Rare Pediatric Disease Priority Review Vouchers

Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

This guidance provides information on the implementation of section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA),[1] which added section 529 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act).[2] Under section 529, FDA[3] will award priority review vouchers to sponsors of certain rare pediatric disease product applications that meet the criteria specified in that section.

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 Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND OVERVIEW

Section 529 of the FD&C Act is intended to encourage development of new drug and biological products ("drugs") for the prevention and treatment of certain rare pediatric diseases.[4] Although there are existing incentive programs to encourage the development and study of drugs for rare diseases, pediatric populations, and unmet medical needs, section 529 provides an additional incentive for rare pediatric diseases, which may be used alone or in combination with other incentive programs. These other incentive programs include: orphan-drug designation and the associated benefits under the Orphan Drug Act for rare disease therapies;[5] programs that encourage or require the study of drugs used in pediatric populations under the Best

[1] Public Law 112-144, enacted July 9, 2012.

[2] 21 U.S.C. 360ff. Unless otherwise noted, references to "sections" in this guidance are to sections of the FD&C Act.

[3] Throughout this document, we use the terms "we" and "FDA" interchangeably.

[4] For the purposes of this guidance, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological drug products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[5] Public Law 97-414, as amended, codified at sections 526-528 of the FD&C Act (21 U.S.C. 360aa-360ee).

Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA);[6] and various programs to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions.[7] Even so, Congress has recognized that there remain unmet medical needs among patients with rare diseases that occur primarily in pediatric populations. By enacting section 529, Congress intended to stimulate new drug development for rare pediatric diseases by offering additional incentives for obtaining FDA approval of these products.

Under section 529, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act[8]) for a rare pediatric disease drug may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act[9] or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug.

On September 30, 2016, the Advancing Hope Act of 2016 updated the definition of "rare pediatric disease" (see Question 1) and created a requirement for sponsors seeking a rare pediatric disease priority review voucher to request the voucher upon submission of the rare pediatric disease product application (see Question 14). In addition, the Advancing Hope Act

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[6] *See, e.g.*, Public Law 107-109 (January 4, 2002) and Public Law 108-155 (December 3, 2003), codified in sections 505A and 505B of the FD&C Act (21 U.S.C. 355a-355c).

[7] These programs include, among others, fast track designation, breakthrough therapy designation, accelerated approval, priority review designation, regenerative medicine advanced therapy designation, and programs for certain tropical disease products and antibiotics. For more information, you may refer to the FDA Guidance, Expedited Programs for Serious Conditions – Drugs and Biologics, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf; FDA Guidance, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, *available at* https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf, FDA Draft Guidance, Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269221.pdf; FDA Draft Guidance, Tropical Disease Priority Review Vouchers, *available at* http://www.fda.gov/downloads/Drugs/Guidances/UCM080599.pdf; and Food and Drug Administration Innovation and Safety Act (FDASIA), Public Law 112-144, Title VIII—Generating Antibiotic Incentives Now.

[8] The statutory definition for the term "human drug application" is "an application for--

(A) approval of a new drug submitted under section 355(b) of this title, or

(B) licensure of a biological product under subsection (a) of section 262 of Title 42.

Such term does not include a supplement to such an application, does not include an application with respect to whole blood or a blood component for transfusion, does not include an application with respect to a bovine blood product for topical application licensed before September 1, 1992, an allergenic extract product, or an in vitro diagnostic biologic product licensed under section 262 of Title 42, does not include an application with respect to a large volume parenteral drug product approved before September 1, 1992, does not include an application for a licensure of a biological product for further manufacturing use only, and does not include an application or supplement submitted by a State or Federal Government entity for a drug that is not distributed commercially. Such term does include an application for licensure, as described in subparagraph (B), of a large volume biological product intended for single dose injection for intravenous use or infusion."

Section 735(1) of the FD&C Act (21 U.S.C. 379g(1)). The definition does not cover applications for medical devices.

[9] Because 505(b)(2) new drug applications (NDAs) are submitted under section 505(b)(1), all references to NDAs submitted under section 505(b)(1) include 505(b)(2) applications.

clarified that no sponsor of a rare pediatric disease product application may receive more than one priority review voucher issued under any section of the FD&C Act for the same drug. On December 13, 2016, the 21st Century Cures Act extended the rare pediatric disease priority review voucher program as follows:

> [FDA] may not award any [rare pediatric disease] priority review vouchers…after September 30, 2020, unless the rare pediatric disease product application (A) is for a drug that, not later than September 30, 2020, is designated…as a drug for a rare pediatric disease; and (B) is, not later than September 30, 2022, approved under section 505(b)(1) of [the FD&C Act] or section 351 of the [PHS Act].[10]

Therefore, under the sunset provisions as applicable at the time of issuance of this draft guidance, after September 30, 2020, FDA may only award a voucher if the drug has rare pediatric disease designation, and that designation was granted by September 30, 2020. After September 30, 2022, FDA may not award any rare pediatric disease priority review vouchers.

This guidance revises the draft guidance of the same title issued in November 2014 to reflect these updates. This guidance is intended to assist developers of rare pediatric disease products in assessing whether their product may be eligible for rare pediatric disease designation and a rare pediatric disease priority review voucher. It also clarifies the process for requesting such designations and vouchers, sponsor responsibilities upon approval of a rare pediatric disease product application, and the parameters for using and transferring a rare pediatric disease priority review voucher.

III. DEFINITIONS, POLICIES, AND PROCEDURES — QUESTIONS AND ANSWERS

A. Rare Pediatric Disease Product Applications

Q1. What is a "rare pediatric disease"?

Section 529(a)(3) defines a "*rare pediatric disease*" as a disease that meets each of the following criteria:

> (A) The disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents [; ***and***]
> (B) The disease is a rare disease or condition, within the meaning of section 526 [of the FD&C Act].

Serious or life-threatening manifestations primarily affect children

[10] Section 529(b)(5). Congress may consider whether to extend these time restrictions in the future, so interested persons should consult current law with respect to these restrictions.

Of note, section 529 describes the pediatric population as from birth through 18 years.[11] This age range differs from how FDA defines the pediatric population in other contexts. Generally, for drug and biological products, FDA considers the pediatric population to include patients from birth through 16 years.[12] This guidance uses the term "children" to mean the definition of the pediatric population in section 529: individuals aged from birth to 18 years.

FDA interprets the current definition of "rare pediatric disease" and its reference to "serious or life-threatening manifestations of the disease or condition" using the following principles:

- A manifestation of the disease or condition should be serious or life-threatening in children aged 0 through 18 years of age. Manifestations include expressions and symptoms of the disease or condition. Note that "manifestations" does not mean the onset of the disease or condition or the onset of treatment. For example, if a disease or condition's onset typically begins in childhood, but manifestations of the disease or condition do not become serious or life-threatening until adulthood, the disease or condition is not a rare pediatric disease. Similarly, if treatment for the disease or condition begins in childhood, but under current standard of care the manifestations of the disease or condition are not serious or life-threatening in children, the disease or condition is not a rare pediatric disease.
- FDA will consider the manifestations of the disease or condition in the context of standard of care for the disease or condition. Specifically, FDA will consider what manifestations of the disease or condition are serious or life-threatening in children under standard treatment for the disease or condition. Therefore, FDA will not consider the serious or life-threatening manifestations of the disease or condition that only occur when the disease is left untreated if that is not the standard of care.
- FDA will assess the serious or life-threatening manifestations of the disease or condition and determine which manifestations primarily affect children and which primarily affect adults. Factors in determining if a manifestation primarily affects children include: timing and rate of disease progression (e.g., end-stage organ disease occurs in childhood), manifestations of abnormal growth or development, and whether the proportion of children is greater than the proportion of adults with the given manifestation. If the disease or condition has a manifestation that primarily affects children, FDA will consider the disease or condition to be a rare pediatric disease.[13]
- The serious and life-threatening manifestations of the disease or condition that primarily affect children will also be a factor in determining whether the application qualifies for a voucher (see Questions 3 and 4).

[11] We interpret "from birth to 18 years" as including all individuals less than 19 years of age (i.e., as from 0 through 18 years). Similarly, FDA interprets 21 CFR 201.57(c)(9)(iv), which describes a pediatric age range as "from birth to 16 years," as including all individuals less than 17 years of age (i.e., as from 0 through 16 years).

[12] *See* 21 CFR 201.57(c)(9)(iv).

[13] That is not to say that manifestations that primarily affect adults cannot also be serious or life-threatening in children. But based on the statutory definition, FDA is required to determine which manifestations primarily affect children and which primarily affect adults. For example, FDA has determined that impaired lung function is a serious or life-threatening manifestation of cystic fibrosis that primarily affects adults, but can also be serious or life-threatening in children. FDA considers cystic fibrosis to be a rare pediatric disease based on other manifestations of the disease that do primarily affect children.

Rare disease or condition

Section 526 of the FD&C Act defines a "rare disease or condition" as any disease or condition that affects (1) less than 200,000 persons in the United States (U.S.) or (2) affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug.

A drug may also meet the "rare disease or condition" requirement if it is for an "orphan subset" of a disease or condition that otherwise affects 200,000 or more persons in the U.S.[14] In order for such drug to qualify as a drug for a "rare pediatric disease," the orphan subset must be serious or life-threatening and the serious or life-threatening manifestations of the orphan subset must primarily affect individuals aged from birth to 18 years.[15]

The calculation of prevalence estimates will depend on whether the drug is a therapeutic drug or a vaccine, diagnostic drug,[16] or preventive drug, as follows:

- *For therapeutic drugs*, prevalence estimates of the entire affected U.S. population should be based on the number of individuals diagnosed with the disease or condition. For some diseases and conditions, individuals may have an underlying genetic abnormality at birth but may not develop manifestations of the disease until later, if ever. In these instances, whether individuals are considered "diagnosed" for the purpose of estimating prevalence may depend on whether the product is intended to treat an underlying genetic abnormality, attenuate or prevent progression of the clinical expression of the disease, or treat the clinical symptoms or manifestations of the disease.
- *For vaccines, diagnostic drugs, and preventive drugs*, prevalence estimates should be based on the number of persons of all ages to whom the drug will be administered in the U.S. annually.

For information on how to document prevalence in designation requests, see the responses to Questions 9 and 15.

[14] An "orphan subset" requires demonstration that use of the drug outside of the subset of interest (in the remaining persons with the disease or condition) would not be appropriate owing to one or more properties of the drug, such as drug toxicity, mechanism of action, or previous clinical experience with the drug. *See* 21 CFR 316.3(b)(13); 21 CFR 316.20(b)(6).

[15] *See* Section 529(a)(3)(A).

[16] An application may qualify as a rare pediatric disease product application if it is for a drug or biologic that is a diagnostic for the management of a disease or condition. We note, however, that such diagnostic products must be the subject of a NDA or BLA to qualify as a rare pediatric disease product application, as diagnostic products that are the subject of medical device applications are not eligible for a rare pediatric diseases priority review voucher. An application for a drug for the initial diagnosis of a disease or condition will not qualify as a rare pediatric disease product application.

Qualifying as a drug for a "rare pediatric disease" is not sufficient to receive a priority review voucher. For sponsors to receive such a voucher, the application for the drug must meet all of the remaining eligibility criteria described in response to Question 2.[17]

Q2. What is a "rare pediatric disease product application"?

The term *rare pediatric disease product application* is defined in section 529(a)(4) of the FD&C Act. It refers to an application that:

- Is a human drug application as defined in section 735(1) of the FD&C Act[18]:
  - For prevention or treatment[19] of a *rare pediatric disease* (see Questions 1 and 3);
  - That contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act.
- That FDA deems eligible for priority review.[20]
- Is submitted under section 505(b)(1) of the FD&C Act[21] or section 351(a) of the Public Health Service Act.
- Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population (see Question 4).
- Does not seek approval for an adult indication in the original rare pediatric disease product application (see Question 5); and
- Is approved after the date of enactment of the Advancing Hope Act of 2016 (September 30, 2016).[22]

[17] *See* section 529(a)(4).
[18] See footnote 8.
[19] See footnote 15.
[20] Certain applications may receive priority review pursuant to a statutory mandate (i.e., sections 524A and 505A of the FD&C Act). However, in determining whether an application qualifies for priority review within the meaning of this provision (i.e., section 529(a)(4)(C) of the FD&C Act), if a rare pediatric disease priority review voucher is requested, the Agency will determine whether the application satisfies the criteria for eligibility for a priority review designation, i.e., whether the drug treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. For more information on the priority review designation see footnote 7, referring to FDA's guidance Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014).
[21] See footnote 9.
[22] Note that there are limitations on when rare pediatric disease priority review vouchers can be awarded: FDA may not award a voucher if the application was submitted to FDA prior to October 7, 2012 (i.e., 90 days after enactment of the Prescription Drug User Fee Amendments (PDUFA) of 2012), section 529(b)(3); and see Section II of this guidance for a description of the sunset provision for awarding vouchers under the law as applicable at the time of issuance of this draft guidance.

Q3. What does it mean to be "for" prevention or treatment of a rare pediatric disease?[23]

To be eligible for a voucher, the drug should be (1) approved for a rare pediatric disease and (2) treat or prevent a serious or life-threatening manifestation of the disease or condition that affects children. These serious or life-threatening manifestations may be the manifestations that primarily affect children, but they are not required to be, so long as the approved indication is clinically meaningful to pediatric patients with the disease or condition. For example:

- A drug may meet this standard if the approved indication is explicitly for treatment or prevention of a serious or life-threatening manifestation of the disease or condition that affects children.
- A drug may also meet this standard if the drug treats or prevents the underlying cause of the disease or condition and the approved indication is for treatment or prevention of the disease or condition generally.

The intent of the statute is to award a voucher for a drug that benefits the pediatric patients with the rare pediatric disease or condition. FDA will look at the totality of the evidence to determine if the approval is clinically meaningful for the serious or life-threatening manifestations of the disease that affect children.

FDA encourages sponsors to work with the relevant review division or office in CBER or CDER to ensure they are studying the drug in a way that establishes safety and efficacy for the drug "for" a rare pediatric disease. The priority review voucher request should include scientific justification of how the approved indication will be clinically meaningful to pediatric patients with the disease or condition. We expect a written description of the data and endpoints from the submitted studies that supports a determination that the drug is for pediatric patients with the rare pediatric disease as described above.

Q4. What does "relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population" mean?

We interpret "relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population" to mean that, to be eligible for a voucher, the approved product:

- should have been studied in a clinically meaningful pediatric population with the rare disease (although the studies may also include adults in appropriate circumstances), and
- the pediatric data should have been critical to obtaining adequate labeling for the pediatric population in terms of safety, effectiveness, and dosage information (although data from studies including adults may also have supported the pediatric labeling in appropriate circumstances).

[23] *See* Section 529(a)(4)(A)(i).

It is important that applicants seeking a voucher submit data adequate for labeling the drug for use by the full range of affected pediatric patients, within reasonable limits (i.e., all pediatric patient age ranges affected by the disease that are reasonable to include in the studies without undue delays in completing the studies and submitting the application). The studied pediatric population should be clinically meaningful and represent more than a token pediatric population. Such labeling aligns with the intent of section 529, which is to help address the unmet medical needs of pediatric patients with rare pediatric diseases.

Note that sponsors are not required to study a manifestation of the disease or condition that primarily affects pediatric patients, but the studies should support approval for a rare pediatric disease in a way that is clinically meaningful to pediatric patients with the disease or condition (see Question 3).

Q5. What does "Does not seek approval for an adult indication in the original rare pediatric disease product application" mean?

An applicant cannot receive a rare pediatric disease priority review voucher if the application seeks approval for an adult indication in the original rare pediatric disease product application. We interpret this criterion to mean that, to preserve voucher eligibility, the applicant cannot seek approval for a *different* adult indication (i.e., for a different disease/condition) in the original rare pediatric disease application. If the applicant seeks approval for use by pediatric and adult populations with the rare pediatric disease, the applicant will still be eligible for a voucher if the approved use includes pediatric use, as described in Questions 3 and 4. If the applicant obtains approval for use *only* in an adult population with the rare pediatric disease, the applicant is ineligible for a voucher.

Thus, under this interpretation, an applicant can preserve voucher eligibility even if the applicant seeks approval for use by adults in addition to pediatric patients with the rare pediatric disease. One reason we are interpreting the statute in this way is to avoid incentivizing sponsors to exclude adults affected by the rare pediatric disease from clinical trials or to exclude adult data from the subsequent marketing application solely for the sake of voucher eligibility, when such exclusions may not be scientifically or ethically acceptable for the reasons described below.

Clinical Trial Design – Clinical Trials for a Potential Rare Pediatric Disease Product May Need to Include Individuals Over 18 Years of Age for Scientific or Ethical Reasons: Clinical trials for rare diseases and conditions are challenging because, among other factors, the small patient populations limit the opportunities for study and verification of results. Because such clinical trials are likely to be small and at risk of being underpowered, FDA expects that rare disease clinical development programs will attempt to include all patients with the rare disease or condition that are available for study and who could reasonably be expected to benefit from the intervention, regardless of the age of the patient (where feasible and appropriate based on the disease/condition and expected effects of intervention).[24] Indeed, studies using novel therapies should generally be conducted in young adults (18 to 21 years of age) prior to exposing

[24] *See, e.g.*, ICH and FDA Guidance, "E11 Clinical Investigation of Medicinal Products in the Pediatric Population," Section II.A, *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129477.pdf.

adolescents and younger pediatric patients; for children to be included in early phase investigations, there must be a prospect of direct benefit for an individual child to be studied in a clinical trial in which more than a minor increase over minimal risk is presented by an intervention or procedure.[25] For all of these reasons, it may not be scientifically or ethically appropriate to exclude those over 18 years of age from a clinical trial evaluating a potential rare pediatric disease product.

Data to Include in a Marketing Application – Available Adult Safety and Effectiveness Data Must be Included in the Application: If clinical safety and effectiveness data are available in an adult population (i.e., individuals over 18 years) at the time of the submission of an original application for a potential rare pediatric disease product, these data must be included in the application for FDA's review.[26] In many cases, if there is a population over 18 years of age with the rare pediatric disease that could benefit from the product and for whom there are available data to support the evaluation of the safety and effectiveness of the product, labeling for such a population should be sought in the original product application.

As noted, seeking approval for use in both adults and pediatric patients with the rare pediatric disease will not affect voucher eligibility. However, we remind applicants seeking a voucher that – whether or not they seek approval for use in an adult population – we expect them to submit data adequate for labeling the drug for use by the full range of affected pediatric patients (see response to Question 4).

Note that after a sponsor has been awarded a rare pediatric disease priority review voucher for approval of a drug, the sponsor can develop the same drug for additional indications, including a different adult indication, without losing the voucher.

Q6. What user fees apply to a rare pediatric disease product application?

User fees for human drug applications are described in section 736 of the FD&C Act.[27] In general, a rare pediatric disease product application is subject to these statutory requirements like any other application. Such applications may, however, be eligible for exemptions from some fees if they have received orphan-drug designation. See FDA's Guidance for Industry User Fee Waivers, Reductions, and Refunds for Drug and Biological Products.[28]

User fees also apply to applications for which a rare pediatric disease priority review voucher is used, as described in Question 22.

Q7. What are the sponsor's responsibilities after approval of a rare pediatric disease product application?

[25] 21 CFR 50.52 and 50.53; *see also* ICH and FDA Guidance, "E11 Clinical Investigation of Medicinal Products in the Pediatric Population," footnote 19, Section II.C.
[26] 21 CFR 314.50(d)(5)(iv); 21 CFR 601.2; 21 U.S.C. 379h.
[27] 21 U.S.C. 379h.
[28] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf.

The sponsor of an approved rare pediatric disease product application must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

- the estimated population in the U.S. with the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
- the estimated demand in the U.S. for the product, and
- the actual amount of product distributed in the U.S.[29]

Sponsors should submit such reports to the review division or office within CDER or CBER that reviewed the new drug application (NDA)/ biologics license application (BLA) for the rare pediatric disease product. This report should be prominently marked, "Rare Pediatric Disease Product Post-Approval Report."

B. Requesting Rare Pediatric Disease Designation

Q8. What is the rare pediatric disease designation process?

Under section 529(d), a sponsor may choose to request rare pediatric disease designation. FDA strongly recommends that sponsors planning to request a voucher request rare pediatric disease designation. Under the law as applicable at the time of issuance of this draft guidance, FDA may not award any vouchers after September 30, 2020, unless the application is for a drug that was designated as a drug for a rare pediatric disease by September 30, 2020.[30]

If a sponsor chooses to request such designation, section 529(d)(2) provides that it shall do so "at the same time" that they submit a request for orphan-drug designation under section 526[31] or a request for fast track designation under section 506.[32] FDA will recognize a request for rare pediatric disease designation to be submitted "at the same time" as a request for orphan-drug designation or fast track designation if the requests are received by FDA within two weeks of each other.

Note that, while a request for rare pediatric disease designation may be submitted at the same time as a request for orphan-drug designation or fast track designation, each request should be submitted as a separate proposal (i.e., they should not be submitted in one combined package). The sponsor should indicate in the rare pediatric disease designation request whether or not it is requesting orphan-drug designation or fast track designation at the same time. See Question 10 for how to submit a rare pediatric disease designation request.

We remind sponsors of the timing for orphan-drug and fast track designation requests:

[29] Section 529(e)(2).

[30] Section 529(b)(5). FDA may not award any rare pediatric disease priority review vouchers after September 30, 2022, even for applications for drugs granted rare pediatric disease designation by September 30, 2020.

[31] 21 U.S.C. 360bb.

[32] 21 U.S.C. 356.

Timing of Requests for Orphan-Drug Designation: Under section 526, orphan-drug designation requests must be submitted before the sponsor's filing of a marketing application for the drug for the orphan use.[33]

Timing of Requests for Fast Track Designation: Requests for fast track designation may be submitted at the time of original submission of the investigational new drug (IND) application or any time thereafter prior to receiving marketing approval of the NDA or BLA, although FDA encourages that such requests be submitted no later than the sponsor's pre-NDA/BLA meeting because many of the features of fast track designation will no longer be applicable after that time.[34]

If sponsors submit a timely request for rare pediatric disease designation, section 529(d)(3) directs FDA to make a decision on the request no later than 60 days after submission.[35] The statute directs FDA to decide whether to designate the drug as a drug for a "rare pediatric disease" *and* whether to designate the application for the drug as "a rare pediatric disease product application,"[36] as described in response to Question 11.

FDA recognizes that some sponsors may wish to submit a rare pediatric disease designation request at a different time – for example, if they had already submitted requests for orphan-drug and/or fast track designation before the enactment of FDASIA, or if for whatever reason they have no interest in submitting either such request but do want to submit a rare pediatric disease designation request. FDA is willing to accept designation requests submitted at a different time than that provided by statute as long as FDA receives the designation request before FDA has filed the NDA/BLA for the drug for the relevant indication. Although we will aim to respond to such requests in a timely manner, the 60-day response deadline does not apply. We will not accept requests for rare pediatric disease designation received after FDA has already filed the NDA/BLA for the drug for the relevant indication.

Whether or not a sponsor receives rare pediatric disease designation for its drug, the sponsor must include a request for a rare pediatric disease priority review voucher in its original NDA/BLA submission (either in the initial package or up until the point of NDA/BLA filing) in

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[33] Section 526(a)(1). For more information on orphan-drug designation, see 21 CFR part 316 and http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm.

[34] These features include more frequent interactions with the FDA review team, including meetings to discuss study design and other issues, possible rolling review of portions of the marketing application before receipt of the complete application, and possible priority review if supported by clinical data at the time of BLA or NDA submission. For more information on fast track designation and priority review, see FDA Guidance, Expedited Programs for Serious Conditions—Drugs and Biologics, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf. *See also* http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm.

[35] FDA interprets this language, "not later than 60 days after the request is submitted," to mean that FDA must respond within 60 days after receiving the request.

[36] Section 529(d)(3).

order to be eligible to receive a voucher.[37] See responses to Questions 14 and 15 for information on requesting such a voucher.

Q9. What information should these designation requests contain?

Sponsors should include the following information in rare pediatric disease designation requests:

(1) The name and address of the sponsor and the name of the sponsor's primary contact person and/or resident agent including title, address, telephone number, and email address;

(2) The non-proprietary and trade name, if any, of the drug, or, if neither is available, the chemical name or a meaningful descriptive name of the drug;

(3) The proposed dosage form and route of administration;

(4) A description of the rare pediatric disease for which the drug is being or will be investigated; the proposed use of the drug; and the IND number if previously assigned;

(5) A description of the drug to include (i) the identity of the active moiety, if it is a drug composed of small molecules, or of the principal molecular structural features, if it is composed of macromolecules, and (ii) its physical and chemical properties, if these characteristics can be determined;

(6) An explanation of the mechanism of action, with supportive data, suggesting that the drug may be effective in the rare pediatric disease;[38]

(7) The basis for concluding that the drug is for a "rare disease or condition." This basis is established when a sponsor provides the following information, as described in Section 526 of the FD&C Act:[39]

(i) Documentation, with appended authoritative references, to demonstrate that (a) the estimated prevalence of the affected patient population in the U.S. – those diagnosed with the disease or condition – is below 200,000 at the time of submission of the request for designation, or (b) if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the U.S. are fewer than 200,000 per year. Please provide a list of sources for the information, including dates of the information provided and

[37] Section 529(b)(4)(A)(i).

[38] As explained in response to Question 31, FDA expects a lesser level of supportive data for rare pediatric disease designation than for orphan-drug designation because of the many differences between the two programs. In vitro data supporting the mechanism of action of the drug in the disease or in a related disease may suffice for rare pediatric disease designation, whereas that level of data would not generally suffice for orphan-drug designation.

[39] *See* 21 CFR 316.20.

literature citations (see response to Question 1 for more information on estimating prevalence); or

(ii) For drugs intended for diseases or conditions affecting 200,000 or more people in the U.S., or for a vaccine, diagnostic drug, or preventive drug that would be given to 200,000 or more persons in the U.S. per year, a summary of the sponsor's basis for believing that the disease or condition occurs so infrequently that there is no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the U.S. We ask that sponsors include the same sort of cost and related information as is detailed at 21 CFR 316.21(c).

(8) Documentation, with appended authoritative references, to demonstrate that the rare disease or condition for which the drug is proposed is a "rare pediatric disease" as defined in section 529(a)(3)(A), meaning that the disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years (see response to Question 1). The sponsor should include an analysis of the serious or life-threatening manifestations of the disease and evidence supporting whether each serious or life-threatening manifestation primarily affects children or adults. Please provide a list of sources for the information, including dates of the information provided and literature citations.

(9) Where a sponsor requests designation of a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people ("orphan subset" of non-rare disease or condition), a demonstration 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 Question 1 and footnote 13). Such properties of the drug may include drug toxicity, mechanism of action, or previous clinical experience with the drug.

If a sponsor is submitting a rare pediatric disease designation request at the same time as or shortly after a request for orphan-drug designation for the drug, it can cross-reference any of the above information already contained in their orphan-drug designation request.[40] The sponsor should indicate in the rare pediatric disease designation request whether or not it is requesting orphan-drug designation or fast track designation at the same time as the request for rare pediatric disease designation.

Q10. What is the process for submitting rare pediatric disease designation requests?

Sponsors should submit two copies, with at least one hard copy, of the completed, dated, and signed rare pediatric disease designation requests, with the information specified in response to

[40] Cross-referencing of information in previously submitted orphan-drug designation requests may not be appropriate if the information is outdated, for example, if prevalence estimates for the disease have changed in the intervening time between submission of the orphan-drug designation request and submission of the rare pediatric disease designation request.

Question 9 to the Office of Orphan Products Development, Food and Drug Administration, Bldg. 32, rm. 5295, 10903 New Hampshire Ave., Silver Spring, MD 20993.

Q11. How will FDA respond to such designation requests?

The statute requires that FDA, in responding to rare pediatric disease designation requests, decide whether to designate the drug as a drug for a "rare pediatric disease" *and* whether to designate the associated marketing application as a "rare pediatric disease product application."[41] The Office of Orphan Products Development (OOPD) and the Office of Pediatric Therapeutics (OPT) will issue the designation response in consultation with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as appropriate. This designation response will take one of the following forms:

A Deficiency Letter: FDA will send a deficiency letter within the timeframe specified in Question 8 if the request lacks the information described in Question 9 or contains inaccurate or incomplete information. In the deficiency letter, we will ask the sponsor to respond within 60 days or else request an extension of time to respond within that same timeframe; otherwise, FDA may consider the designation request voluntarily withdrawn.

Designating the Drug as a Drug for a "Rare Pediatric Disease" and Either Denying or Conditionally Designating the Application as a "Rare Pediatric Disease Product Application": FDA will designate a drug as a drug for a "rare pediatric disease" within the timeframe specified in response to Question 8 if the sponsor provides adequate information to demonstrate that the drug is for a rare pediatric disease (including appropriate prevalence estimates with appended authoritative references) and an adequate explanation, with supportive data, of the drug's mechanism of action suggesting that the drug may be effective in the rare pediatric disease (see response to Question 9). FDA will evaluate prevalence as of the time of submission of the designation request. If FDA designates the drug as a drug for a "rare pediatric disease," these prevalence estimates generally will not be reevaluated at the time of NDA/BLA submission,[42] but FDA will evaluate the remaining eligibility criteria to determine whether the NDA/BLA is eligible for a priority review voucher (see Question 2).

Even if FDA designates the drug as a drug for a "rare pediatric disease," FDA cannot definitively designate any associated marketing application as a "rare pediatric disease product application" because eligibility cannot be determined unless and until the application is approved or licensed. This is because eligibility depends on the contents of the application as well as certain facts at the time of approval or licensure (see Question 2). Short of designating the application, FDA has two options in responding to the application portion of a designation request:

[41] Section 529(d)(3)(A) and (B).

[42] FDA does reserve the right to revisit a decision on prevalence estimates if it becomes apparent that information relevant to that question and available at the time of the submitted request for designation was not provided to FDA or known by FDA at the time of designation decision.

(1) *to conditionally designate the application* as a "rare pediatric disease product application" assuming that, at the time of approval or licensure, it will meet all of the eligibility criteria set forth in section 529(a)(4). The final answer to a conditional designation of an application will come in the form of a voucher award or non-award at the time of marketing approval, if the sponsor requests such a voucher in the NDA/BLA. As described in responses to Questions 14 and 15, even sponsors who receive rare pediatric disease designation must include a voucher request in their original NDA/BLA submission if they remain interested in receiving a voucher.[43]

(2) *to deny designating the application* if, at the time of submission of the designation request, it appears the application will fail to meet at least one of the criteria to be a rare pediatric disease product application (see Question 2). Even sponsors who have been denied such designation may request a voucher in their NDA/BLA submission if they believe they are eligible (see responses to Questions 14 and 15).

Neither Designating the Drug as a Drug for a "Rare Pediatric Disease" Nor Designating the Application as a "Rare Pediatric Disease Product Application": If FDA determines that the drug is not in fact a drug for a "rare pediatric disease," FDA will deny rare pediatric disease designation of both the drug and the application. Reasons for such denial include:

- the drug is not for a "rare disease or condition" under section 526 (e.g., prevalence in the U.S. is 200,000 or greater), and the drug is not for an "orphan subset" of a non-rare disease or condition;
- the drug is not for a disease or condition (or "orphan subset" of a disease or condition) that "is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years";
- there is insufficient evidence to support the necessary prevalence estimates or to demonstrate an orphan subset;
- lack of an adequate explanation, with supportive data, of the drug's mechanism of action suggesting that the drug may be effective in the rare pediatric disease;
- the request contains an untrue statement of material fact, omits material information, or is otherwise ineligible for designation.

Even if a sponsor is denied rare pediatric disease designation, the sponsor can request a rare pediatric disease priority review voucher at the time of NDA/BLA submission if the sponsor believes the submission is eligible (see responses to Questions 14 and 15).

Voluntarily Withdrawn Letter: FDA may consider a designation request voluntarily withdrawn if the sponsor fails to respond to a deficiency letter, or to request an extension of time to respond, within 60 days of the deficiency letter date. In the event FDA considers a request voluntarily withdrawn, FDA will notify the sponsor in writing. As above, such sponsors can still request a voucher in the NDA/BLA submission if they believe they are eligible.

[43] Section 529(b)(4)(A)(i).

Not Accepted Letter: As noted in response to Question 8, FDA will not accept requests for rare pediatric disease designation received after FDA has already filed the NDA/BLA for the drug for the relevant indication. Such sponsors may still receive a voucher if they requested a voucher in the NDA/BLA submission and they are otherwise eligible.

Q12. What if a sponsor chooses not to submit a rare pediatric disease designation request before submitting the marketing application?

Sponsors who choose not to submit a rare pediatric disease designation request may nonetheless receive a priority review voucher if they request such a voucher in their original marketing application,[44] meet all of the eligibility criteria, and (under the law as applicable at the time of issuance of this draft guidance) the application is approved by September 30, 2020. The determination of whether the drug is for a "rare pediatric disease" will occur as described above, except the prevalence determination will be based on the prevalence at the time of NDA/BLA submission rather than the prevalence at the time of designation request.

We encourage sponsors who are interested in receiving a rare pediatric disease priority review voucher to notify FDA early of their interest (e.g., no later than a pre-NDA/BLA meeting). However, notification before submission of the rare pediatric disease product application is not required. The process for requesting a voucher at the time of NDA/BLA submission is described in Questions 14 and 15.

C. Requesting a Rare Pediatric Disease Priority Review Voucher

Q13. Do sponsors need to receive rare pediatric disease designation before requesting a priority review voucher?

In general, a sponsor does not need to receive rare pediatric disease designation for its drug in order to request a priority review voucher. However, under the law as applicable at the time of issuance of this draft guidance, FDA may not award a voucher after September 30, 2020, unless the application is for a drug that was designated as a drug for a rare pediatric disease by September 30, 2020 and the application is approved by September 30, 2022.

Q14. When should sponsors request a rare pediatric disease priority review voucher?

Whether or not sponsors have requested rare pediatric disease designation, sponsors seeking a rare pediatric priority review voucher must submit a voucher request in the original submission of the potential rare pediatric disease product application – either in the initial package sent or up until the point of NDA/BLA filing.[45] This voucher request should be prominently marked, "Rare Pediatric Disease Priority Review Voucher Request," and be included or referenced in a cover letter.

Q15. What information should sponsors include in a priority review voucher request?

[44] Section 529(b)(4)(A)(i).
[45] *Id*.

This request for a voucher should describe how the application meets the eligibility criteria in section 529(a)(4) of the FD&C Act (See Question 2). The sponsor should address how the application meets each of the criteria, even if FDA already designated the application as a rare pediatric disease product application at the designation stage.

Depending on whether the sponsor has already received rare pediatric disease designation for the drug, the contents of the voucher request should include the following to support that the drug is for the prevention or treatment of a rare pediatric disease:

Sponsors Who Have Received Rare Pediatric Disease Designation for the Drug: Sponsors who have received rare pediatric disease designation for the drug should include that designation letter with the voucher request and need not re-analyze prevalence estimates at the time of NDA/BLA submission.

Sponsors Who Have Requested but Not Received Rare Pediatric Disease Designation for the Drug: Sponsors who have requested but not received rare pediatric disease designation should include in a voucher request the latest designation correspondence from FDA (i.e., an acknowledgment letter, deficiency letter, denial letter, or voluntarily withdrawn letter). Note that under the law as applicable at the time of issuance of this draft guidance, if sponsor does not have rare pediatric disease designation for their drug by September 30, 2020, FDA may not award a voucher after September 30, 2020.

If the designation request has been denied or withdrawn, then the voucher request should include new prevalence estimates as of the time of NDA/BLA submission; otherwise, the sponsor can cross-reference the information in its designation request and provide additional information as necessary. In particular:

- Sponsors who have received only an *acknowledgment letter* in response to a designation request should cross-reference their designation request (with associated prevalence estimates).
- Sponsors who have received a *deficiency letter* should include a response to the deficiency letter with their voucher requests or else cross-reference a previously submitted deficiency response.
- Sponsors who have received *denial letters* should explain how their drug is for a "rare pediatric disease" despite this denial, based on new information about the drug or the disease/condition, and include new prevalence estimates as of the time of NDA/BLA submission (with supporting documentation described in Question 9 items (7)-(8)).
- Sponsors who have received *voluntarily withdrawn letters* should likewise include new prevalence estimates as of the time of NDA/BLA submission (with supporting documentation described in Question 9 items (7)-(8)).

Sponsors Who Have Not Requested Rare Pediatric Disease Designation: Sponsors who have not requested rare pediatric disease designation should include in a voucher request prevalence estimates as of the time of NDA/BLA submission, with supporting documentation

described in Question 9 items (7)-(8). Note that if a sponsor does not have rare pediatric disease designation for their drug, FDA may not award a voucher after September 30, 2020.

D. Using and Transferring a Rare Pediatric Disease Priority Review Voucher

Q16. What is a priority review?

The "priority review" awarded by the voucher is the same as the priority review referred to in the current PDUFA goals letter, which commits FDA to a goal of completing a certain percentage of priority reviews within the prescribed time frames. For example, in a PDUFA goals letter, FDA may commit to completing 90 percent of priority reviews within the prescribed time frames. FDA's current PDUFA goals letter is available on its website.[46] FDA intends to treat any human drug application for which a PRV is used as if it were any other priority review drug application under the goals letter.

Q17. What is a priority review voucher and when is it awarded?

Under section 529(a)(2) of the FD&C Act, a *priority review voucher* is a voucher that FDA issues to the sponsor of a rare pediatric disease product application at the time of the marketing application approval. This voucher entitles the holder to designate a single human drug application submitted under section 505(b)(1) of the FD&C Act[47] or section 351 of the PHS Act as qualifying for a priority review. Such a subsequent application would not have to meet the usual requirements for a priority review, but it would have to be submitted after the approval of the rare pediatric disease product application.

Q18. What form will the voucher take?

We will include information related to the priority review voucher in the approval letter for the rare pediatric disease product application. This letter will include a priority review voucher identification number, which should be referenced when redeeming or transferring the voucher.

Q19. How and when can a voucher be used?

The application using the priority review voucher must be submitted under section 505(b)(1) of the FD&C Act[48] or section 351 of the PHS Act and is not limited to drugs for rare pediatric diseases. The application using the voucher may be for a new indication of the same drug whose approval led to the award of the voucher. The sponsor redeeming the voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application (hereinafter "the intended submission date").[49] This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric

[46] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf.
[47] See footnote 9.
[48] See footnote 9.
[49] Section 529(b)(4)(B)(i).

Disease Priority Review Voucher." Upon submitting this notification to FDA, the sponsor is obligated to pay the priority review user fee described in the response to Question 22.[50]

The voucher cannot be used if the application is submitted before the intended submission date. If a sponsor does not submit the application on the intended submission date, the sponsor should inform FDA as soon as possible of the new intended submission date. If the sponsor decides not to use the voucher for the application described in the notification, the sponsor should withdraw the notification from FDA. The sponsor should submit a new notification informing FDA, at least 90 days before application submission, of its intent to submit a different human drug application with a priority review voucher and include the intended submission date.[51]

Q20. Will these vouchers be transferable?

Yes. The sponsor of a rare pediatric disease drug receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor.[52] The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application.[53]

Q21. What is the procedure for voucher transfer?

Each person to whom a voucher is transferred must notify FDA of the change of voucher ownership within 30 days after the transfer.[54] This notification should be prominently marked, "Transfer of Rare Pediatric Disease Priority Review Voucher" and submitted to the NDA/BLA. It should include a letter from the previous owner to the current owner and a letter from the current owner to the previous owner, each acknowledging the transfer. Any sponsor redeeming a voucher should include these transfer letters in the application submitted to FDA (in addition to notifying FDA of the intent to submit an application with a priority review voucher, as described in response to Question 19). A complete record of transfer must be made available to FDA in order to redeem a transferred voucher.[55]

Q22. What fees apply when using a priority review voucher?

The sponsor of a human drug application that is the subject of a priority review voucher must pay a priority review user fee in addition to any other required user fee.[56] The amount of the priority review user fee will be determined each fiscal year and is based on the difference between the average costs incurred by FDA, in the previous fiscal year, of reviewing a priority review NDA/BLA and an NDA/BLA that is not subject to priority review.[57] Payment of this

[50] *Id*.
[51] *Id*.
[52] Section 529(b)(2).
[53] Section 529(b)(4)(B)(ii).
[54] Section 529(b)(2)(B).
[55] *Id*. *See also* section 529(b)(4)(B).
[56] Section 529(c)(1).
[57] Section 529(c)(2).

extra fee, to which the sponsor is legally committed as a result of the notification of its intent to use the voucher, is not subject to waivers, exemptions, reductions, or refunds.[58]

FDA will establish the fee amount before the beginning of each fiscal year and will publish the fee schedule in the *Federal Register*.

Q23. When do I pay the priority review voucher user fee?

The priority review voucher user fee is due upon notifying FDA of the intent to submit an application with a priority review voucher, as described in the response to Question 19.[59] It is payable in accordance with procedures established by FDA, which will be described in the *Federal Register* notice that sets the fees for each fiscal year. The application will be considered incomplete if the priority review voucher user fee and all other applicable user fees are not paid in accordance with FDA payment procedures.[60]

Q24. If I present a voucher to FDA for priority review, am I guaranteed a 6-month review on my drug application?

Although FDA's goal is to take action on the application within 6 months after the 60-day filing period for an application involving a new molecular entity or within 6 months after the date of receipt of an application not involving a new molecular entity,[61] this timeframe is not guaranteed. Note that "take action" in this context means that FDA aims to complete its review of the filed application and issue an approval or complete response letter within this timeframe; it does not mean that the application will be approved within this timeframe.

E. Specific Eligibility Questions

Q25. Is eligibility for a priority review voucher affected by whether the sponsor intends to market the rare pediatric disease drug after approval?

The statute does not describe marketing of a rare pediatric disease drug as a prerequisite to receiving a priority review voucher. However, under section 529(e)(1), FDA may revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

Q26. Are drug-drug combinations eligible for priority review vouchers?

A drug-drug combination (also referred to as a fixed-combination drug) is eligible for a voucher if the product meets the criteria established in section 529(a)(4) of the FD&C Act. In general, an application for a fixed-combination drug submitted under section 505(b) of the FD&C Act will be eligible for a voucher if the product contains a *drug substance*, no active moiety of which has

[58] Section 529(c)(4)(C).
[59] Section 529(c)(4)(A).
[60] Section 529(c)(4)(B).
[61] See footnote 45.

been approved in any other application under section 505(b) of the FD&C Act.[62] For example, an application for a fixed-combination drug that contains a drug substance with a single, new active moiety may be eligible for a voucher, even if the fixed-combination also contained a drug substance with a previously approved active moiety.

Q27. Are drugs eligible for a priority review voucher if they have been approved and used in other countries but have not been previously approved by FDA?

Yes, as long as they meet all the criteria for a rare pediatric disease product application described in section 529(a)(4) (see section III.A.).

Q28. Is a drug that is already approved by FDA for another indication eligible for a priority review voucher for a rare pediatric disease product application?

No. As noted, for an application to qualify for a rare pediatric disease priority review voucher, it must be for a human drug that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act.[63]

Q29. Would a new pediatric formulation for a drug already approved for adults be eligible for a rare pediatric disease priority review voucher?

No. As noted, an application for a drug containing a previously approved active ingredient (including any ester or salt of the active ingredient) is not eligible to receive a rare pediatric disease priority review voucher.

Q30. Would an application for a rare pediatric disease drug submitted to FDA before enactment of PDUFA of 2012 (under FDASIA) but not yet approved qualify for a voucher?

No. The rare pediatric disease product sponsor may not receive a rare pediatric disease priority review voucher if the application was submitted to FDA prior to October 7, 2012 (90 days after the date of the enactment of PDUFA of 2012).[64]

[62] See section 529(a)(4)(A)(ii) of the FD&C Act. Because section 529(a)(4)(A)(ii) of the FD&C Act contains the same phrase ("no active ingredient (including any ester or salt of the active ingredient)" that has been previously approved) as is used in sections 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act, FDA will follow, for drugs approved under the FD&C Act, its guidance on exclusivity for combination drugs under those provisions. See the guidance for industry *New Chemical Entity Exclusivity Determinations for Certain Fixed-Drug Combination Drug Products* (2014). For biological products approved under the PHS Act, FDA will make decisions on eligibility under section 529(a)(4)(A)(ii) of the FD&C Act on a case-by-case basis.

[63] Section 529(a)(A)(ii).

[64] Section 529(b)(3).

F. Relationship between Rare Pediatric Disease Designation and Orphan-Drug Designation

Q31. Will a drug that receives rare pediatric disease designation also qualify for orphan-drug designation?

We anticipate that many rare pediatric disease drugs will qualify for designation as orphan drugs (if such designation is sought) because a "rare pediatric disease" also must be a "rare disease or condition" as defined in section 526, including those that affect fewer than 200,000 persons in the U.S.[65] There are instances, however, where a drug may qualify as a drug for a "rare pediatric disease" but not qualify for orphan-drug designation, or vice versa, as explained below. The following examples illustrate situations in which a drug might receive rare pediatric disease designation but not also immediately qualify for orphan drug designation:

- Assume that a drug receives "rare pediatric disease" designation but is considered the "same drug" under the orphan drug regulations as an already approved drug for the same orphan use. 21 CFR 316.3(b)(14). This drug would not be eligible to receive orphan-drug designation absent a plausible hypothesis that it may be clinically superior to the already approved drug. 21 CFR 316.20(a) and (b)(5). *Note:* Even though this drug may receive "rare pediatric disease" designation, the application for the drug may not qualify as an "application for a rare pediatric disease product application" – and hence not be likely to receive a priority review voucher – if it contains a previously approved active ingredient (including any ester or salt of the active ingredient).

- Assume a sponsor plans to develop a drug for a rare pediatric disease but so far has very little data suggesting that the drug may be effective in that disease (e.g., only in vitro data supporting the drug's mechanism of action in a related disease). It is possible that this level of data may suffice for rare pediatric disease designation but generally it would not suffice for orphan-drug designation. This is because, to qualify for orphan-drug designation, an applicant must supply sufficient information to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of the rare disease or condition.[66] The sponsor may eventually obtain orphan designation for the drug after developing or obtaining more supportive data for use of the drug for the rare disease or condition, including in vivo and/or clinical data in the rare disease or condition.

If a drug receives orphan-drug designation, it may be eligible for orphan-drug exclusivity, tax credits for qualified clinical testing, orphan product grant funding, as well as fee exemptions under section 736 of the FD&C Act. For information regarding these orphan drug incentives, please contact the OOPD at orphan@fda.hhs.gov or 301-796-8660. For information regarding user fee exemptions, please contact the User Fee staff in CDER's Office of Management at 301-796-7900.

[65] Section 529(a)(3)(B). *See also* section 526.

[66] See 21 CFR 316.25(a)(2).

G. Agency's Responsibilities and Roles

Q32. What are the Agency's responsibilities if it issues a priority review voucher under section 529 or if it approves a drug application for which the sponsor used such a voucher?

As per section 529(f)(1), FDA will publish a notice in the *Federal Register* and on its website[67] within 30 days after issuing a priority review voucher under section 529 and within 30 days after approving a drug application for which the sponsor used such a voucher.

Q33. What are the different roles played by CDER, CBER, OOPD, and OPT?

CDER and CBER

The applicable review divisions and offices within CDER and CBER have the responsibility for premarket review of the rare pediatric disease product applications and for determining whether an application meets the eligibility criteria for receiving a priority review voucher. CDER and CBER will consult with OOPD and OPT as to whether a disease/condition is a "rare pediatric disease" as defined in section 529(a)(3).

OOPD and OPT

OOPD and OPT, both within the Office of the Commissioner, are distinct from CDER and CBER and are responsible for determining whether a drug (including a biological product) qualifies for designation as a drug for a "rare pediatric disease" as defined in section 529(a)(3), if such designation is requested.

Specifically, OOPD determines if the drug is for a rare disease or condition within the meaning of Section 526. OPT determines if the drug is for a disease that is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years. OOPD and OPT will consult with CDER and CBER as appropriate.

OOPD is also responsible for granting orphan-drug designation to drugs (including biological products) under section 526 and 21 CFR part 316. As noted in Question 31, whether a drug receives orphan-drug designation is a different question from whether it receives designation as a drug for a "rare pediatric disease." Questions about the orphan designation program should be directed to OOPD.

In the event a sponsor does not request rare pediatric disease designation but does request a rare pediatric disease priority review voucher at the time of NDA/BLA submission, the review division or office within CDER and CBER will consult with OOPD and OPT, as appropriate, as to whether the disease/condition is a "rare pediatric disease" as defined in section 529(a)(3).

[67] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm375479.htm

875
876 **Q34. Whom should I contact if I have questions about a rare pediatric disease product**
877 **application?**
878
879 Sponsors with questions not addressed in this guidance should contact OOPD for questions
880 related to designation as a rare disease, OPT for questions related to designation as a rare
881 pediatric disease, and the appropriate review division or office within CDER or CBER for
882 questions related to rare pediatric disease product applications. CDER and CBER encourage
883 early interaction with potential sponsors on these issues (e.g., in a pre-IND meeting or early in
884 the clinical development program).