Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Orphan Products Development (OOPD)

July 2018

Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases

Guidance for Industry

Additional copies are available from:
Office of Orphan Products Development
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32, Rm. 5295
Silver Spring, MD 20993
Tel: 301-796-8660; E-mail: orphan@fda.hhs.gov
https://www.fda.gov/orphan

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Orphan Products Development (OOPD)

July 2018

Contains Nonbinding Recommendations

Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases Guidance for Industry

I. INTRODUCTION

This guidance is intended for sponsors of drugs and biological products (hereafter *drugs*[1]) who are considering submitting requests for orphan-drug designation for their drugs under section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA) does not expect to grant any additional orphan-drug designation to drugs for pediatric subpopulations of common diseases (i.e., diseases or conditions with an overall prevalence of 200,000 or greater). Pediatric-subpopulation designations that have already been granted will not be affected by this change.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Congress enacted the Orphan Drug Act (ODA) to give sponsors incentives to develop drugs to prevent, diagnose, or treat rare diseases and conditions, including in pediatric patients with such diseases.[2] Orphan-drug designation may cover diseases in pediatric patients in several ways, including the following:

1. If a disease is rare (i.e., the prevalence of the disease is less than 200,000), a drug may be eligible for designation for the entire disease. The pediatric population, as part of the population being affected by that disease, would be covered under that orphan designation.

[1] For the purposes of this guidance, the term *drugs* refers to both human drug and biological products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.

[2] Pub. L. 97-414 (1983), codified as amended at 21 U.S.C. §§ 360aa - 360ee. The ODA generally defines a *rare disease or condition* as any disease or condition that affects fewer than 200,000 persons in the United States.

2. If a disease is *common* (i.e., the prevalence of the disease is 200,000 or greater), a drug may be eligible for orphan designation for a valid *orphan subset* of the disease.[3] For example, if the prevalence of the pediatric population affected by the disease is less than 200,000 and if it would not be appropriate to use the drug in the adult population of the disease, the drug may be eligible for orphan designation for the pediatric population as an orphan subset.
3. If the disease in the pediatric population is in fact a different disease from the disease in the adult population, and the prevalence of that pediatric population is less than 200,000, the disease in the pediatric population is itself a rare disease for which a drug may be eligible for orphan-drug designation.

For each orphan-drug designation request, FDA determines whether a given medical condition constitutes a distinct disease or condition based on a number of factors assessed cumulatively, including: pathogenesis of the disease or condition; course of the disease or condition; prognosis of the disease or condition; and resistance to treatment. These factors are analyzed in the context of the specific drug for which designation is requested.[4]

In addition, FDA had historically granted orphan-drug designation to drugs intended for use in pediatric subpopulations of common diseases or conditions (i.e., diseases or conditions with an overall prevalence of 200,000 or greater in the U.S.) if the prevalence in the pediatric subpopulation in the U.S. is below 200,000.[5] For example, if a given common disease occurs in both adults and children, the *pediatric subpopulation* would be the portion of those individuals with the disease who are younger than 17 years of age.[6] And if the prevalence of this given disease in the pediatric subpopulation were less than 200,000 in the U.S., this subpopulation would be considered a *rare pediatric subpopulation.* In such a case, upon a sponsor's request, FDA has granted *pediatric-subpopulation designation* to the sponsor's drug. This was a specific type of orphan-drug designation, in which FDA granted designation to a drug for use in a rare pediatric subpopulation of a common disease or condition.

[3] The orphan drug regulations define an *orphan subset* to mean "that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but 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…." See 21 CFR § 316.3(b)(13). Therefore, a sponsor requesting orphan-drug designation for a drug for use in an orphan subset must "demonstrate that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug." See 21 CFR § 316.20(b)(6). For more on factors that may inform whether or not an appropriate orphan subset exists, see FDA, *Orphan Drug Regulations, Final Rule*, 78 Fed. Reg. 35117, 35119-35120 (June 12, 2013).

[4] See FDA, *Orphan Drug Regulations, Final Rule*, at 35120.

[5] The term *common disease or condition* is used interchangeably with *non-rare disease or condition* in this document; both refer to diseases or conditions with an overall prevalence of 200,000 or greater in the U.S.

[6] The regulation governing labeling requirements defines the *pediatric population* as including patients aged "birth to 16 years, including age groups often called neonates, infants, children, and adolescents." See 21 CFR § 201.57(c)(9)(iv). FDA has interpreted this regulation to mean birth to younger than 17 years (i.e., birth through 16 years of age). For the purposes of orphan-drug designation, FDA also defines *pediatric* as birth through 16 years of age.

Two examples of pediatric-subpopulation designations include designations of drugs to treat pediatric ulcerative colitis and pediatric HIV. Each of these diseases (e.g., ulcerative colitis or HIV) is common (i.e., the total prevalence is 200,000 or greater in the U.S.), but because the prevalence of the disease in the pediatric population in the U.S. falls below 200,000, FDA has granted pediatric-subpopulation designation for drugs for use in pediatric subpopulations with these two diseases.

FDA began the practice of pediatric-subpopulation designation before the enactment of legislation to specifically promote the study of drugs in the pediatric population. Sponsors had historically failed to include pediatric populations in the research and development of their drugs for common diseases or conditions at that time. To foster research in pediatric populations, FDA decided to apply orphan drug development incentives to promote the development of drugs for indications with a prevalence of 200,000 or greater in the total population, but with less than 200,000 in the pediatric population for use in those pediatric populations.[7]

In the meantime, Congress has created several programs intended to promote pediatric studies:

- In 1997, the Food and Drug Administration Modernization Act of 1997 (FDAMA) created a pediatric exclusivity provision that provided an additional six months of market exclusivity when a sponsor submits reports of pediatric studies that fairly respond to a written request from FDA and are conducted in accordance with generally applicable scientific principles and protocols.[8]
- In 2002, this incentive program was reauthorized under the Best Pharmaceuticals for Children Act (BPCA).[9]
- In 2003, the Pediatric Research Equity Act (PREA) was enacted, codifying a similar FDA regulation that had been struck down by the courts that 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.[10]
- In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) permanently reauthorized the BPCA and PREA.[11] In addition, the FDA Reauthorization Act of 2017 (FDARA) extended the scope of PREA to require pediatric studies of certain

[7] The financial incentives provided by orphan-drug designation include tax credits to defray the cost of conducting clinical trials and eligibility for seven years of market exclusivity. Additionally, no user fee is required for orphan drug product submissions, except when an application also includes an indication for a non-rare disease or condition.

[8] See Pub. L. 105-115 (1997), codified at section 505A of the FD&C Act (21 U.S.C. 355a).

[9] See Pub. L. 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a).

[10] See Pub. L. 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Section 505B, which has been amended several times since 2003, is often still referred to as "PREA," a convention we will adopt in this guidance.

[11] Pub. L. No. 112-144 (2012).

> adult oncology drugs that are directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.[12]

Sections 505A and 505B of the FD&C Act, as added by BPCA and PREA, and subsequently reauthorized without sunset dates, have proven successful in promoting pediatric studies of drugs that are used in children. Since their enactment, the successful completion of pediatric studies has led to the addition of new pediatric information in labeling for more than 700 products.[13] Additionally, the rare pediatric disease (RPD) priority review voucher (PRV) program, established under FDASIA, rewards sponsors that attain marketing approval for new drugs for use in rare pediatric diseases with vouchers for priority review of future marketing applications, intending to provide an added incentive for studies of rare pediatric diseases.[14]

III. CLARIFICATION

Despite their successes, these statutory provisions have also resulted in substantial changes to the regulatory landscape. Thus, not only have they rendered pediatric-subpopulation designation no longer necessary to promote pediatric studies, they have inadvertently introduced complications that could potentially inhibit the achievement of that goal.

Section 505B(k) of the FD&C Act contains a statutory exemption from the requirement to conduct pediatric studies under PREA for certain drugs with orphan designation (i.e., *the PREA orphan exemption*).[15] Under this exemption, PREA 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 the application contains a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.[16] As a result, this

---

[12] See Pub. L. 115-52 (2017), codified at section 505B(a)(1)(B) of the FD&C Act (21 U.S.C. 355c(a)(1)(B)). We note that FDARA also included other changes to section 505B, including a removal of the PREA orphan exemption for molecularly targeted oncology drugs for which pediatric studies are required under the new provision. These changes are outside of the scope of this guidance.

[13] See FDA, New Pediatric Labeling Information Database located at https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase.

[14] See Pub. L. 112-144 (2012), codified at section 529 of the FD&C Act (21 U.S.C. 360ff).

[15] Section 505B(k) of the FD&C Act (21 U.S.C. 355c(k)), as amended by FDARA, reads as follows:

(k) Relation to Orphan drugs --

> (1) In General; Exemption for Orphan Indications – Unless the Secretary requires otherwise by regulation and except as provided in paragraph (2), this section does not apply to any drug or biological product for an indication for which orphan designation has been granted under section 526.
>
> (2) Applicability Despite Orphan Designation of Certain Indications – This section shall apply with respect to a drug or biological product for which an indication has been granted orphan drug designation under section 526 if the investigation described in subsection (a)(3) applies to the drug or biological product as described in subsection (a)(1)(B).

FDA has interpreted section 505B(k)(1) to mean that if a sponsor holds orphan-drug designation for a pediatric subpopulation of a disease, the PREA orphan exemption applies to the sponsor seeking marketing approval for the adult population of that same disease.

[16] Section 505B(k)(2), as created by section 504 of FDARA, substantially resolves this issue for applications subject to section 505B(a)(1)(B).

provision would exempt a sponsor holding pediatric-subpopulation designation for a disease from the requirement to conduct the pediatric studies normally required under PREA when seeking approval of an adult indication of that same disease.

To better illustrate this example, if FDA granted pediatric-subpopulation designation to a sponsor's drug for pediatric ulcerative colitis and the sponsor submitted an NDA or BLA for the drug to treat ulcerative colitis in adults, under PREA, the sponsor would be exempt from the requirement to conduct pediatric studies in ulcerative colitis. Although some sponsors with pediatric-subpopulation designation for their drugs have completed (or plan to complete) pediatric studies in the disease for which they hold designation, other sponsors with pediatric-subpopulation designation for their drugs may never conduct pediatric studies in the disease for which they hold designation.[17]

The interaction between granting pediatric-subpopulation designation and the PREA orphan exemption has created a kind of loophole. This is because obtaining pediatric-subpopulation designation provides orphan incentives to study a drug in the pediatric population with the disease but does not *mandate* the conduct of those studies. As a result, a sponsor could use pediatric-subpopulation designation to obtain an exemption from the requirement to conduct the very studies the designation program was meant to incentivize. FDA has concluded that the pediatric-subpopulation designation is no longer necessary to promote the conduct of pediatric studies and could ultimately inhibit the achievement of that goal, possibly even jeopardizing the Agency's ability to require those studies under PREA.

To close this loophole, FDA does not expect to grant any additional pediatric-subpopulation designation (i.e., designation for rare pediatric subpopulations of common diseases). Pediatric-subpopulation designation is no longer necessary to stimulate the study of drugs in pediatric populations now that various programs, such as PREA and BPCA, have proven to be effective in achieving those ends.

However, as discussed in Section II of this guidance, orphan-drug designation may otherwise cover diseases in pediatric patients and this remains unchanged. As a result, assuming a given drug meets all other criteria for designation, FDA intends to still grant orphan-drug designation to a drug to prevent, diagnose, or treat the following:

1. A rare disease that includes a rare pediatric subpopulation;
2. A pediatric subpopulation that constitutes a valid orphan subset;[18] and
3. A rare disease that is in fact a different disease in the pediatric population as compared to the adult population.

[17] Section 505(g) of FDARA required FDA to report to Congress on any drugs with orphan designation for which a marketing application has been submitted without containing important pediatric information in the product labeling.

[18] See footnote 3. Moreover, as scientific understanding evolves, FDA will continue to consider how targeted therapies and the diseases they treat may qualify as orphan subsets.

Pediatric-subpopulation designations that have already been granted will not be affected. Therefore, a sponsor that holds orphan-drug designation for a drug for use in a pediatric subpopulation of a common disease is still eligible for the applicable benefits of orphan designation.[19]

[19] FDA may revoke orphan-drug designation in accordance with 21 CFR § 316.29.