

FDA Issues Draft Guidance on Orphan Drug Designation in Pediatric Subpopulations

New guidance intends to limit product sponsors' exclusions from the requirement to study pharmaceuticals in pediatric patients.

On December 20, 2017, the US Food and Drug Administration (FDA or Agency) issued draft guidance stating that the Agency no longer intends to grant orphan drug designation to drugs for treating pediatric subpopulations of common diseases, which include diseases or conditions affecting more than 200,000 persons in the United States. The draft guidance, *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases*, sets forth the Agency's position with respect to the use of orphan drug designation in pediatric subpopulations. In particular, the draft guidance is intended to limit access to a provision in the Pediatric Research Equity Act (PREA) that may exempt a sponsor holding a pediatric-subpopulation orphan designation from conducting the pediatric studies normally required under PREA when seeking approval of the adult indication of the same common disease.

This *Client Alert* highlights key provisions in the draft guidance that may be relevant to manufacturers developing pharmaceutical products designed to treat common diseases.

Background: Orphan Designation in Pediatric Subpopulations

Congress enacted the Orphan Drug Act (ODA) in 1983 to provide pharmaceutical product sponsors with incentives to develop drugs for rare diseases and conditions.¹ Under the ODA, FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or for which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product in the United States.² Companies that receive orphan drug designation for a product candidate qualify for various incentives including tax credits for clinical trial costs, relief from eventual application fees, and seven years of marketing exclusivity after the drug is approved.

Although orphan drug designation is limited to rare diseases and conditions, FDA has historically granted orphan drug designation for use in pediatric subpopulations of common diseases or conditions if the prevalence in the pediatric subpopulation (aged 0 to 16 years³) in the US is below 200,000 (Pediatric-Subpopulation Designation).⁴ For example, FDA would not designate a drug intended to treat ulcerative

colitis as an orphan drug, as the condition affects more than 200,000 individuals in the United States. However, FDA has granted orphan drug designation to drugs intended to treat ulcerative colitis in pediatric patients, as the condition affects fewer than 200,000 pediatric patients each year, and several products have received FDA approval and orphan drug exclusivity for the pediatric indication.⁵

FDA began the practice of Pediatric-Subpopulation Designation prior to the enactment of legislation specifically intended to promote the research and development of drugs for pediatric populations. Because drug sponsors had not historically included pediatric populations in their research and development programs, FDA applied orphan drug development incentives in an attempt to increase the development of drugs for pediatric subpopulations in common diseases.⁶ Since the time that FDA adopted this approach, Congress has enacted several programs intended to promote pediatric studies. Notably, in 2003 Congress passed PREA,⁷ which required that certain marketing applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration contain an assessment of safety and effectiveness (including dosing information) for the proposed indication in all relevant pediatric subpopulations.⁸

Exclusion of Drugs Granted Pediatric-Subpopulation Designation from PREA Pediatric Study Requirements

According to FDA, the introduction of PREA and other statutory provisions designed to promote pediatric drug development has rendered Pediatric-Subpopulation Designation unnecessary. Moreover, FDA believes that such ongoing designation has introduced unintended complications that have the potential to inhibit the development of pediatric drugs.⁹ Specifically, the Federal Food, Drug, and Cosmetic Act (FDCA) exempts certain drugs with orphan designation from the requirement to conduct pediatric studies under PREA (the PREA Orphan Exemption).¹⁰ Under the PREA Orphan Exemption, the requirement to conduct pediatric assessments does not apply to any application for a drug for an indication for which orphan designation has been granted when that application would otherwise trigger PREA because it contains a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.¹¹

According to FDA, the interplay between the PREA Orphan Exemption and Pediatric-Subpopulation Designation may permit drug sponsors to sidestep pediatric study requirements meant to promote pediatric disease research.¹² As an example of this, the draft guidance describes the situation in which FDA grants Pediatric-Subpopulation Designation to a sponsor's drug for ulcerative colitis, and subsequently approves a New Drug Application for the drug for adult form of the disease. In this situation, the Pediatric-Subpopulation designation would exempt the drug sponsor from the requirement to conduct studies for pediatric ulcerative colitis under PREA, despite the fact that the prevalence of ulcerative colitis as a whole is greater than 200,000 and despite the fact that pediatric ulcerative colitis does not meet the definition of an "orphan subset" pursuant to 21 CFR § 316.3(b)(13) (discussed below).¹³ Although Pediatric-Subpopulation Designation would, in theory, provide incentives for the sponsor to study the drug in a pediatric population in order to obtain approval and orphan drug exclusivity in the pediatric indication, the PREA Orphan Exemption would still apply even if the drug sponsor never develops the drug for pediatric use.¹⁴ A sponsor could thereby use Pediatric-Subpopulation Designation to avoid pediatric study requirements.

Eliminating Pediatric-Subpopulation Designation

To avoid this situation, FDA explains that it no longer intends to grant Pediatric-Subpopulation Designation.¹⁵ According to the draft guidance, because congressionally enacted programs such as PREA have been effective in promoting pediatric drug development, FDA believes that Pediatric-

Subpopulation Designation is no longer necessary for achieving this end.¹⁶ Accordingly, if a sponsor requests orphan drug designation for a pediatric subpopulation of a common disease, even if the pediatric subpopulation prevalence is below 200,000, FDA will only grant orphan drug designation to that pediatric subpopulation if one of two circumstances exist:

- The disease in the pediatric population constitutes a valid orphan subset, and the drug meets all the other criteria for orphan designation. The Orphan Drug regulations define the term “orphan subset” to mean “use of the drug in a subset of persons with a non-rare disease or condition ... [where] use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.”¹⁷ In the draft guidance, the Agency notes that a sponsor requesting an orphan designation in this context would need to demonstrate that affected individuals outside the orphan subset would not be appropriate candidates for the drug.¹⁸
- The sponsor can adequately demonstrate that the disease in the pediatric subpopulation is a different disease from the disease in the adult population, and the drug meets all other criteria for orphan designation. The Agency notes in the draft guidance that a sponsor seeking orphan designation in this manner may need to provide evidence distinguishing the pediatric disease from the adult form, and that such evidence may include efficacy results that, as a scientific matter, cannot be extrapolated to pediatric populations.¹⁹

Conclusion

In the *Federal Register* notice announcing the availability of the draft guidance, FDA indicated that it does not intend to implement this policy until the draft guidance is finalized, and in the interim, FDA will refrain from issuing final decisions on requests for Pediatric-Subpopulation Designation. If FDA ultimately finalizes this guidance in substantially its current form, sponsors of drugs intended to treat common diseases may be required to revise their existing pediatric study plans to either incorporate PREA requirements or to generate the evidence required for FDA to grant orphan designation to a pediatric subpopulation as discussed in the draft guidance.

The new policy, if and when enacted, could eliminate orphan drug designation and exclusivity for certain drugs that are effective not just in a rare disease or condition, but also in a more common disease or condition. FDA has historically supported granting orphan drug status to drugs for rare diseases or conditions even if they are also effective in one or more common diseases or conditions as a way to incentivize development and approval of therapies for the rare disease or condition. However, this policy has come under criticism recently by individuals who argue that it may have the negative effect of blocking generic competition and causing higher drug prices for widely used blockbuster drugs.²⁰

Parties interested in submitting comments to FDA on the draft guidance are advised to do so by March 19, 2018, to ensure that FDA considers those comments prior to preparing the final version of the guidance.

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Endnotes

¹ 21 U.S.C. §§ 360aa - 360ee (as amended).

² 21 U.S.C. § 360bb.

³ 21 C.F.R. § 201.57.

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- ⁴ FDA, *Draft Guidance for Industry: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases*, at 2 (Dec. 20, 2017), available at <https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM589710.pdf>, (hereinafter referred to as: "Pediatric Subpopulation Draft Guidance")
- ⁵ For example, Colazal (alsalazide disodium) and Remicade (infliximab) received orphan drug designation for treatment of pediatric patients with ulcerative colitis in 2005 and 2003, respectively, and both later received approval and orphan drug exclusivity for the indication extending to 2013 and 2018, respectively. See FDA, Orphan Drug Designations and Approvals (search term "colitis"), <https://www.accessdata.fda.gov/scripts/opdlisting/ood/listResult.cfm?StartRow=1&EndRow=25> (last viewed Dec. 19, 2017).
- ⁶ *Id.*
- ⁷ 21 U.S.C. § 355c.
- ⁸ *Id.* In addition, the FDA Reauthorization Act of 2017 (FDARA) extended the scope of PREA to require pediatric studies of certain adult oncology drugs that are directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. See 21 U.S.C. § 355c(a)(1)(B).
- ⁹ Pediatric Subpopulation Draft Guidance, at 3.
- ¹⁰ 21 U.S.C. § 355c(k).
- ¹¹ *Id.*
- ¹² Pediatric Subpopulation Draft Guidance, at 4. The potential for Pediatric-Subpopulation Designation to affect pediatric drug development has also been discussed by FDA Commissioner Scott Gottlieb, who noted that "[b]y granting the drug a pediatric orphan designation, it means the drug never has to actually be studied for a pediatric use. It's a loophole that is in direct opposition to what Congress intended." Scott Gottlieb, *FDA is Advancing the Goals of the Orphan Drug Act*, (Sep. 12 2017), available at <https://blogs.fda.gov/fdavoices/index.php/2017/09/fda-is-advancing-the-goals-of-the-orphan-drug-act/>
- ¹³ Pediatric Subpopulation Draft Guidance, at 4;
- ¹⁴ *Id.*
- ¹⁵ *Id.*
- ¹⁶ *Id.*
- ¹⁷ 21 C.F.R. § 316(b)(6).
- ¹⁸ Pediatric Subpopulation Draft Guidance, at FN2.
- ¹⁹ *Id.* at 4-5.
- ²⁰ See Scott Gottlieb, *FDA is Advancing the Goals of the Orphan Drug Act*, (Sep. 12 2017), available at <https://blogs.fda.gov/fdavoices/index.php/2017/09/fda-is-advancing-the-goals-of-the-orphan-drug-act/>