Keenan Decl. ¶¶ 21–25.

³⁶ *See id.* ¶ 26.

³⁷ *See id.* Some pediatric HeFH patients achieve treatment goals at doses below 20 mg, in which case the 20 mg dose of Crestor[®] is not administered. *Id.* ¶ 9.

AstraZeneca's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

This language is based on the omission of labeling for pediatric HeFH, and will be understood as a reference to the pediatric HeFH labeling in Crestor[®] given that the age range of patients ages 8 to less than 10 years tracks to the information in the Crestor[®] labeling for pediatric HeFH.³⁸ The disclaimer makes no reference to HoFH and omits 7-year olds altogether, who are within the approved pediatric HoFH population. The disclaimer thus does not alert the physician to the omission of critical information on use in pediatric HoFH.³⁹

These risks present serious safety and efficacy concerns. Over-treatment of a pediatric HoFH patient could lead to severe skeletal muscle effects (e.g., myopathy and rhabdomyolysis) or acute renal failure. *See* Label § 5.1. The risk that physicians treating pediatric HoFH patients will exceed the 20 mg dose shown effective in the Pediatric HoFH Study is exacerbated by the severe potential consequences of inadequate treatment of HoFH, and the understanding that HoFH patients generally have a lower and more unpredictable response to statin therapy.⁴⁰ On the other hand, under-treatment could allow the disease to progress rapidly, resulting in accelerated onset of cardiovascular disease and increased risk of angina pectoris or myocardial infarction.⁴¹

Because Crestor[®] satisfies all three of the criteria set forth in the Otsuka Letter, AstraZeneca is entitled to “de facto exclusivity for use of the drug in all populations.” Otsuka Letter at 10 n.27. Indeed, failure to grant AstraZeneca the benefit of this Policy would constitute an unexplained departure from past agency practice, in violation of the Administrative Procedure Act. *See Ramaprakash v. FAA*, 346 F.3d 1121, 1124–25 (D.C. Cir. 2003).

Although FDA relied in part on the Best Pharmaceuticals for Children Act (“BPCA”), 21 U.S.C. § 505A(o), in denying Otsuka's citizen petition, that statute does not provide carve-out authority, or authority to add a pediatric labeling disclaimer,⁴² here because it unambiguously

³⁸ As required under the terms of the March 2013 settlement agreement, AstraZeneca granted Watson a waiver of its Crestor[®] orphan drug exclusivity rights on May 31, 2016. *See* Walters Decl. ¶ 7. As a result, the labeling for Watson's generic rosuvastatin product includes (or will soon include) the key Pediatric HoFH Study information described above. *Id.* ¶ 8.

³⁹ *See Id.* ¶ 27.

⁴⁰ *Id.* ¶ 24.

⁴¹ *See id.* ¶ 26.

⁴² Where section 505A(o) does apply, it authorizes FDA after carving out protected labeling to include an affirmative disclaimer statement in the labeling to alert prescribers that the drug is not labeled for pediatric use and to include “a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.” 21 U.S.C. § 355a(o)(2).

applies to labeling protected only by patent and Hatch-Waxman exclusivity. In particular, section 505A(o)(1) provides that

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.*

21 U.S.C. § 355A(o)(1) (emphasis added).

AstraZeneca’s pediatric HoFH labeling is not protected only “by patent or by exclusivity under” 21 U.S.C. § 355(j)(5)(F). Instead, it is protected by orphan drug exclusivity, which arises from section 355cc(a) of the FDCA—a provision not mentioned in any way in section 505A(o). *See* 21 U.S.C. § 360cc(a) (providing seven years of exclusivity for drugs approved to treat “a rare disease or condition”). Because section 505A(o)’s text is plain and unambiguous, FDA’s “sole function . . . is to enforce [the statute] according to its terms.” *Sebelius v. Cloer*, 133 S. Ct. 1886, 1896 (2013) (quoting *Hartford Underwriters Ins. Co. v. Union Planters Bank, N.A.*, 530 U.S. 1, 6 (2000)).

FDA has consistently read section 505A(o) according to its plain terms. Immediately following BPCA’s passage in 2002, FDA stated in response to a citizen petition filed by BMS that section 505A(o) addresses pediatric labeling only protected by “patent exclusivity” or “3-year exclusivity under section 505(j)(5)(D)(iii) & (iv) of the [FDCA].” Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, to C. Boyden Gray, Wilmer Cutler & Pickering, No. 01P-0586/CP1, at 1 & n.2 (Jan. 24, 2002). Similarly, officials in FDA’s Center for Drug Evaluation and Research have twice acknowledged that section 505A(o) “does not address the carve-out of protected pediatric information from [section] 505(b)(2) product labeling” because section 505A(o) refers only to applications submitted under 21 U.S.C. § 355(j). Memorandum from Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst – Pediatric and Maternal Health Staff, to Division of Hematology Products, Ref. ID 2911472, at 3 (Feb. 28, 2011); Memorandum from Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst – Pediatric and Maternal Health Staff, to Division of Neurology Products et al., Ref. ID 3245307, at 8 (Jan. 15, 2013). Just as FDA has followed the plain language of section 505A(o) with respect to section 505(b)(2) NDAs, it must follow the plain language authorizing a carve out of labeling only protected by patent or Hatch-Waxman exclusivity, and not the orphan-drug-exclusivity protected labeling at issue in this Citizen Petition.

Indeed, the “fix” enacted in section 505A(o) was a deliberate and carefully crafted step to “override” FDA’s pediatric-labeling requirements, 147 Cong. Rec. H10210, but not when orphan exclusivity applies. The legislative history is replete with references to three-year exclusivity, as

that was the exclusivity protection afforded BMS for Glucophage, *see, e.g.*, 147 Cong. Rec. H8105 (“H.R. 2887 closes this potential loophole by instructing the FDA to approve generic drugs without proprietary pediatric labeling awarded to product sponsors under the Hatch-Waxman Act.”); *id.* H10210 (statement of Rep. Eshoo) (“[T]he bill we will vote on today and send to the President closes the ‘Glucophage loophole’ which allowed one company to get an additional 3 years of marketing exclusivity.”).

Importantly, although Congress went beyond the specifics of the Glucophage precedent in crafting section 505A(o), it added only a type of labeling protection not at issue here—that provided by the patent laws. Congress took this step despite the fact that Glucophage had no patent protection. *See* 147 Cong. Rec. H8551 (statement of Rep. Pallone) (“There are no patents blocking the approval of generics in this case [Glucophage].”). This incremental step reflects careful Congressional attention to the specific areas that Congress believed needed reform and does not extend to labeling specially protected by orphan exclusivity.

* * *

In short, carving out AstraZeneca’s protected pediatric HoFH labeling may give rise to a broad range of potential safety and efficacy risks, and FDCA section 505A(o) does not provide authority for FDA to address the issue through alternate labeling. Because these risks satisfy all the criteria for de facto exclusivity under the Policy set forth in FDA’s Otsuka Letter, FDA may not carve out the protected labeling—and therefore may not approve generic rosuvastatin ANDAs or section 505(b)(2) NDAs—prior to the expiration of Crestor[®]’s period of orphan drug exclusivity.

B. FDA May Not Carve Out AstraZeneca’s Protected Labeling Because FDA Lacks Authority To Carve Out Pediatric Labeling Protected By Orphan Drug Exclusivity

FDA may not carve out AstraZeneca’s protected pediatric HoFH labeling for an additional and independent reason: none of FDA’s carve-out authorities applies to pediatric labeling protected by orphan drug exclusivity, regardless of a factual inquiry into whether the omitted labeling raises a safety issue.

1. The FDCA And FDA’s Pediatric-Labeling Regulations Present A Barrier To Generic-Drug Approvals

FDA’s pediatric-labeling regulations mandate that dosing, specific indications, and safety data pertaining to pediatric uses “must appear in all prescription drug labeling.” 21 C.F.R. §§ 201.57(a), (a)(6)–(7), (a)(13), (c)(2)(i)(B), (c)(3)(i)(H). Thus, “[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.” *Id.* § 201.57(c)(9)(iv)(B). Similarly, 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,” that information must be included in labeling in the “Pediatric use” subsection, discussed as applicable in detail under the “Clinical Pharmacology” and “Clinical Studies” sections, pediatric dosage must be given under the “Dosage and Administration” section, and the “Pediatric use” subsection of the labeling must cite limitations on pediatric use. *Id.* § 201.57(c)(9)(iv)(C). FDA has explained that “[a] drug product that is not in compliance with [the pediatric-labeling rules] would be considered misbranded and an unapproved new drug under the [FDCA].” 59 Fed. Reg. 64,240, 64,247 (1994).⁴³

These FDA pediatric-labeling regulations create a barrier to approval of a generic drug when (i) the reference-listed 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.⁴⁴ In this scenario, the generic manufacturer cannot secure approval: The pediatric-labeling rules require the 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.

This was the scenario presented in the Glucophage (metformin) precedent. At the time, “the *only* obstacle” to approval of generic metformin was a perceived “loophole in the Waxman-Hatch [Act]” that provided total exclusivity whenever the sponsor of a reference-listed drug obtained exclusivity with respect to one or more pediatric indications. 147 Cong. Rec. H8551 (Nov. 28, 2001) (statement of Rep. Pallone) (emphasis added). “FDA’s Office of Generic Drugs” was “unable to allow . . . generics onto the market due to” the “monopoly” BMS obtained under FDA regulations. *Id.*

The foregoing context shows why section 505A(o) was necessary and how the statute was intended to operate within FDA’s overall regulatory framework. Section 505A(o) was enacted because FDA’s carve-out authority was limited by operation of FDA’s own 1994 pediatric-labeling regulations. On the one hand, FDA had authority under its general 1992 carve-out regulations to allow generic drugs to omit certain labeling,⁴⁵ but, on the other hand,

⁴⁴ *See also* 147 Cong. Rec. H10209 (Dec. 18, 2001) (“In 1994, the FDA created an exception to [its general carve-out] regulation[s], concerning acceptable label omissions, affording pioneer drug manufacturers extended total marketing exclusivity based on the development of new pediatric use indications. In particular, the FDA adopted regulations requiring that pediatric information be included in the labeling of every prescription drug. *See* 21 C.F.R. § 201.57(f)(9)(ii).”).

⁴⁵ Via regulations promulgated in 1992, FDA has interpreted section 505(j)(2)(A)(v)’s exception for

FDA's later-in-time 1994 pediatric-labeling regulations precluded omissions of pediatric information by requiring such information to be included on the label or requiring the drug to be considered misbranded. Congress understood this problem when it enacted section 505A(o).

Indeed, Congress did not act in a vacuum when it enacted section 505A(o). Rather, in late 2001, Congress confronted a specific situation that demonstrated the need for a change in the law, and that situation drove the enactment of section 505A(o). Under then-existing law, FDA's grant of three-year exclusivity for Glucophage resulted in "total marketing exclusivity" because, under FDA's 1994 pediatric-labeling regulations, generics could not omit the three-year-exclusive pediatric indication from their labels. *See* 147 Cong. Rec. H10209 (Dec. 18, 2001) ("Under existing law, that grant resulted in total marketing exclusivity with respect to Glucophage for the applicable period because BMS has acquired exclusive rights to the only pediatric use indication that applied under the pediatric labeling requirements."); *id.* at H8105 (Nov. 13, 2001) (statement of Rep. Dingell) ("Because FDA has granted three-year exclusivity to the pediatric label of Glucophage, Bristol has argued that no generic may be marketed during the pendency of its labeling exclusivity.").

Congress clearly understood that the so-called Glucophage problem arose in the context of the statutes and regulations discussed above. Indeed, a memorandum in the *Congressional Record* explains that FDA's 1994 pediatric-labeling regulations superseded the 1992 general carve-out regulations by "requiring that pediatric information be included in the labeling of every prescription drug." 147 Cong. Rec. H10209 (Dec. 18, 2001). As reflected in that memorandum, the practical effect of FDA's 1994 pediatric-labeling regulations was to afford Glucophage a three-year period of "total marketing exclusivity" for all uses, rather than just for the three-year-exclusive pediatric indication. *See id.*

2. Section 505A(o) Unambiguously Addresses Only Patent And Hatch-Waxman Exclusivity

Congress enacted section 505A(o) to close the Glucophage "loophole." *See, e.g.*, 147 Cong. Rec. H8105 (Nov. 13, 2001) (statement of Rep. Dingell) ("H.R. 2887 closes this potential loophole by instructing the FDA to approve generic drugs without proprietary pediatric labeling awarded to product sponsors under the Hatch-Waxman Act."); *id.* at H8552 (Nov. 28, 2001) (statement of Rep. Pallone) ("Mr. Speaker, there is currently a legislative fix in place in the House and Senate version of the pediatric exclusivity bill that would close this loophole and allow generic versions of this diabetes drug to compete with Bristol's Glucophage."); H.R. Rep. No. 107-277 (2001), at 38 ("[Section 505A(o)] does make clear that if a manufacturer does claim

labeling changes made "because the new drug and the listed drug are produced or distributed by different manufacturers" as allowing generic drugs to "omi[t] . . . an indication or other aspect of labeling" that is "protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Act." 21 C.F.R. § 314.94(a)(8)(iv).

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.”).

Notably, Congress did not amend or alter FDA’s longstanding pediatric-labeling regulations, which remain in effect today, when it enacted section 505A(o). Instead, Congress expanded FDA’s carve-out authority for pediatric labeling with respect to labeling protected only by patent and Hatch-Waxman exclusivity. *See* 21 U.S.C. § 355A(o)(1) (referring to “labeling pertaining to pediatric use” that is protected only “by patent or by exclusivity under [§ 355(j)(5)(F)(iii) or (iv)]”). FDA has repeatedly acknowledged this limited scope, as noted in Part II.A, *supra*.

Because section 505A(o) does not address *other* forms of exclusivity—including exclusivity afforded by the Orphan Drug Act, 21 U.S.C. § 360cc(a)—the barrier to generic-drug approvals presented in the Glucophage precedent remains with respect to orphan drug exclusivity. Indeed, it is well-settled that agencies and courts shall construe statutes without adding words to or modifying the statutory text. *See Utility Air Regulatory Grp. v. EPA*, 134 S. Ct. 2427, 2446 (2014) (“an agency may not rewrite clear statutory terms to suit its own sense of how the statute should operate”); *62 Cases, More or Less, Each Containing Six Jars of Jam v. United States*, 340 U.S. 593, 596 (1951) (“[O]ur problem is to construe what Congress has written. After all, Congress expresses its purpose by words. It is for us to ascertain – neither to add nor to subtract, neither to delete nor to distort.”).

3. FDA’s General Carve-Out Provisions Do Not Provide Authority To Carve Out AstraZeneca’s Protected Labeling

In 1992, FDA promulgated a series of general “carve-out” regulations. *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 reference-listed drug in specified ways. For example, the regulations provide that a generic drug label may differ from the reference-listed 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).

These general carve-out regulations do not fill the void left by section 505A(o) for at least five reasons.

First, FDA understood that its general carve-out authorities were insufficient when it evaluated generic metformin ANDAs in 2001. Were that not the case, section 505A(o) would have been unnecessary. To the extent FDA is now of the view that it could have resolved the Glucophage problem by exercising its general carve-out authorities, that view constitutes an unexplained departure from past agency practice, in violation of the Administrative Procedure

Act. *See Ramaprakash*, 346 F.3d at 1124–25.

Similarly, to the extent FDA now believes that the problem posed in the Glucophage precedent was not a legal inability to carve out protected pediatric information, but rather an inability to do so only when a carve out would (as a factual matter) present a safety risk, FDA’s stance is revisionist history. The *Congressional Record* shows that the Glucophage problem was the product of the same-label and pediatric-labeling requirements: “The FDA’s Office of Generic Drugs has numerous generic versions of this diabetes drug awaiting approval. However, the office is unable to allow these generics onto the market due to Bristol’s monopoly. There are no patents blocking the approval of generics in this case. The only obstacle is a . . . loophole in the Waxman-Hatch exclusivity.” 147 Cong. Rec. H8551 (Nov. 28, 2001) (statement of Rep. Pallone).

Contemporaneous trade press coverage likewise shows that FDA interpreted its regulations as prohibiting carve outs of protected pediatric labeling. Articles indicate that FDA “delayed” and placed “on hold” approval of “[g]enerics for Bristol-Myers Squibb’s diabetes drug Glucophage (metformin) and anti-anxiety agent BuSpar (buspirone) . . . because of Waxman/Hatch exclusivity for pediatric labeling.” *FDA Discontinued Label Guidance on Hold*, The Pink Sheet (Apr. 8, 2002).⁴⁶ Gary Buehler, Director of FDA’s Office of Generic Drugs, explained that FDA’s approval process for generic metformin ANDAs “stopped . . . because of a problem with pediatric labeling,” and that “the ideal solution” for this problem was new legislation by Congress. *Glucophage Generics Should Be Addressed by Congress*, *OGD’s Buehler Says*, The Pink Sheet (Nov. 5, 2001). Congress responded to that call for action on the understanding that, prior to the enactment of 21 U.S.C. § 505A(o), “[a] pharmaceutical company [wa]s prohibited under the law . . . to market a dru[g] . . . without the pediatric indication being on the label.” 147 Cong. Rec. H8101 (Nov. 13, 2001) (statement of Rep. Tauzin).

Second, Congress was aware of FDA’s conclusion that it lacked legal authority to carve out protected pediatric information, yet did not provide authority to carve out labeling protected by orphan drug exclusivity in section 505A(o). FDA must presume that the disparate inclusion was intentional, particularly because Congress was considering orphan drug legislation during the same time period. *Cf. Russello v. United States*, 464 U.S. 16, 23 (1983) (“[I]t is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion” of statutory terms.).

This reading finds further support in the *expressio unius* canon of statutory interpretation.

⁴⁶ *See also Bristol BuSpar Pediatric Labeling May Delay Second Round of Generics*, The Pink Sheet (Oct. 1, 2001) (FDA delayed approval of BuSpar ANDAs based on the argument that “FDA cannot approve a generic that does not include the same pediatric labeling as the innovator”); *see also id.* (“The FDA rhetoric . . . has been [that] they cannot approve a generic drug with the label that doesn’t have a pediatric indication for it if in fact the innovator product does have a pediatric indication.”).

See *Leatherman v. Tarrant Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993); *TRW Inc. v. Andrews*, 534 U.S. 19, 28–29 (2001). The negative phrasing employed in section 505A(o) defines FDA’s approval authority no less than positive phrasing would have done. Cf. *Marine Space Enclosures, Inc. v. Fed. Maritime Comm’n*, 420 F.2d 577, 583-84 (D.C. Cir. 1969) (interpreting a statute that required a hearing prior to the Commission’s decision to “disapprove, cancel or modify any agreement” to require a hearing prior to approval of an agreement).

Here, Congress simply chose to define FDA’s approval authority by limiting the circumstances in which FDA cannot *deny* approval when it comes to carve outs of pediatric labeling, rather than defining when FDA shall *grant* approval in the face of such carve outs. Under either formulation, however, the outcome is the same. Congress directed when FDA shall approve generic drugs (i.e., “shall not be considered ineligible for approval . . . or misbranded”), assuming that other conditions for approval are satisfied. When the statute directs FDA not to disapprove an ANDA that omits labeling protected only by patent or three-year-exclusivity, FDA has no license to grant approvals omitting, as here, pediatric indications or information protected by other forms exclusivity.⁴⁷

Third, section 505A(o) speaks directly to the question of when FDA may carve out pediatric labeling information, whereas other statutory provisions (e.g., the “different manufacturer” exception to the same-labeling statute) address carve-out authority only generally. Thus, under the “commonplace [canon] of statutory construction that the specific governs the general,” section 505A(o) provides the exclusive means by which protected pediatric labeling may be carved out. *RadLAX Gateway Hotel, LLC v. Amalgamated Bank*, 132 S.Ct. 2065, 2071 (2012). Because section 505A(o) does not address orphan drug exclusivity, FDA lacks carve-out authority with respect to AstraZeneca’s protected orphan drug labeling.

Indeed, the absence of any reference to orphan drug exclusivity in section 505A(o) reflects an intentional Congressional choice to omit orphan drug exclusivity from the categories of pediatric information that may be omitted from generic drug labeling. This conclusion is reinforced because orphan drug exclusivity long predated section 505A(o). See *United States v. Langley*, 62 F.3d 602, 605 (4th Cir. 1995) (“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.” (quotation marks omitted)).

⁴⁷ Congress’s expression of FDA’s approval authority in a double negative (i.e., “shall not be considered ineligible or misbranded”) acts as a positive constraint. In other words, in the absence of satisfying the double negative condition, FDA cannot grant approval. See *Adams v. State Livestock Facilities Siting Review Bd.*, 787 N.W. 2d 941 (Wisc. Ct. App. 2010); *Ford Motor Co. v. Kahne*, 379 F. Supp. 2d 857, 861 n.3 (E.D. Mich. 2005). Moreover, there are no “contrary indications that adopting a particular rule or statute was probably not meant to signal any exclusion” of orphan drug exclusivity. See *Marx v. Gen. Revenue Corp.*, 133 S. Ct. 1166, 1175 (2013).

Moreover, language elsewhere in section 505A(o) demonstrates that Congress was well aware of orphan drug exclusivity. Specifically, in sections 505A(b) and 505A(c), in addressing the interaction of pediatric exclusivity with patent and regulatory protections, Congress specifically mentioned orphan drug exclusivity in other contexts not relevant to the issue at hand. *See* 21 U.S.C. §§ 355A(b)(1)(A)(ii), 355A(c)(1)(A)(ii).

Accordingly, Congress would have specifically included orphan drug exclusivity in section 505A(o) had Congress intended orphan drug exclusivity to be a category of exclusivity that may be omitted from generic drug labeling. Indeed, when it enacted section 505A(o), Congress was not picking from an endless universe of patent and regulatory protections; there are only a handful of such categories, two of which are specified in section 505A(o).

Had Congress intended that *all* exclusivities could be carved out from a generic drug's label, Congress could have spoken broadly and used the term "exclusivity" alone without specifically referring to "orphan drug exclusivity." Congress intentionally chose not to use such a broad, catch-all term in section 505A(o), even though it has done so elsewhere. *Compare* 21 U.S.C. § 355(j)(10)(A)(i) (a drug shall "be eligible for approval and shall not be considered misbranded . . . if the application is otherwise eligible for approval under this subsection but for expiration of patent, *an exclusivity period*, or of a delay in approval" (emphasis added)). Congress's failure to employ such terminology provides further evidence that section 505A(o) was not intended to sweep in all forms of exclusivity.

Fourth, FDA's pediatric-labeling rules trump the general carve-out rules. The pediatric-labeling rules are categorical; they say that all pediatric labeling must be included. And these rules were adopted in 1994, *after* FDA adopted its general carve-out rules in 1992. *See* 57 Fed. Reg. 17,950, 17,984-86, 17,992 (1992). Thus, the later-in-time labeling rules override the carve-out rules to the extent the two conflict. *See, e.g., Boudette v. Barnette*, 923 F.2d 754, 757 (9th Cir. 1991) ("When two statutes conflict the general rule is that the statute last in time prevails."); *Maceren v. INS*, 509 F.2d 934, 941 (9th Cir. 1974) (when regulations conflict, "the earlier regulation should give way to the later in time").⁴⁸

Fifth, and finally, the Orphan Drug Act ("ODA") has always provided a seven-year period of exclusivity for approved orphan drugs since its enactment 33 years ago. *See* Pub. L. No. 97-414, § 527, 96 Stat. 2049, 2051 (1983) (codified at 21 U.S.C. § 360cc). Similarly, ever since their adoption, FDA's orphan drug regulations have provided that, when a drug receives

⁴⁸ To the extent FDA interprets its pediatric-labeling and general-carve-out regulations differently, its interpretation is erroneous. *Auer* deference does not apply because FDA's regulations are not ambiguous. *See Christensen v. Harris Cnty.*, 529 U.S. 576, 588 (2000) ("*Auer* deference is warranted only when the language of the regulation is ambiguous."). Even if it did apply, an interpretation of the regulations that allowed a carve out here would be "plainly erroneous or inconsistent with the regulation[s]." *Auer v. Robbins*, 519 U.S. 452, 461 (1997).

orphan drug exclusivity, “no approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years.” 21 C.F.R. § 316.3(b)(12); *see also* 57 Fed. Reg. 62,076, 62,086 (1992). These provisions, including the incentives provided to drug companies to develop drugs for the treatment of rare diseases and the policy reasons for those incentives, are well-known to Congress, and apply with special force to a pediatric orphan disease or condition.⁴⁹ Those incentives and policy considerations were not merely in the background but instead were under active consideration by Congress when section 505A(o) was enacted.

In fact, the legislative record reflects that Congress was considering orphan drug exclusivity contemporaneously with its debate over section 505A(o). On August 1, 2001, the Senate Health, Education, Labor and Pensions (“HELP”) Committee held a markup of the BPCA. *See* S. Rep. No. 107-79 (2001), at 5. Two days later, on August 3, 2001, Senator Kennedy, Chairman of the HELP Committee, introduced a bill entitled “Rare Diseases Act of 2001,” to provide statutory authorization for the existing Office of Rare Diseases at the National Institutes of Health (“NIH”) and to increase the funding for FDA’s Orphan Product Research Grant program. S. 1379, 107th Cong. (2001); 147 Cong. Rec. S8952 (Aug. 3, 2001). In commenting on the bill, Chairman Kennedy noted “that Congress has had a longstanding interest in rare diseases” and “[i]n 1983, . . . enacted the Orphan Drug Act to promote the development of treatments for rare diseases and disorders.” 147 Cong. Rec. S8952.

The text of Senator Kennedy’s bill itself reflected an understanding of the continuing need to strongly incentivize drug manufacturers to develop drugs for orphan diseases. The findings in the bill stated, “[f]or many years, the 25,000,000 Americans suffering from the over 6,000 rare diseases and disorders were denied access to effective medicines because prescription drug manufacturers could rarely make a profit from marketing drugs for such small groups of patients. The prescription drug industry did not adequately fund research into such treatments.” S. 1379, 107th Cong., 1st Sess., at 2. “The Orphan Drug Act created financial incentives for the research and production of such orphan drugs. New federal programs at the National Institutes of Health and the Food and Drug Administration encouraged clinical research and commercial product development for products that target rare diseases.” *Id.* at 3. The legislation recognized that, “[d]espite the tremendous success of the [ODA], rare diseases and disorders deserve greater emphasis,” and so the legislation had the purpose of establishing an Office of Rare Diseases at the NIH and “increas[ing] the national investment in the development of diagnostics and treatments for patients with rare diseases and disorders.” *Id.* at 3–4.

In parallel with its consideration of these orphan drug exclusivity provisions, on October 4, 2001, the HELP Committee issued a report on S. 838, an early version of BPCA. *See* S. Rep. No. 107-79 (2001). Shortly thereafter, on October 16, 2001, the HELP Committee marked up the Rare Diseases Act. *See id.* at 5. Only two days later, the Senate passed BPCA (S. 838) with

⁴⁹ *See, e.g.*, 21 U.S.C. § 360ff (establishing rare pediatric disease priority review voucher program).

an amendment containing what is now codified in section 505A(o). *See* 147 Cong. Rec. S10816–19 (Oct. 18, 2001); *id.* S10844–46 (Oct. 18, 2001). On December 12, 2001, the Senate considered and passed the BPCA legislative vehicle that ultimately was enacted (S. 1789) containing what is now codified in section 505A(o). *See* 147 Cong. Rec. S13070–76 (Dec. 12, 2001). Six days later, on December 18, 2001, the Senate HELP Committee issued a report on the Rare Diseases Act, which was enacted later in 2002. *See* S. Rep. No. 107-129; Rare Diseases Act of 2002, Pub. L. No. 107-280, 116 Stat. 1988 (Nov. 6, 2002). The first paragraph of that December 18, 2001, Senate HELP Committee Report clearly evidences the HELP Committee’s understanding and recognition of the importance of the Orphan Drug Act, including its orphan drug exclusivity incentive afforded to drug manufacturers: “To address a longstanding unmet need to develop new treatments, diagnostics, and cures for rare diseases and disorders, Congress enacted the Orphan Drug Act of 1983 (Pub. L. 97-414). This Act created financial incentives, such as market exclusivity, tax credits, and research grants, for the research and production of orphan drugs, and established the Orphan Products Board at the [FDA]. Congress sought through the Act to encourage the development of new ‘orphan’ treatments, diagnostics, and cures for the millions of Americans with rare diseases who did not have access to effective medicines because prescription drug manufacturers were unlikely to develop and market drugs for such small groups of patients.” S. Rep. No. 107-129, at 1–2 (emphasis added). That same December 18th HELP Committee Report noted that “[t]he Orphan Drug Act provided seven years of market exclusivity and expanded tax credits to companies for the development and marketing of orphan drugs.” *Id.* at 3 (emphasis added).⁵⁰

In short, Congress was, at the very same time, actively considering in parallel both orphan drug exclusivity and the pediatric labeling omission provisions in section 505A(o). The same Senators who enacted section 505A(o) knew exactly what they were doing by limiting it to labeling protected only by patent protection and three-year exclusivity, and by not including orphan drug exclusivity within the scope of section 505A(o). Indeed, the foregoing legislative history of Congress’ consideration of orphan drug exclusivity in parallel with Congress’ consideration of pediatric labeling omissions in section 505A(o) reflects precisely why Congress omitted orphan drug exclusivity from section 505A(o): Congress understood the value and impact of orphan drug exclusivity and eschewed enactment of language that would in any way diminish that protection in the case of a pediatric orphan disease or condition.

The Pediatric HoFH Study provides an example of how the incentives created by the

⁵⁰ A comparable legislative record is found in the House of Representatives. For example, during an October 11, 2001, markup of the BPCA legislation (H.R. 2887) by the House Committee on Energy and Commerce, Representative Waxman noted that drug manufacturers “get even more exclusivity” for orphan drugs. Tr. of Record of Markup on H.R. 2985 American Spirit Fraud Prevention Act of 2001, H.R. 2887, Best Pharmaceuticals for Children Act, and H.R. 2983 Price-Anderson Reauthorization Act of 2001, House of Representatives, Committee on Energy and Commerce, at 68 (Oct. 11, 2001).

Orphan Drug Act and FDA's pediatric-labeling regulations work in practice. Pediatric HoFH is an important public-health issue with unmet medical need. Although the market for HoFH treatment is small (due to the small number of pediatric HoFH patients), AstraZeneca agreed to invest time and resources in the Pediatric HoFH Study based in large part on the incentives created by Congress and FDA regulations.⁵¹ Without those incentives, it is not realistic to expect that a drug manufacturer would invest time and resources in investigating treatment for small pediatric patient populations.

* * *

For all the foregoing reasons, FDA lacks legal authority to carve out AstraZeneca's protected labeling, and may not lawfully approve ANDAs or section 505(b)(2) NDAs for generic rosuvastatin calcium until (i) AstraZeneca's orphan drug exclusivity expires, (ii) FDA revises its pediatric-labeling rules through notice-and-comment rulemaking, or (iii) Congress amends section 505A(o) to cover orphan drug exclusivity. Although FDA and the United States District Court for the District of Maryland concluded in the *Otsuka* litigation that FDA has authority to carve out pediatric labeling protected by orphan drug exclusivity,⁵² that conclusion is incorrect and should be overturned for the reasons given above.

ENVIRONMENTAL IMPACT

The actions requested in this Petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

Information on the economic impact of this Petition will be submitted upon request of the Commissioner.

CERTIFICATION

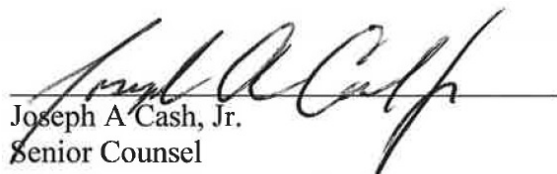
I certify that, to my best knowledge and belief: (a) this Petition includes all information and views upon which the Petition relies; (b) this Petition includes representative data and/or information known to the Petitioner which are unfavorable to the Petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the Petition were disclosed to me. I further certify that the information upon which I have

⁵¹ See Keenan Decl. ¶ 20.

⁵² See *Otsuka Letter* at 10–15; see also *Otsuka Pharm. Co. v. Burwell*, No. GJH-15-852, 2015 WL 1962240 (D. Md. Apr. 29, 2015)

based the action requested herein first became known to the party on whose behalf this Petition is submitted on or about the following date: February 14, 2014 (the date on which FDA awarded Orphan Drug designation to Crestor for pediatric HoFH) and May 27, 2016 (the date on which FDA approved sNDA 21-366/S-033). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: AstraZeneca Pharmaceuticals. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



Joseph A. Cash, Jr.
Senior Counsel
AstraZeneca Pharmaceuticals
FOP 3-131
1800 Concord Pike
Wilmington, DE 19850
Tel.: (302) 885-6359⁵³

Attachments

cc: Elizabeth Dickinson, Esq.
Chief Counsel
Food and Drug Administration

John M. Engel, Esq.
Managing Member
EngelNovitt, PLLC

Timothy Hester
Covington & Burling LLP

⁵³ This contact information was added at FDA request. The remainder of this Citizen Petition remains unchanged.