

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

## Draft Guidance for Industry

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For questions regarding this draft guidance document, contact the Office of Orphan Products Development at [orphan@fda.hhs.gov](mailto:orphan@fda.hhs.gov) or 301-796-8660.

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

December 2017

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## Contains Nonbinding Recommendations

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## Guidance for Industry

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### I. INTRODUCTION

This guidance is intended for sponsors of drugs and biological products (hereafter ‘drugs’)<sup>1</sup> that submit orphan drug designation requests under section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA) no longer intends to grant orphan drug designation to drugs for pediatric subpopulations of common diseases (i.e., diseases or conditions with an overall prevalence of over 200,000), unless the use of the drug in the pediatric subpopulation meets the regulatory criteria for an orphan subset,<sup>2</sup> or unless the disease in the pediatric subpopulation is considered a different disease from the disease in the adult population.

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 provide sponsors with incentives to develop drugs for rare diseases and conditions.<sup>3</sup> FDA has historically granted orphan drug designation to

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<sup>1</sup> For the purposes of this guidance, the term ‘drugs’ refers to both human drugs and biological products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.

<sup>2</sup> 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).

<sup>3</sup> Pub. L. No. 97-414, 96 Stat. 2049 (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. For each orphan drug designation request, FDA determines whether a given medical condition constitutes a

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drugs for use in pediatric subpopulations of common diseases or conditions (i.e., diseases or conditions with an overall prevalence of over 200,000 in the U.S.) if the prevalence in the pediatric subpopulation in the U.S. is below 200,000 (hereinafter, this practice is referred to as “pediatric-subpopulation designation”).<sup>4,5</sup> Examples of pediatric-subpopulation designations include designations of drugs for pediatric ulcerative colitis and pediatric HIV. Each of these diseases (e.g., ulcerative colitis or HIV) is common, i.e., the total prevalence exceeds 200,000 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 in these diseases.

FDA began this practice of pediatric-subpopulation designation before pediatric-specific legislation to promote the study of drugs in the pediatric population was enacted. Because sponsors had historically failed to include pediatric populations in the research and development of their drugs for common diseases or conditions at that time, FDA applied orphan drug development incentives to promote the development of drugs for indications with a prevalence greater than 200,000 in the total population but less than 200,000 in the pediatric population for use in those pediatric populations.<sup>6</sup>

Since the time that FDA began granting pediatric-subpopulation designation to incentivize pediatric studies, Congress created several programs that promote pediatric studies and changed the regulatory landscape. 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. In 2002, this incentive program was reauthorized under the Best Pharmaceuticals for Children Act (BPCA).<sup>7</sup> In 2003 Congress passed the Pediatric Research Equity Act (PREA), 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

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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. See FDA, *Orphan Drug Regulations, Final Rule*, 78 Fed. Reg. 35117, 35120 (June 12, 2013).

<sup>4</sup> 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 over 200,000 in the U.S.

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> See Pub. L. 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a).

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safety and effectiveness (including dosing information) for the proposed indication in all relevant pediatric subpopulations.<sup>8</sup> The Food and Drug Administration Safety and Innovation Act (FDASIA) permanently reauthorized the BPCA and PREA in 2012.<sup>9</sup> 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 the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.<sup>10</sup>

The successful completion of pediatric studies under BPCA and PREA, both of which have now been reauthorized without sunset dates, has led to the addition of new pediatric information in labeling for over 600 products since the enactment of these two laws.<sup>11</sup> These initiatives have proven successful in promoting pediatric studies of drugs that are used in children. 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, in order to provide an added incentive for studies of rare pediatric diseases.<sup>12</sup>

### III. DISCUSSION

The introduction of these statutory provisions has not only rendered pediatric-subpopulation designation no longer necessary to promote pediatric studies, but has inadvertently introduced complications that have the potential to actively 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 (“the PREA orphan exemption.”)<sup>13</sup> Under the PREA orphan exemption, PREA does not apply to any application for

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<sup>8</sup> See Pub. L. 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c).

<sup>9</sup> Pub. L. No. 112-144 (2012).

<sup>10</sup> See section 505B(a)(1)(B) of the FD&C Act (21 U.S.C. 355c(a)(1)(B)), as amended by section 504 of FDARA (Pub. L. No. 115-52 (2017)). 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.

<sup>11</sup> FDA, Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, Status Report to Congress (July 2016), available at <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf>.

<sup>12</sup> See section 529 of the FD&C Act (21 U.S.C. 360ff), added by FDASIA (Pub. L. No. 112-144 (2012)).

<sup>13</sup> 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).

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a drug for an indication for which orphan designation has been granted when that application would otherwise trigger PREA as containing a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.<sup>14</sup> The interplay of pediatric-subpopulation designation and the PREA orphan exemption has created an unintended loophole where a sponsor holding pediatric-subpopulation designation can submit a marketing application for use of its drug in the non-orphan adult population of that disease, get a pediatric-subpopulation designation for the pediatric subset of the disease, and, due to this designation, be exempt from conducting the pediatric studies normally required under PREA when seeking approval of the adult indication.

For example, if FDA grants pediatric-subpopulation designation for a sponsor's drug for pediatric ulcerative colitis and the sponsor submits an NDA or BLA for its drug to treat ulcerative colitis in adults, the sponsor would be exempt from having to conduct pediatric studies under PREA by virtue of having the pediatric-subpopulation designation for pediatric ulcerative colitis. This is despite the fact that prevalence of the ulcerative colitis indication 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 under 21 CFR § 316.3(b)(13). Obtaining pediatric-subpopulation designation provides orphan incentives to study the drug in the pediatric population with the disease but, unlike PREA, does not mandate the sponsor to conduct those studies and, in fact, may jeopardize the Agency's ability to require those studies under PREA. Thus a sponsor can use pediatric-subpopulation designation to obtain an exemption from the requirement to conduct the very studies the designation program was meant to incentivize.

In order to close the loophole created by the interaction of the practice of granting pediatric-subpopulation designation and the PREA orphan exemption, FDA intends to no longer continue to grant pediatric-subpopulation designation. 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. Therefore, if a sponsor requests orphan drug designation for a pediatric subpopulation of a common disease, and even if the pediatric subpopulation prevalence is below 200,000, FDA will not grant orphan drug designation to that pediatric subpopulation unless:

1. the disease in the pediatric population constitutes a valid orphan subset, and the drug meets all the other criteria for orphan designation<sup>15</sup>; or
2. 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. For example, if, as a scientific matter, efficacy from

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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.

<sup>14</sup> Section 505B(k)(2), as created by section 504 of FDARA, substantially resolves this issue for applications subject to section 505B(a)(1)(B).

<sup>15</sup> See n.1, supra.

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clinical studies in the adult population could not be extrapolated to the pediatric subpopulation, such information may help demonstrate that the disease in the pediatric and adult populations may be considered different diseases.

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