PEDIATRIC CANCER STATUES, REGULATIONS AND GUIDANCES

COMPENDIUM

KIDS V CANCER

JANUARY 2023

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RACE FOR CHILDREN ACT: AMENDMENTS TO SEC. 505B OF THE FD&C ACT

PEDIATRIC RESEARCH EQUITY ACT AS AMENDED BY THE RACE FOR CHILDREN ACT AUTHORIZES THE FDA TO REQUIRE A PEDIATRIC STUDY FOR ANY NEW DRUG OR BIOLOGIC APPLICATION FOR A DRUG IF ITS MOLECULAR TARGET IS RELEVANT TO PEDIATRIC CANCER.

US CODE

21 U.S.C. § 355c. Research into pediatric uses for drugs and biological products

(a) New drugs and biological products

(1) In general

(A) General requirements

Except with respect to an application for which subparagraph (B) applies, a person that submits, on or after September 27, 2007, an application (or supplement to an application) for a drug-

(i) under section 355 of this title for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration; or

(ii) under section 262 of title 42 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, shall submit with the application the assessments described in paragraph (2).

(B) Certain molecularly targeted cancer indications

A person that submits, on or after the date that is 3 years after August 18, 2017, an original application for a new active ingredient under section 355 of this title or section 262 of title 42, shall submit with the application reports on the investigation described in paragraph (3) if the drug or biological product that is the subject of the application is-

(i) intended for the treatment of an adult cancer; and

(ii) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.

(2) Assessments

(A) In general

The assessments referred to in paragraph (1)(A) shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate-

(i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and

(ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.

(B) Similar course of disease or similar effect of drug or biological product

(i) In general

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(ii) Extrapolation between age groups

A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

(iii) Information on extrapolation

A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 355 of this title or section 262 of title 42.

(3) Molecularly targeted pediatric cancer investigation

(A) In general

With respect to a drug or biological product described in paragraph (1)(B), the investigation described in this paragraph is a molecularly targeted pediatric cancer investigation, which shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.

(B) Extrapolation of data

Paragraph (2)(B) shall apply to investigations described in this paragraph to the same extent and in the same manner as paragraph (2)(B) applies with respect to the assessments required under paragraph (1)(A).

(C) Deferrals and waivers

Deferrals and waivers under paragraphs (4) and (5) shall apply to investigations described in this paragraph to the same extent and in the same manner as such deferrals and waivers apply with respect to the assessments under paragraph (2)(B).

(4) Deferral

(A) In general

On the initiative of the Secretary or at the request of the applicant, the Secretary may defer submission of some or all assessments required under paragraph (1)(A) or reports on the investigation required under paragraph (1)(B) until a specified date after approval of the drug or issuance of the license for a biological product if-

(i) the Secretary finds that-

(I) the drug or biological product is ready for approval for use in adults before pediatric studies are complete;

(II) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or

(III) there is another appropriate reason for deferral; and

(ii) the applicant submits to the Secretary-

(I) certification of the grounds for deferring the assessments or reports on the investigation;

(II) a pediatric study plan as described in subsection (e);

(III) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and

(IV) a timeline for the completion of such studies.

(B) Deferral extension
(i) In general

On the initiative of the Secretary or at the request of the applicant, the Secretary may grant an extension of a deferral approved under subparagraph (A) for submission of some or all assessments required under paragraph (1)(A) or reports on the investigation required under paragraph (1)(B) if-

(I) the Secretary determines that the conditions described in subclause (II) or (III) of subparagraph (A)(i) continue to be met; and

II) the applicant submits a new timeline under subparagraph (A)(ii)(IV) and any significant updates to the information required under subparagraph (A)(ii).

(ii) Timing and information

If the deferral extension under this subparagraph is requested by the applicant, the applicant shall submit the deferral extension request containing the information described in this subparagraph not less than 90 days prior to the date that the deferral would expire. The

Secretary shall respond to such request not later than 45 days after the receipt of such letter. If the Secretary grants such an extension, the specified date shall be the extended date. The sponsor of the required assessment under paragraph (1)(A) or reports on the investigation under paragraph (1)(B) shall not be issued a letter described in subsection (d) unless the specified or extended date of submission for such required studies has passed or if the request for an extension is pending. For a deferral that has expired prior to July 9, 2012, or that will expire prior to 270 days after July 9, 2012, a deferral extension shall be requested by an applicant not later than 180 days after July 9, 2012. The Secretary shall respond to any such request as soon as practicable, but not later than 1 year after July 9, 2012. Nothing in this clause shall prevent the Secretary from updating the status of a study or studies publicly if components of such study or studies are late or delayed.

(C) Annual review

(i) In general

On an annual basis following the approval of a deferral under subparagraph (A), the applicant shall submit to the Secretary the following information:

(I) Information detailing the progress made in conducting pediatric studies.

(II) If no progress has been made in conducting such studies, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time.

(III) Projected completion date for pediatric studies.

(IV) The reason or reasons why a deferral or deferral extension continues to be necessary.

(ii) Public availability

Not later than 90 days after the submission to the Secretary of the information submitted through the annual review under clause (i), the Secretary shall make available to the public in an easily accessible manner, including through the Internet Web site of the Food and Drug Administration-

(I) such information;

(II) the name of the applicant for the product subject to the assessment or investigation;

(III) the date on which the product was approved; and

(IV) the date of each deferral or deferral extension under this paragraph for the product.

(5) Waivers

(A) Full waiver

On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments or reports on the investigation for a drug or biological product under this subsection if the applicant certifies and the Secretary finds that-

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or

(iii) the drug or biological product-

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) is not likely to be used in a substantial number of pediatric patients.

(B) Partial waiver

On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments or reports on the investigation for a drug or biological product under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that-

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

(iii) the drug or biological product-

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(II) is not likely to be used by a substantial number of pediatric patients in that age group; or

(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(C) Pediatric formulation not possible

If a partial waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation. An applicant seeking such a partial waiver shall submit to the Secretary documentation detailing why a pediatric formulation cannot be developed and, if the waiver is granted, the applicant's submission shall promptly be made available to the public in an easily accessible manner, including through posting on the Web site of the Food and Drug Administration.

(D) Labeling requirement

If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

(b) Marketed drugs and biological products
(1) In general

The Secretary may (by order in the form of a letter) require the sponsor or holder of an approved application for a drug under section 355 of this title or the holder of a license for a biological product under section 262 of title 42 to submit by a specified date the assessments described in subsection (a)(2), if the Secretary finds that-

(A)(i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and

(ii) adequate pediatric labeling could confer a benefit on pediatric patients;

(B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; or

(C) the absence of adequate pediatric labeling could pose a risk to pediatric patients.

(2) Waivers
(A) Full waiver

At the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under this subsection if the applicant certifies and the Secretary finds that-

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed); or

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.

(B) Partial waiver

At the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that-

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

(iii)(I) the drug or biological product-

(aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(bb) is not likely to be used in a substantial number of pediatric patients in that age group; and

(II) the absence of adequate labeling could not pose significant risks to pediatric patients; or

(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(C) Pediatric formulation not possible

If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation. An applicant seeking either a full or partial waiver shall submit to the Secretary documentation detailing why a pediatric formulation cannot be developed and, if the waiver is granted, the applicant's submission shall promptly be made available to the public in an easily accessible manner, including through posting on the Web site of the Food and Drug Administration.

(D) Labeling requirement

If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

(3) Effect of subsection

Nothing in this subsection alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(c) Meaningful therapeutic benefit

For the purposes of paragraph (4)(A)(iii)(I) and (4)(B)(iii)(I) of subsection (a) and paragraphs (1)(B) and (2)(B)(iii)(I)(aa) of subsection (b), a drug or biological product shall be considered to represent a meaningful therapeutic benefit over existing therapies if the Secretary determines that-

(1) if approved, the drug or biological product could represent an improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or

(2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options.

(d) Submission of assessments and reports on the investigation

If a person fails to submit a required assessment described in subsection (a)(2) or the investigation described in subsection (a)(3), fails to meet the applicable requirements in subsection (a)(4), or fails to submit a request for approval of a pediatric formulation described in subsection (a) or (b), in accordance with applicable provisions of subsections (a) and (b), the following shall apply:

(1) Beginning 270 days after July 9, 2012, the Secretary shall issue a non-compliance letter to such person informing them of such failure to submit or meet the requirements of the applicable subsection. Such letter shall require the person to respond in writing within 45 calendar days of issuance of such letter. Such response may include the person's request for a deferral extension if applicable. Such letter and the person's written response to such letter shall be made publicly available on the Internet Web site of the Food and Drug Administration 60 calendar days after issuance, with redactions for any trade secrets and confidential commercial information. If the Secretary determines that the letter was issued in error, the requirements of this paragraph shall not apply. The Secretary shall inform the Pediatric Advisory Committee of letters issued under this paragraph and responses to such letters.

(2) The drug or biological product that is the subject of an assessment described in subsection (a)(2) or the investigation described in subsection (a)(3), applicable requirements in subsection (a)(4), or request for approval of a pediatric formulation, may be considered misbranded solely because of that failure and subject to relevant enforcement action (except that the drug or biological product shall not be subject to action under section 333 of this title), but such failure shall not be the basis for a proceeding-

(A) to withdraw approval for a drug under section 355(e) of this title; or

(B) to revoke the license for a biological product under section 262 of title 42.

(e) Pediatric study plans

(1) In general

An applicant subject to subsection (a) shall submit to the Secretary an initial pediatric study plan prior to the submission of the assessments described under subsection (a)(2) or the investigation described in subsection (a)(3).

(2) Timing; content; meetings

(A) Timing

An applicant shall submit the initial pediatric study plan under paragraph (1)-

(i) before the date on which the applicant submits the assessments under subsection (a)(2) or the investigation described in subsection (a)(3); and

(ii) not later than-

(I) 60 calendar days after the date of the end-of-Phase 2 meeting (as such term is used in section 312.47 of title 21, Code of Federal Regulations, or successor regulations); or

(II) such other time as may be agreed upon between the Secretary and the applicant.

Nothing in this section shall preclude the Secretary from accepting the submission of an initial pediatric study plan earlier than the date otherwise applicable under this subparagraph.

(B) Content of initial pediatric study plan

The initial pediatric study plan shall include-

(i) an outline of the pediatric study or studies that the applicant plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach);

(ii) any request for a deferral, partial waiver, or waiver under this section, if applicable, along with any supporting information; and

(iii) other information specified in the regulations promulgated under paragraph (7).

(C) Meetings

The Secretary-

(i) shall meet with the applicant-

(I) if requested by the applicant with respect to a drug or biological product that is intended to treat a serious or life-threatening disease or condition, to discuss preparation of the initial pediatric study plan, not later than the end-of-Phase 1 meeting (as such term is used in section 312.82(b) of title 21, Code of Federal Regulations, or successor regulations) or within 30 calendar days of receipt of such request, whichever is later;

(II) to discuss the initial pediatric study plan as soon as practicable, but not later than 90 calendar days after the receipt of such plan under subparagraph (A); and

(III) to discuss the bases for the deferral under subsection (a)(4) or a full or partial waiver under subsection (a)(5);

(ii) may determine that a written response to the initial pediatric study plan is sufficient to communicate comments on the initial pediatric study plan, and that no meeting under clause (i)(II) is necessary; and

(iii) if the Secretary determines that no meeting under clause (i)(II) is necessary, shall so notify the applicant and provide written comments of the Secretary as soon as practicable, but not later than 90 calendar days after the receipt of the initial pediatric study plan.

(3) Agreed initial pediatric study plan

Not later than 90 calendar days following the meeting under paragraph (2)(C)(i)(II) or the receipt of a written response from the Secretary under paragraph (2)(C)(iii), the applicant shall document agreement on the initial pediatric study plan in a submission to the Secretary marked "Agreed Initial Pediatric Study Plan", and the Secretary shall confirm such agreement to the applicant in writing not later than 30 calendar days of receipt of such agreed initial pediatric study plan.

(4) Deferral and waiver

If the agreed initial pediatric study plan contains a request from the applicant for a deferral, partial waiver, or waiver under this section, the written confirmation under paragraph (3) shall include a recommendation from the Secretary as to whether such request meets the standards under paragraphs (3) or (4) of subsection (a).

(5) Amendments to the agreed initial pediatric study plan

At the initiative of the Secretary or the applicant, the agreed initial pediatric study plan may be amended at any time. The requirements of paragraph (2)(C) shall apply to any such proposed amendment in the same manner and to the same extent as such requirements apply

to an initial pediatric study plan under paragraph (1). The requirements of paragraphs (3) and (4) shall apply to any agreement resulting from such proposed amendment in the same manner and to the same extent as such requirements apply to an agreed initial pediatric study plan.

(6) Internal committee

The Secretary shall consult the internal committee under section 355d of this title on the review of the initial pediatric study plan, agreed initial pediatric study plan, and any significant amendments to such plans.

(7) Required rulemaking

Not later than 1 year after July 9, 2012, the Secretary shall promulgate proposed regulations and issue guidance to implement the provisions of this subsection.

(f) Review of pediatric study plans, assessments, deferrals, deferral extensions, and waivers

(1) Review

Beginning not later than 30 days after September 27, 2007, the Secretary shall utilize the internal committee established under section 355d of this title to provide consultation to reviewing divisions on initial pediatric study plans, agreed initial pediatric study plans, and any significant amendments to such plans, and assessments prior to approval of an application or supplement for which a pediatric assessment is required under this section and all deferral, deferral extension, and waiver requests granted pursuant to this section.

(2) Activity by committee

The committee referred to in paragraph (1) may operate using appropriate members of such committee and need not convene all members of the committee.

(3) Documentation of committee action

For each drug or biological product, the committee referred to in paragraph (1) shall document, for each activity described in paragraph (4) or (5), which members of the committee participated in such activity.

(4) Review of pediatric study plans, assessments, deferrals, deferral extensions, and waivers

Consultation on initial pediatric study plans, agreed initial pediatric study plans, and assessments by the committee referred to in paragraph (1) pursuant to this section shall occur prior to approval of an application or supplement for which a pediatric assessment is required under this section. The committee shall review all requests for deferrals, deferral extensions,

and waivers from the requirement to submit a pediatric assessment granted under this section and shall provide recommendations as needed to reviewing divisions, including with respect to whether such a supplement, when submitted, shall be considered for priority review.

(5) Retrospective review of pediatric assessments, deferrals, and waivers

Not later than 1 year after September 27, 2007, the committee referred to in paragraph (1) shall conduct a retrospective review and analysis of a representative sample of assessments submitted and deferrals and waivers approved under this section since December 3, 2003. Such review shall include an analysis of the quality and consistency of pediatric information in pediatric assessments and the appropriateness of waivers and deferrals granted. Based on such review, the Secretary shall issue recommendations to the review divisions for improvements and initiate guidance to industry related to the scope of pediatric studies required under this section.

(6) Tracking of assessments and labeling changes

The Secretary, in consultation with the committee referred to in paragraph (1), shall track and make available to the public in an easily accessible manner, including through posting on the Web site of the Food and Drug Administration-

(A) the number of assessments conducted under this section;

(B) the specific drugs and biological products and their uses assessed under this section;

(C) the types of assessments conducted under this section, including trial design, the number of pediatric patients studied, and the number of centers and countries involved;

(D) aggregated on an annual basis-

(i) the total number of deferrals and deferral extensions requested and granted under this section and, if granted, the reasons for each such deferral or deferral extension;

(ii) the timeline for completion of the assessments;

(iii) the number of assessments completed and pending; and

(iv) the number of postmarket non-compliance letters issued pursuant to subsection (d), and the recipients of such letters;

(E) the number of waivers requested and granted under this section and, if granted, the reasons for the waivers;

(F) the number of pediatric formulations developed and the number of pediatric formulations not developed and the reasons any such formulation was not developed;

(G) the labeling changes made as a result of assessments conducted under this section;

(H) an annual summary of labeling changes made as a result of assessments conducted under this section for distribution pursuant to subsection (h)(2);

(I) an annual summary of information submitted pursuant to subsection (a)(3)(B); and

(J) the number of times the committee referred to in paragraph (1) made a recommendation to the Secretary under paragraph (4) regarding priority review, the number of times the Secretary followed or did not follow such a recommendation, and, if not followed, the reasons why such a recommendation was not followed.

(g) Labeling changes

(1) Dispute resolution

(A) Request for labeling change and failure to agree

If, on or after September 27, 2007, the Commissioner determines that a sponsor and the Commissioner have been unable to reach agreement on appropriate changes to the labeling for the drug that is the subject of the application or supplement, not later than 180 days after the date of the submission of the application or supplement that receives a priority review or 330 days after the date of the submission of an application or supplement that receives a standard review-

(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

(ii) if the sponsor does not agree within 30 days after the Commissioner's request to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Committee.

(B) Action by the Pediatric Advisory Committee

Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Committee shall-

(i) review the pediatric study reports; and

(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

(C) Consideration of recommendations

The Commissioner shall consider the recommendations of the Pediatric Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application or supplement to make any labeling changes that the Commissioner determines to be appropriate.

(D) Misbranding

If the sponsor of the application or supplement, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application or supplement to be misbranded.

(E) No effect on authority

Nothing in this subsection limits the authority of the United States to bring an enforcement action under this chapter when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

(2) Other labeling changes

If, on or after September 27, 2007, the Secretary makes a determination that a pediatric assessment conducted under this section does or does not demonstrate that the drug that is the subject of such assessment is safe and effective in pediatric populations or subpopulations, including whether such assessment results are inconclusive, the Secretary shall order the labeling of such product to include information about the results of the assessment and a statement of the Secretary's determination.

(h) Dissemination of pediatric information
(1) In general

Not later than 210 days after the date of submission of an application (or supplement to an application) that contains a pediatric assessment under this section, if the application (or supplement) receives a priority review, or not later than 330 days after the date of submission of an application (or supplement to an application) that contains a pediatric assessment under this section, if the application (or supplement) receives a standard review, the Secretary shall make available to the public in an easily accessible manner the medical, statistical, and clinical pharmacology reviews of such pediatric assessments, and shall post such assessments on the Web site of the Food and Drug Administration.

(2) Dissemination of information regarding labeling changes

Beginning on September 27, 2007, the Secretary shall require that the sponsors of the assessments that result in labeling changes that are reflected in the annual summary

developed pursuant to subsection (f)(6)(H) distribute such information to physicians and other health care providers.

(3) Effect of subsection

Nothing in this subsection shall alter or amend section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(i) Adverse event reporting
(1) Reporting in first 18-month period

Beginning on September 27, 2007, during the 18-month period beginning on the date a labeling change is made pursuant to subsection (g), the Secretary shall ensure that all adverse event reports that have been received for such drug (regardless of when such report was received) are referred to the Office of Pediatric Therapeutics. In considering such reports, the Director of such Office shall provide for the review of such reports by the Pediatric Advisory Committee, including obtaining any recommendations of such committee regarding whether the Secretary should take action under this chapter in response to such reports.

(2) Reporting in subsequent periods

Following the 18-month period described in paragraph (1), the Secretary shall, as appropriate, refer to the Office of Pediatric Therapeutics all pediatric adverse event reports for a drug for which a pediatric study was conducted under this section. In considering such reports, the Director of such Office may provide for the review of such reports by the Pediatric Advisory Committee, including obtaining any recommendation of such Committee regarding whether the Secretary should take action in response to such reports.

(3) Preservation of authority

Nothing in this subsection shall prohibit the Office of Pediatric Therapeutics from providing for the review of adverse event reports by the Pediatric Advisory Committee prior to the 18-month period referred to in paragraph (1), if such review is necessary to ensure safe use of a drug in a pediatric population.

(4) Effect

The requirements of this subsection shall supplement, not supplant, other review of such adverse event reports by the Secretary.

(j) Scope of authority

Nothing in this section provides to the Secretary any authority to require a pediatric assessment of any drug or biological product, or any assessment regarding other populations or uses of a drug or biological product, other than the pediatric assessments described in this section.

(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 360bb of this title.

(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 designation under 360bb [1] of this title if the investigation described in subsection (a)(3) applies to the drug or biological product as described in subsection (a)(1)(B).

(l) New active ingredient
(1) Non-interchangeable biosimilar biological product

A biological product that is biosimilar to a reference product under section 262 of title 42, and that the Secretary has not determined to meet the standards described in subsection (k)(4) of such section for interchangeability with the reference product, shall be considered to have a new active ingredient under this section.

(2) Interchangeable biosimilar biological product

A biological product that is interchangeable with a reference product under section 262 of title 42 shall not be considered to have a new active ingredient under this section.

(m) List of primary molecular targets

(1) In general

Within one year of August 18, 2017, the Secretary shall establish and update regularly, and shall publish on the internet website of the Food and Drug Administration-

(A) a list of molecular targets considered, on the basis of data the Secretary determines to be adequate, to be substantially relevant to the growth and progression of a pediatric cancer, and that may trigger the requirements under this section; and

(B) a list of molecular targets of new cancer drugs and biological products in development for which pediatric cancer study requirements under this section will be automatically waived.

(2) Consultation

In establishing the lists described in paragraph (1), the Secretary shall consult the National Cancer Institute, members of the internal committee under section 355d of this title, and the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, and shall take into account comments from the meeting under subsection (c).

(3) Rule of construction

Nothing in paragraph (1) shall be construed-

(A) to require the inclusion of a molecular target on the list published under such paragraph as a condition for triggering the requirements under subsection (a)(1)(B) with respect to a drug or biological product directed at such molecular target; or

(B) to authorize the disclosure of confidential commercial information, as prohibited under section 331(j) of this title or section 1905 of title 18.

(June 25, 1938, ch. 675, §505B, as added Pub. L. 108–155, §2(a), Dec. 3, 2003, 117 Stat. 1936 ; amended Pub. L. 110–85, title IV, §402(a), Sept. 27, 2007, 121 Stat. 866 ; Pub. L. 111–148, title VII, §7002(d)(2), Mar. 23, 2010, 124 Stat. 816 ; Pub. L. 112–144, title V, §§501(b), 505–506(b), 509(b), July 9, 2012, 126 Stat. 1040–1044 , 1048; Pub. L. 114–255, div. A, title III, §§3101(a)(2)(D), 3102(3), Dec. 13, 2016, 130 Stat. 1153 , 1156; Pub. L. 115–52, title V, §§503–504(b), 505(e), Aug. 18, 2017, 131 Stat. 1038–1041 , 1047.)

REGULATIONS

21 C.F.R. Part 601—assessments, deferrals, waivers, post market studies

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§601.27 Pediatric studies.
§601.28 Annual reports of postmarketing pediatric studies.

§ 601.27 Pediatric studies.

(a) ***Required assessment.*** Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) ***Deferred submission.***

(1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) ***Waivers*** -

(1) ***General.*** FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) ***Full waiver.*** An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) ***Partial waiver.*** An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) ***FDA action on waiver.*** FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) ***Definition of "meaningful therapeutic benefit".*** For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) ***Exemption for orphan drugs.*** This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

§ 601.28 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of each product under the license to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(a) or (b) of this chapter):

(a) ***Summary.*** A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) ***Clinical data.*** Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) ***Status reports.*** A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and, if so, the status of these studies shall be reported to FDA in annual progress reports of postmarketing studies under § 601.70 rather than under this section.

[65 FR 59718, Oct. 6, 2000, as amended at 65 FR 64618, Oct. 30, 2000; 70 FR 14984, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

GUIDANCES

FDA GUIDANCE FOR INDUSTRY: How to Comply with the Pediatric Research Equity Act (September 2005)

Guidance for Industry

How to Comply with the Pediatric Research Equity Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Grace Carmouze, 301-594-7337 or Leonard Wilson, 301-827-0373.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 2005
Procedural

How to Comply with the Pediatric Research Equity Act

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U.S. Department of Health and Human Services
Food and Drug Administration
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GUIDANCE FOR INDUSTRY[1]

How to Comply with the Pediatric Research Equity Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA). PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21 U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products.[2] Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances (see section 505B(b) of the Act).

This guidance has been prepared by the PREA Working Group at the Food and Drug Administration (FDA).

For purposes of this guidance, references to "drugs" and "drug and biological products" includes drugs approved under section 505 of the Act (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

Paperwork Reduction Act Public Burden Statement: According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The draft guidance contains information collections approved in OMB Nos. 0910-0001 (expires May 31, 2008) and 1910-0433 (expires March 31, 2007). In addition, the time required to complete this information collection is estimated to average from 8 to 50 hours per response, including the time to prepare and submit an application containing required studies or request a waiver from such studies.

Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under section 505B(a) of the Act. Issues under section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance.

This guidance addresses the pediatric assessment,[1] the pediatric plan (see section V.A), waivers and deferrals, compliance issues, and pediatric exclusivity provisions.

FDA's guidance documents, including this guidance, 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

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of the Pediatric Rule, a final rule issued by FDA on December 2, 1998 (63 FR 66632), and suspended by court order on October 17, 2002.[2]

Under the Pediatric Rule, approval actions taken or applications submitted on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. The Pediatric Rule was designed to work in conjunction with the *pediatric exclusivity* provisions of section 505A of the Act (21 U.S.C. 355a), an incentive signed into law to encourage sponsors or holders of approved applications to voluntarily perform the pediatric studies described in a Written Request[3] issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

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[1] For purposes of this guidance, the term "pediatric assessment" describes the required submissions under PREA that contain data, primarily from required pediatric clinical studies, that are adequate to assess safety and effectiveness and support dosing and administration for claimed indications in all relevant pediatric populations (section 505B(a)(1) and (2) of the Act). Generally, the terms "pediatric assessment" and "pediatric studies" are used interchangeably.

[2] The Pediatric Rule was codified at 21 CFR 314.55 and 601.27, with additional amendments to 21 CFR 201, 312, 314, and 601.

[3] FDA issues Written Requests for pediatric studies under 21 U.S.C. 355a.

On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily. On April 24, 2002, FDA issued an advance notice of proposed rulemaking (ANPRM) soliciting comments on the most appropriate ways to update the Pediatric Rule in a manner consistent with other mechanisms for obtaining studies created by the BPCA.

On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement **(**Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D. D.C. 2002)). When the Court enjoined FDA from enforcing the Pediatric Rule in October 2002, the ANPRM was also rendered obsolete.

As noted above, PREA codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule's suspension.

III. OVERVIEW — REQUIREMENTS OF PREA

A. PREA Statutory Requirements

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). It also authorizes FDA to require holders of approved NDAs and BLAs for marketed drugs and biological products to conduct pediatric studies under certain circumstances (section 505B(b) of the Act).

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

B. Scope of Requirements

Applications Affected by PREA

Because section 4(b) of PREA makes the legislation retroactive, all approved applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration submitted on or after April 1, 1999 (including those approved when the Pediatric Rule was suspended), are subject to PREA. Under PREA, holders of such approved applications that did not previously include pediatric assessments, waivers, or deferrals must submit their pediatric assessments or requests for waiver or deferral (section 4(b)(2)(B) of PREA). If a waiver request is denied and/or studies are deferred, FDA will require the applicable studies as postmarketing studies. (For additional information on applicable deferral dates, see section IV.B and Attachment C.)

Orphan Drugs

PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526."[4] FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

Generic Drugs Under 505(j) of the Act (21 U.S.C. 355(j))

Because PREA applies only to applications (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and because an abbreviated new drug application (ANDA) submitted under section 505(j) of the Act for a duplicate version of a previously approved drug product does not involve such changes, PREA does not impose pediatric assessment requirements on ANDAs for generic drugs. However, ANDAs submitted under an approved suitability petition under section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. If clinical studies are required under PREA for a product submitted under an approved suitability petition and a waiver is not granted, that application is no longer eligible for approval under an ANDA.

Because PREA is retroactive, all approved and pending ANDAs submitted on or after April 1, 1999 (when the Pediatric Rule became effective) and prior to December 3, 2003 (when PREA was enacted) under suitability petitions for changes in dosage form, route of administration, or active ingredient in combination products are subject to PREA. Although some ANDAs submitted under suitability petitions after April 1, 1999, and prior to December 3, 2003, would not have been approved as ANDAs had PREA been in effect at the time of approval, PREA's retroactivity does not require FDA to revoke those previous approvals. Instead, as with NDAs and BLAs, holders of approved and pending ANDAs submitted under suitability petitions between April 1, 1999 and December 3, 2003, who have not already obtained waivers, must submit postapproval pediatric studies or a request for a waiver or deferral of the pediatric assessment requirement (section 505B(a)(2) of the Act). If a waiver request is denied for a product already submitted or approved in an ANDA based upon a suitability petition during this time frame, FDA will require the applicable studies as postmarketing studies.

IV. THE PEDIATRIC ASSESSMENT

A. What Is the Pediatric Assessment? (Section 505B(a)(2) of the Act)

Under PREA, the pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to:

[4] Section 526 is codified at 21 U.S.C. 360bb.

Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations

Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

B. When to Submit the Pediatric Assessment in Compliance with PREA

Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived. If a deferral has been granted, the pediatric assessment will be due on or before the date specified by the Agency (section 505B(a)(3) of the Act).

As noted above, PREA is retroactive and requires pediatric assessments for all applications submitted between April 1, 1999, and the present. To address potential gaps in pediatric information for applications approved between April 1, 1999, and the present resulting from, among other things, the suspension of the Pediatric Rule in October 2002, PREA provides for waivers or deferrals in cases where pediatric study requirements were never addressed and for extensions of certain deferrals issued previously under the Pediatric Rule (see Attachment C for a chart of deferral dates under PREA).

If an application previously was granted a waiver of pediatric studies under the Pediatric Rule, the waiver will continue to apply under PREA (section 4(b)(2)(A) of PREA).

C. What Types of Data Are Submitted as Part of the Pediatric Assessment?

The data submitted under PREA will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. PREA does not require applicants to conduct separate safety and effectiveness studies in pediatric patients in every case. PREA states:

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(Section 505B(a)(2)(B)(i) of the Act.)

If extrapolation from adult effectiveness data is inappropriate, adequate and wellcontrolled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.

PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (section 505B(a)(2)(B)(ii) of the Act). Whether or not pediatric studies in more than one age group are necessary depends on expected

therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant age groups.

Applicants should contact the appropriate review division to discuss the types of pediatric studies needed to complete their pediatric assessments.

V. THE PEDIATRIC PLAN AND SUBMISSIONS

A. When to Develop a Pediatric Plan

A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic.

Early consultation and discussions are particularly important for products intended for lifethreatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings. For products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase 1 meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval. In general, studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products because the urgency of the need for the products may justify early trials despite the relative lack of safety and effectiveness information.

For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting. Information to support any planned request for a waiver or deferral of pediatric studies also should be submitted as part of the background package for this meeting. The review division will provide its best judgment about (1) the pediatric assessment that will be required for the product, (2) whether its submission can be deferred, and (3) if deferred, the date studies will be due. In addition, if relevant, FDA encourages applicants to include a discussion of their intent to qualify for and the studies needed to earn pediatric exclusivity (see section VIII for a discussion of PREA and pediatric exclusivity).

When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records. Alternatively, a separate letter may be sent to the applicant conveying FDA's decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission generally will also be included in the meeting minutes or separate letter.

B. What Ages to Cover in a Pediatric Plan

PREA requires, unless waived or deferred, the submission of a pediatric assessment for certain applications for the claimed indications in all relevant pediatric populations. As discussed in section VI, PREA authorized FDA to waive assessments when: 1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and 2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act). Thus, PREA requires the pediatric assessment to evaluate safety and effectiveness for the claimed indication(s) for each age group in which the drug or biological product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number[5] of pediatric patients.

Under PREA, a drug or biological product is considered to represent a *meaningful therapeutic benefit* over existing therapies if FDA estimates that (1) "if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population," or (2) "the drug or biological product is in a class of products or for an indication for which there is a need for additional options" (section 505B(c) of the Act). Improvement over marketed products might be demonstrated by showing (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) enhancement of compliance; or (4) safety and effectiveness in a new subpopulation for which marketed products are not currently labeled.

The BPCA defines "pediatric studies" or "studies" to include studies in all "pediatric age groups (including neonates in appropriate cases)" in which a drug is anticipated to be used (section 505A(a) of the Act. For purposes of satisfying the requirements of PREA, the appropriate age ranges to be studied may vary, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients age "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)).

The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA if the drug represents an important advancement and use in these age groups for the approved indication is anticipated. However, it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when "necessary studies are impossible or highly impracticable," or when "there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in that age group" (section 505B(a)(4)(B)(i) and (ii) of the Act).

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[5] PREA does not define a "substantial number." In the past, FDA generally has considered 50,000 patients to be a substantial number of patients (see, for example, October 27, 1997, DHHS Public Meeting on FDA's Proposed Regulations to Increase Pediatric Use Information for Drugs and Biologics). The Agency, however, will take into consideration the nature and severity of the condition in determining whether a drug or biological product will be used in a substantial number of pediatric patients.

C. Must the Sponsor Develop a Pediatric Formulation?

PREA requires pediatric assessments to be gathered "using appropriate formulations for each age group for which the assessment is required" (section 505B(a)(2)(A) of the Act). Under PREA, applicants must submit requests for approval of the pediatric formulation used in their pediatric studies, and failure to submit such a request may render the product misbranded (section 505B(d) of the Act). FDA interprets the language "request for approval of a pediatric formulation" to mean that applicants must submit an application or supplemental application for any not previously approved formulation(s) used to conduct their pediatric studies. Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

PREA does, however, specifically authorize FDA to waive the requirement for pediatric studies in one or more age groups requiring a pediatric formulation if the applicant certifies and FDA finds that "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed" (section 505B(a)(4)(B)(iv) of the Act). This exception is limited to the pediatric groups requiring that formulation (section 505B(a)(4)(C). FDA believes that this partial waiver provision will generally apply to situations where the applicant can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation. In certain cases, the Agency may seek appropriate external expert opinion (e.g., from an advisory committee) to assess whether a waiver should be granted (see section VI.A and B for more detailed information on waivers).

D. When to Initiate Pediatric Studies

As discussed in section V.A, applicants may initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than might occur for less serious diseases. The medical need for these products may justify early pediatric trials despite a relative lack of safety and effectiveness data. In some cases, pediatric studies of a drug or biological product for a life-threatening disease may begin as early as phase 1 or phase 2, when the initial safety data in adults become available.

The Agency recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until after approval of the drug or biological product for use by adults — for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults after initial marketing.

The Agency recommends that for products with a narrow therapeutic index, the nature of the disease in the pediatric population to be studied and the context in which the drug will be used should factor into the decision on when to initiate the studies in the affected pediatric patient population. For example, studies for an oncology drug product with a narrow therapeutic index might be conducted in children with a life-threatening cancer at an earlier stage in the drug development process than studies for a new aminoglycoside antimicrobial used to treat acute pyelonephritis infections in children. In the latter case, there are several therapeutic options

available, so the investigational drug would likely be studied in children after the approval in adults for this condition.

E. What Information Must Be Submitted to FDA

Pediatric studies of drugs conducted under an investigational new drug application (IND) are subject to the rules governing INDs, including the content and format requirements of 21 CFR 312.23 and the IND safety and annual reporting requirements described in 21 CFR 312.32 and 312.33, respectively.

• When study reports are submitted as part of an application or supplement to an application, the content and format must meet the relevant general requirements for submission (see 21 CFR 314.50 for NDA requirements and 21 CFR 601.2 for BLA requirements).

VI. WAIVERS AND DEFERRALS

A. What Is a Waiver?

PREA authorizes FDA to waive the requirement to submit the pediatric assessment, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

B. How to Apply for a Waiver

1. Criteria for Full Waiver (Section 505B(a)(4)(A) of the Act)

On FDA's initiative or at the request of an applicant, FDA will grant a full waiver of the requirement to submit pediatric assessments if the applicant certifies and FDA finds one or more of the following:

Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).

Another example is a drug or biological product for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occur for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticality. For a list of adult-related conditions that may be candidates for a disease-specific waiver, see Attachment A, Sample Waiver Request Form.

There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

2. Criteria for Partial Waiver (Section 505B(a)(4)(B) of the Act)

On its own initiative or at the request of an applicant, FDA will grant a partial waiver of the requirement to submit pediatric assessments for a drug or biological product with respect to a specific pediatric age group, if the applicant certifies and FDA finds evidence of one or more of the following:

Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (section 505B(a)(4)(B)(i) of the Act).

There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

The applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed (section 505B(a)(4)(B)(iv) of the Act). If a waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation (section 505B(a)(4)(C) of the Act).

3. Information in a Waiver Request

As noted in section V, discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the drug development process. If an applicant believes a full or partial waiver of the pediatric studies requirement is warranted, FDA strongly encourages the applicant to request the waiver at the earliest appropriate time. This guidance includes a sample Waiver Request to assist applicants in providing sufficient information for FDA to determine whether to grant a waiver request (Attachment A). However, the information necessary to support any particular waiver will be determined on a case-by-case basis.

To request a waiver, we recommend an applicant provide:

Product name, applicant name, and indication
Age group(s) included in waiver request

Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority (i.e., one of 2(a)-(d) in Attachment A)
Evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements
Applicant Certification

4. Waiver Decision

The Agency will grant a waiver request if FDA determines that any of the criteria for a waiver enumerated in the statute have been met. As noted above, if a full or partial waiver is granted "because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, this information shall be included in the labeling for the drug or biological product" (section 505B(a)(4)(D) of the Act).

As discussed in section V, for waivers agreed to at the end-of-phase 2 meetings, the meeting minutes will document the waiver of pediatric assessment requirements. Full or partial waiver documentation (meeting minutes or a letter from FDA) should be submitted in the Clinical Data Section of the NDA or BLA and noted in Form FDA-356h under the "Pediatric Use" part of item 8, and also under item 20, "Other." Under "Other," the applicant should identify the location (volume and page number) of the waiver documentation in the NDA or BLA submission.

Decisions to waive the requirement for submission of pediatric assessments that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.

C. What Is a Deferral?

A deferral acknowledges that a pediatric assessment is required, but permits the applicant to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use (section 505B(a)(3) of the Act).

D. How to Apply for a Deferral

1. Criteria for Deferral (Section 505B(a)(3) of the Act)

FDA may defer the timing of submission of some or all required pediatric studies if it finds one or more of the following:

The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

Pediatric studies should be delayed until additional safety or effectiveness data have been collected (section 505B(a)(3)(A)(ii) of the Act).

OR

There is another appropriate reason for deferral (section 505B(a)(3)(A)(iii) of the Act) (e.g., development of a pediatric formulation is not complete).

In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (section 505B(a)(3)(B)(i)-(iii) of the Act).

Information in a Deferral Request

FDA has provided a sample Deferral Request checklist to assist applicants in providing sufficient information for FDA to determine whether to grant a deferral request (Attachment B). To request a deferral, we recommend an applicant provide:

Product name, applicant name, and indication
Age group(s) included in deferral request
Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred)
Reason(s) for requesting a deferral
Evidence justifying that the proposed product meets the criteria for deferral of the pediatric assessment requirement
Description of planned or ongoing studies
Evidence that planned or ongoing studies are proceeding
Projected date for the submission of the pediatric assessment (deferral date)
Applicant certification

Deferral Decision

The decision to defer and the deferral date will be determined on a case-by-case basis. Considerations used in determining whether and how long to defer submission of the pediatric assessment may include:

The need for the drug or biologic in pediatric patients
Availability of sufficient safety data to initiate pediatric trials
The nature and extent of pediatric data needed to support pediatric labeling
The existence of substantiated difficulties in enrolling patients
Evidence of technical problems in developing pediatric formulations

As discussed in section V.A, the meeting minutes or a separate letter will document the deferral of pediatric assessments agreed to at the end-of-phase 2 meetings. For a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. The pediatric assessments deferred under PREA are required postmarketing studies subject to the annual status

reporting and information disclosure provisions of 21 CFR 314.81(b)(2)(vii)(a) and (b) and 21 CFR 601.70.

VII. COMPLIANCE WITH PREA

If a pediatric assessment or a request for approval of a pediatric formulation is not submitted by an applicant in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action (section 505B(d)(1) of the Act). The failure to submit a pediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug under section 505(e) of the Act or the revocation of a license for a biological product under section 351 of the PHSA (section 505B(d)(2) of the Act). However, the Agency could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.[6]

VIII. PREA AND PEDIATRIC EXCLUSIVITY

It is the Agency's policy to offer applicants the opportunity to qualify for ***pediatric exclusivity*** under section 505A of the Act for studies required and conducted under PREA. Under that policy, however, FDA will not issue a Written Request for or grant pediatric exclusivity for studies that have been submitted to the Agency before the Written Request is issued. Therefore, an applicant seeking to qualify for pediatric exclusivity should obtain a Written Request for studies from FDA before submitting the pediatric studies to satisfy PREA. (Note that for marketed drugs and biological products, the Agency is required to issue a Written Request prior to requiring studies under PREA (section 505B(b)(3) of the Act)). To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for pediatric exclusivity under section 505A of the Act (see sections 505A(d) and 505A(h) of the Act).

In addition, there is a noteworthy distinction between the scope of the studies requested under the pediatric exclusivity provisions and what is required under PREA. For pediatric exclusivity under the Act, FDA's authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults (see section 505A(a), which refers only to "information relating to the use of a new drug in the pediatric population"). Under PREA, on the other hand, a pediatric assessment is required only on those indications included in the pending application (section 505B(a), which addresses "the safety and effectiveness of the drug or biological product for the claimed indications"). To learn more about eligibility for pediatric exclusivity, applicants should consult the guidance for industry entitled *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*[7] or should contact the relevant review division.

IX. ADDITIONAL INFORMATION

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[6] See section 302 of the Act (21 U.S.C. 332), Injunction Proceedings; section 304 of the Act (21 U.S.C. 334), Seizure.

[7] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

A. Additional Information Concerning PREA

General information about complying with PREA can be obtained from the Division of Pediatric Drug Development (DPDD), 301-594-7337 or 301-827-7777, e-mail pdit@cder.fda.gov. Additional pediatric information is available at http://www.fda.gov/cder/pediatric.

Specific information about the types of pediatric studies that must be conducted and requirements for submission of assessments for your drug product can be obtained from the appropriate review division.

B. Additional Information Concerning Pediatric Exclusivity

General information and the latest statistical information regarding pediatric exclusivity are located at http://www.fda.gov/cder/pediatric. You can also refer to the guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.

ATTACHMENT A — SAMPLE WAIVER REQUEST

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):
(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

Identify pediatric age group(s) included in your waiver request.

With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)-(d) listed below — choose all that apply):
(a) Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:

_____ Age-related macular degeneration _____ Basal cell and squamous cell cancer
_____ Alzheimer's disease _____ Breast cancer
_____ Amyotrophic lateral sclerosis _____ Colorectal cancer
_____ Arteriosclerosis _____ Endometrial cancer
_____ Infertility _____ Hairy cell cancer
_____ Menopause symptoms _____ Lung cancer (small cell and non-small cell)
_____ Osteoarthritis _____ Oropharynx cancers (squamous cell)
_____ Parkinson's disease _____ Ovarian cancer (non-germ cell)
_____ Pancreatic cancer
_____ Other (please state and justify) _____ Prostate cancer
_____ Renal cell cancer
_____ Uterine cancer

The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation and describe reasons for failure.

Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).

Applicant certification.

ATTACHMENT B — SAMPLE DEFERRAL REQUEST

Product name:
IND/NDA/BLA number (as applicable):

Applicant:
Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

What pediatric age group(s) are included in your deferral request?

Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):

Adult studies completed and ready for approval
Additional postmarketing safety data needed (describe)
Nature and extent of pediatric data needed (explain)
Evidence provided of technological problems with development of a pediatric formulation
Difficulty in enrolling pediatric patients (provide documentation) (f) Other (specify)

What pediatric age group(s) is/are not included in your deferral request?

Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):

Adequate pediatric labeling exists
Studies completed in the specified age group
Requesting a waiver
Currently conducting pediatric studies that will be submitted with application
Other (specify)

Has a pediatric plan been submitted to the Agency?
If so, provide date submitted.
If not, provide projected date pediatric plan is to be submitted.

Suggested deferred date for submission of studies.
ATTACHMENT C — COMPLIANCE DATES FOR APPLICATIONS SUBJECT TO PREA

Categories of Application	Expected Date of Compliance
Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted	Immediate unless FDA specifies later date

Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted	Deferral date + 411 days
Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred	Immediate unless later date is specified in deferral letter
Applications submitted after 12/3/03, studies were deferred	Date specified in deferral letter

The dates in the chart are relevant as follows:

4/1/99 The date the Pediatric Rule became effective
10/17/02 The date that implementation and enforcement of the Pediatric Rule was suspended by court order
12/3/03 The date that PREA was enacted

Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry (July 2020)

Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128 Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

July 2020
Procedural
Contains Nonbinding Recommendations

TABLE OF CONTENTS

Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry[8]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors regarding the submission of an initial pediatric study plan (iPSP) and any amendments to the iPSP. Specifically, this guidance provides the current thinking of the Food and Drug Administration (FDA) regarding implementation of the requirement for sponsors to submit an iPSP, described in section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance addresses the following:

Applications for which an iPSP is required
Timing of an iPSP submission
Content of an iPSP
Content and timing of a requested amendment to an agreed iPSP
A template that is recommend to be used for an iPSP submission[9]
This guidance does not contain a discussion of general requirements for development of drugs for pediatric use under the Pediatric Research Equity Act (PREA) or the Best Pharmaceuticals for Children Act (BPCA).[10]

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[8] This guidance has been prepared by the Pediatric Study Plan Working Group, composed of members from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of the Commissioner (OC) at the Food and Drug Administration.

[9] In addition to consulting guidance, a sponsor is encouraged to contact the specific CDER/CBER review division to discuss specific issues that arise during preparation of the iPSP.

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

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

Over the last 2 decades, the FDA has worked to address the problem of inadequate testing of drugs in pediatric populations and inadequate pediatric use information in drug labeling. In 1994, the FDA published a final rule that required manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support adding pediatric use information to the drug's labeling.[11] However, the 1994 rule did not impose a general requirement that manufacturers carry out studies when existing information was not sufficient to support adding pediatric use information. This initial attempt to encourage sponsors to submit pediatric studies and plans to sufficiently inform use of drugs in pediatric patients was not successful in achieving adequate labeling for most drugs regarding use in the pediatric subpopulation, and product labeling frequently failed to provide directions for safe and effective use in pediatric patients.

To address this continuing problem, the Food and Drug Administration Modernization Act of 1997[12] was signed into law and contained provisions that established incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists. Also, on December 2, 1998, the FDA published a regulation known as the pediatric rule.[13] This rule partially addressed the lack of pediatric use information by requiring manufacturers of certain new and marketed drugs to conduct studies to provide sufficient data and information to support directions for pediatric use for the claimed indications. This pediatric rule also stated that the FDA would provide sponsors with its best judgment on whether pediatric studies would be required and whether their submission would be deferred until after approval. This input was given by the FDA at the end-of-phase 1 meeting, for drugs for life-threatening diseases,[14] and at the end-of-phase 2 meeting, for other drugs.[15]

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[11] See "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling" (59 FR 64240, December 13, 1994).

[12] Public Law 105-115, 111 Stat. 2296 (Nov. 21, 1997).

[13] See "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (63 FR 66632, December 2, 1998).

[14] See 21 CFR 312.81(a).

[15] For additional information on end-of-phase 1 meetings and end-of-phase 2 meetings, see 21 CFR 312.47(b) and 312.82(b).

The pediatric rule also stated that sponsors should submit, at least 1 month in advance of the end-of-phase 2 meeting, certain background information, including a proposed timeline for protocol finalization, enrollment, completion, and data analysis, or, in the alternative, information to support a planned request for waiver or deferral. However, on October 17, 2002, the U.S. District Court for the District of Columbia held that the FDA had exceeded its statutory authority when issuing the pediatric rule and the court enjoined the rule's enforcement.[16]

Congress subsequently passed PREA, which was signed into law on December 3, 2003.[17] Many of the provisions described under the pediatric rule were adopted under PREA. Under PREA as originally enacted and under its reauthorization under the Food and Drug Administration Amendments Act of 2007,[18] a sponsor was not required to submit a proposed timeline and plan for the submission of pediatric studies during the investigational new drug application (IND) phase of drug development. Under the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, for the first time PREA[19] includes a provision that requires a sponsor planning to submit an application for a drug subject to PREA to submit an iPSP early in the development process.[20] The intent of the iPSP is for a sponsor to identify needed pediatric studies early in development and begin planning for these studies. Early dialogue with the FDA on a comprehensive pediatric development plan, including both required pediatric studies under PREA and potential pediatric uses under the BPCA, is intended to result in a more efficient pediatric drug development program. The timing and content of the submission of an iPSP are described below. The FD&C Act, as amended by FDASIA, requires the FDA to issue regulations and guidance to implement these and other provisions.[21]

The FDA Reauthorization Act of 2017 (FDARA), further updated PREA with respect to certain drugs intended for the treatment of an adult cancer and directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer, and for which an original marketing application is submitted on or after August 18, 2020.[22]

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[16] *Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

[17] Public Law 108-155, 117 Stat. 1936 (Dec. 3, 2003).

[18] Public Law 110-85, 121 Stat. 823 (Sept. 27, 2007).

[19] By convention, section 505B is often referred to as *PREA*, after the act that added that section to the FD&C Act. We follow that naming convention in this guidance.

[20] Public Law 112-144, 126 Stat. 993 (July 9, 2012).

[21] See section 505B(e)(7) of the FD&C Act; 21 U.S.C. 355c(e)(7).

[22] Public Law 115-52, 131 Stat. 1005 (Aug. 18, 2017). For additional information on FDA's implementation of these amendments to PREA and on the submission of iPSPs for oncology drugs in light of the amendments, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (December 2019) and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers* (January 2020). When finalized, these guidances will represent FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.

III. APPLICATIONS THAT REQUIRE SUBMISSION OF AN INITIAL PSP

A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP[23] unless the drug is for an indication for which orphan designation has been granted.[24] In addition, a sponsor who is planning to submit, on or after August 18, 2020, an original application for a new active ingredient that is subject to the molecularly targeted cancer drug provision of PREA (i.e., the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) is also required to submit an iPSP,[25] regardless of whether the drug is for an indication for which orphan designation has been granted.[26] By statute, a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a *new active ingredient* for purposes of PREA.[27]

The sponsor must submit an iPSP for any new application or supplement that is subject to PREA, regardless of whether the FDA has previously granted waivers or deferrals under PREA for the same drug.[28] Additionally, for drugs that are being developed specifically for use in pediatric populations, the sponsor should submit an iPSP.

IV. TIMELINES FOR AN INITIAL PSP SUBMISSION

A sponsor must submit an iPSP, if required under PREA, before the date on which the sponsor submits the required assessments or investigation and no later than either 60 calendar days after the date of the end-of-phase 2 meeting or such other time as agreed upon between FDA and the sponsor.[29] The FDA expects to agree to time frames other than those described in this guidance only if there are exceptional circumstances. In the absence of an end-of-phase 2 meeting, the sponsor should submit the iPSP as early as practicable but before the initiation of any phase 3

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[23] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

[24] See section 505B(k)(1) of the FD&C Act; 21 U.S.C. 355c(k)(1).

[25] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(B) of the FD&C Act; 21 U.S.C. 355c(a)(1)(B).

[26] See section 505B(k)(2) of the FD&C Act; 21 U.S.C. 355c(k)(2).

[27] See section 505B(l) of the FD&C Act; 21 U.S.C. 355c(l).

[28] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1).

[29] See section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c(e)(2)(A).

studies, or any combined phase 2 and phase 3 studies, of the drug that is the subject of the iPSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted or will be conducted but not under IND, the sponsor should submit the iPSP no later than 210 calendar days before it submits a marketing application or supplement. Sponsors should contact the appropriate component of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research if they believe exceptional circumstances exist.

The sponsor should submit the iPSP to the relevant drug's IND for review by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research as appropriate. In cases where the sponsor has no active IND for the drug but the sponsor expects to open the IND with an initial phase 3 study, the sponsor should submit the iPSP as a pre-IND submission. In this situation, the FDA encourages the sponsor to schedule a pre-IND meeting before submission of the iPSP, and such submission should precede initiation of any phase 3 studies or combined phase 2 and phase 3 studies. In cases where the drug development program includes the possibility of using expedited programs,[30] the FDA encourages the sponsor to have discussions about the pediatric development plans with the review division as early as possible.

After the sponsor submits an iPSP, the FDA has 90 days to review the iPSP and provide a written response to the iPSP, or meet with the sponsor to discuss the iPSP, as appropriate.[31] This review process includes consultation with FDA's internal Pediatric Review Committee (PeRC).[32] The sponsor then has a second 90-day period during which it may review FDA comments and initiate any needed negotiations to discuss the iPSP. By the end of this second 90-day review period, the sponsor must submit an agreed iPSP.[33] The FDA then has 30 days after receipt of the agreed iPSP to review and issue correspondence confirming agreement or issue correspondence stating disagreement.[34] If the FDA does not agree, the iPSP is considered a *non-agreed iPSP* (see section VIII., Non-Agreed Initial PSPs). The total length of time for review of an iPSP should not exceed 210 days. A sponsor should not submit a marketing application or supplement until the FDA confirms agreement on the iPSP.

V. CONTENT OF THE INITIAL PSP

The FD&C Act requires that an iPSP include "(i) an outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial

[30] For further information on expedited programs, see the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014).

[31] See section 505B(e)(2)(C)(i)(II) and (e)(2)(C)(ii) of the FD&C Act; 21 U.S.C. 355c(e)(2)(C)(i)(II) and (e)(2)(C)(ii).

[32] See section 505B(e)(6) of the FD&C Act; 21 U.S.C. 355c(e)(6).

[33] See section 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(3).

[34] See section 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(3).

waiver, or waiver . . . if applicable, along with any supporting information; and (iii) other information specified in the regulations" issued by the FDA.[35] This section of the guidance describes information that is required or recommended to be included in the iPSP submission. In certain situations, it may be premature to include a detailed outline of a planned pediatric study (or studies) because additional data are needed (e.g., efficacy, safety, potential endpoints). In such cases, the outline of the pediatric studies should include a brief explanation for the lack of more detailed information. The sponsor receives feedback at the time of the review of the iPSP on the planned request for waivers and/or deferrals. For example, the FDA feedback may indicate concurrence with the planned deferral and/or waiver or, if FDA does not concur, include recommendations for the sponsor on the timing of pediatric drug development and on whether to include pediatric data in the initial marketing application instead of obtaining a deferral. However, FDA does not make a formal decision about granting a waiver and/or deferral of required pediatric assessments, or reports on the molecularly targeted pediatric cancer investigation, until the time of the approval of the marketing application.

Appendix: Initial Pediatric Study Plan Template provides a template that we recommend sponsors complete for the iPSP submission.[36] The FDA acknowledges that the development program for a drug, including the design of the pediatric studies, may change as the sponsor collects new data from nonclinical studies, clinical trials, and/or other clinical development programs (e.g., data from drugs in the same or similar class). The iPSP should include a wellconstructed pediatric plan based upon current knowledge of the drug and disease epidemiology; sponsors can submit amendments to an agreed iPSP at any time,[37] including changes to the pediatric plan that need to be considered based on additional data described above (see also section VII., Content and Timing of Requested Amendment to an Initial PSP).

In addition, sponsors can include information in the iPSP (see section 2 in section V.B., Recommendations for the Content of Each Section of the iPSP) about plans for submission of a concurrent or future proposed pediatric study request (PPSR), as appropriate. However, the sponsor should submit the iPSP and PPSR as separate documents to facilitate the FDA's appropriate review and comment.

Although, as stated above, the FDA does not make a formal decision about granting a waiver and/or deferral of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation until approval of the marketing application, the FDA considers the information contained in an agreed iPSP when considering any requests for waiver and/or deferral at the time of the marketing application review.

A. Materially Incomplete iPSPs

Failure to include required information may result in an iPSP that the FDA considers *materially incomplete*. For example, if a sponsor fails to address all pediatric age groups and all indications

[35] See section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B).

[36] The template also is available at https://www.fda.gov/media/84944/download.

[37] See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

for which the drug is being developed that are subject to PREA, the FDA generally considers the iPSP to be materially incomplete.[38] Additionally, if a sponsor fails to provide justification for any planned waivers or deferrals, the FDA may consider the iPSP to be materially incomplete. If the iPSP is considered materially incomplete, the FDA intends to contact the sponsor, and the sponsor should submit a complete iPSP within 30 days to address the identified deficiencies. A new 210-day review period will start when the sponsor submits a complete iPSP.[39]

However, if the sponsor includes sufficient information for the FDA to evaluate the plan, even if the FDA disagrees with the proposed plan, the FDA in general considers the iPSP to be sufficient for initial review. For example, if a sponsor includes a plan to request a full waiver with a justification and the FDA disagrees with this plan, the FDA does not intend to consider such disagreement as grounds for a determination that the iPSP is materially incomplete.

B. Recommendations for the Contents of Each Section of the iPSP

This section provides specific recommendations for the content of each section of the iPSP.

TITLE PAGE

Sponsors should include relevant administrative information on the title page (e.g., drug name, IND number, indication or indications that apply) (see Appendix: Initial Pediatric Study Plan Template).

1. Overview of the Disease/Condition in the Pediatric Population

This section should briefly summarize (1 to 3 pages)[40] available information on the pathophysiology of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in the pediatric population, including neonates. The sponsor should also include available information on the incidence and prevalence of the disease in both the overall population and the pediatric population, including in specific age subgroups when appropriate. Additionally, the sponsor should discuss current understanding of and available evidence supporting any similarities and differences between the disease in adults and in the pediatric population.

2. Overview of the Drug or Biological Product

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[38] The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

[39] See sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(2)(C) and 355c(e)(3).

[40] The recommended page count for each section of the iPSP applies to the overall iPSP and not to the individual active ingredients in the case of a fixed-dose combination product.

This section should briefly summarize (1 to 3 pages) the proposed mechanism of action of the drug, the intended pediatric population that will be studied, and the indications that the sponsor is seeking. In considering the indications to include in an iPSP, the sponsor should consider any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults that may serve as the basis for a Written Request under section 505A of the FD&C Act (21 U.S.C. 355a). The FDA encourages sponsors to discuss the potential therapeutic benefits and/or fulfillment of therapeutic needs in the pediatric population, including neonates, beyond any indication(s) for which pediatric assessments will be required under PREA. Any changes to this discussion of the use of the drug, including any clinical studies that the sponsor may propose other than those required under PREA, will not require an amendment to an agreed iPSP. If a sponsor plans to submit a PPSR asking the FDA to issue a Written Request in the future, the sponsor should include that information in this section of the iPSP as appropriate.[41] Sponsors should submit a separate PPSR when seeking FDA review and comments on proposed pediatric studies that could be conducted under a pediatric Written Request, in addition to those required under PREA and included in the iPSP.

3. Overview of Planned Extrapolation to Specific Pediatric Populations

The iPSP should address whether extrapolation of effectiveness to pediatric populations is planned for the proposed product (1 to 3 pages). Extrapolation of effectiveness from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.[42] Extrapolation of effectiveness assumes that an appropriate pediatric dose can be established either through achieving a similar exposure in children as in adults or by using an appropriate pharmacodynamic or clinical endpoint to achieve the targeted effect.[43] Extrapolation of effectiveness from one pediatric age group to another pediatric age group also may be appropriate.[44] The sponsor should consider all age ranges of pediatric patients, including neonates, when applicable. The sponsor should provide justification for the extrapolation, including any available supporting data for all age groups for which the sponsor intends to extrapolate effectiveness. This justification should include supportive data from all available sources (e.g., sponsor data, published literature, expert panels, workshops). Extrapolation of effectiveness for other drugs in the same class, if previously accepted by the FDA, also may be considered supportive information.

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[41] For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.

[42] See section 505B(a)(2)(B)(i) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(i) and section 505B(a)(3)(B) of the FD&C Act; 21 U.S.C. 355c(a)(3)(B).

[43] For further discussion, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014) and the Pediatric Study Planning & Extrapolation Algorithm in its Appendix. When final, this guidance will represent the FDA's current thinking on this topic.

[44] See section 505B(a)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(ii) and section 505B(a)(3)(B) of the FD&C Act; 21 U.S.C. 355c(a)(3)(B).

In some cases, sponsors may include in the iPSP plans for studies to assess pediatric effectiveness because the ability to extrapolate effectiveness from adults to children is not known at the time of the iPSP submission. Subsequently, if information becomes available to support extrapolation to a pediatric population, the sponsor can then submit a proposed amendment to the agreed iPSP to address plans for extrapolation in the marketing application or supplement.

When determining whether the data are sufficient to support extrapolation of effectiveness, sponsors should include information in the iPSP on the similarities (and differences) between, for example, adults and children (or between one pediatric age group and another) in disease pathogenesis; criteria for disease definition; clinical classification; and measures of disease progression as well as pathophysiologic, histopathologic, and pathobiological characteristics of the disease. In addition, if appropriate, the sponsor should include discussion on similarity in exposure-response relationship for effectiveness between adults and pediatrics based on experience with drugs in the same class or other drugs approved for use in the same disease/disorder. Extrapolation of effectiveness from one pediatric age group to another, often from older to younger patients, and from one formulation to another should be discussed when applicable. The sponsor also should discuss use of modeling and simulation to optimize studies to support extrapolation, when applicable.

In certain circumstances, one may be able to leverage existing safety and dosing information in adults or other pediatric populations to draw inferences about the safety of the drug in one or more pediatric populations. For example, for a drug that is approved for another pediatric indication that has similar dosing as the new indication, it may be possible to use the existing safety data to support safety for the new indication (e.g., if the different disease populations likely have similar susceptibility to any potential adverse effects of the drug). For drugs that may have disparate pediatric and adult safety profiles, such as drugs that act in the central nervous system, the adult safety data may not be sufficient to support safety in the pediatric population.

4. Planned Request for Drug-Specific Waiver(s)

Under PREA, sponsors may request a waiver of pediatric assessments, or reports on the molecularly targeted pediatric cancer investigation, at the time of the submission of the new drug application (NDA), biologics license application (BLA), or supplement.[45] FDA does not formally grant or deny a request for a waiver in response to the iPSP. The FDA formally grants a waiver(s) when it issues an approval letter for an NDA, BLA, or supplement. PREA authorizes the FDA to grant a full waiver of required pediatric assessments or reports on the molecularly

[45] Under PREA, a pediatric assessment "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." Section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). A molecularly targeted pediatric cancer investigation "shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling." Section 505B(a)(3)(A) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A). For waiver requirements, see section 505B(a)(5) of the FD&C Act; 21 U.S.C. 355c(a)(5).

targeted pediatric cancer investigation if it finds that: (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); (2) there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups; or (3) the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.[46]

In addition, PREA authorizes the FDA to grant a partial (i.e., with respect to a specific pediatric age group) waiver of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation if it finds that: (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed); (2) there is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group; (3) the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.[47]

This section should discuss the plans to request a waiver (either full or partial) of the requirement to provide data from pediatric studies (1 to 3 pages). Because the information in this section will be relevant to formal requests for a full or partial waiver when the sponsor submits the NDA/BLA, the information in this section should be as complete as possible and updated as needed. The sponsor should provide justification with a summary of supporting data, for all age groups for which the waiver will be sought. This justification should include supportive data from all available sources (e.g., sponsor data, published literature, expert panels, workshops). Full or partial waivers previously granted for other drugs in the same class can be considered supportive information.

For indications that have extremely limited applicability to the pediatric population because the pathophysiology of the relevant disease occurs for the most part only in adults, the FDA generally does not intend to require sponsors to provide additional evidence that studies are impossible or highly impracticable.[48] The FDA anticipates that the partial waiver provision based on failure to produce a pediatric formulation may, for example, apply to situations where the sponsor can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation for a particular pediatric age group.

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[46] See section 505B(a)(5)(A) of the FD&C Act; 21 U.S.C. 355c(a)(5)(A).

[47] See section 505B(a)(5)(B) of the FD&C Act; 21 U.S.C. 355c(a)(5)(B); see also section 505B(a)(5)(C) of the FD&C Act; 21 U.S.C. 355c(a)(5)(C).

[48] The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

If, early in the preapproval development period (e.g., end-of-phase 1 or end-of-phase 2 meeting), the FDA agrees that a plan for a waiver is reasonable, such agreement would reflect the FDA's best judgment at that time. However, the FDA does not formally grant a waiver until it issues an approval letter for an NDA, BLA, or supplement. If, before approval of an application, the sponsor becomes aware of new or additional information that affects the plan for a waiver of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, the sponsor should submit at the earliest possible time an amended iPSP with an updated plan. If the FDA becomes aware of new information, it intends to notify the sponsor at the earliest possible time and request that the sponsor amend the iPSP to reflect the new information (see section VI., Relationship of Agreed Initial PSP to the Requirement to Submit a Pediatric Study Plan with an Application). Such a requested amendment could include a plan for deferral of pediatric studies if appropriate.

Sponsors submitting a plan for a full waiver of pediatric studies should complete only sections 1, 2, 4, and 12 of the iPSP template (see Appendix: Initial Pediatric Study Plan Template). For sponsors submitting a plan for a full waiver of pediatric studies, based on an indication that appears on the list of adult-related conditions that rarely or never occur in children,[49] the iPSP should be limited to a one-page plan that specifies that the drug product is intended for the treatment of such an adult-related condition. This one-page plan should also include a sentence that the sponsor plans to request a full waiver of pediatric studies.

If pediatric studies will be waived because evidence exists that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling.[50] Generally, this information would be included in the *Pediatric Use* subsection of labeling and also may be included in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections, depending on the seriousness of any safety concern that would be the grounds for waiver of pediatric studies.

5. Planned Request for Deferral(s) of Pediatric Studies

Under PREA, sponsors may request deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation at the time of the submission of the NDA, BLA, or supplement.[51] The FDA does not formally grant or deny a request for a deferral at the

[49] See Adult-Related Conditions That Qualify for a Waiver Because They Rarely or Never Occur in Pediatrics, available at https://www.fda.gov/media/101440/download. The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

[50] See section 505B(a)(5)(D) of the FD&C Act; 21 U.S.C. 355c(a)(5)(D).

[51] See section 505B(a)(4) of the FD&C Act; 21 U.S.C. 355c(a)(4). Under PREA, a pediatric assessment required under section 505B(a)(1)(A) of the FD&C Act "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the

time of iPSP review. Rather, the FDA formally grants a deferral when it issues an approval letter for an NDA, BLA, or supplement. It is important to include in the iPSP any plan to submit a request for a deferral for any study required under PREA that will not be submitted as part of a planned application (i.e., NDA, BLA, efficacy supplement). Because the sponsor must submit with the NDA/BLA an agreed iPSP when there are plans for requests for deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation,[52] the information in this section should be as complete as possible and updated as needed.

If new information, such as data from ongoing or planned studies, indicates that a criterion for a waiver (or partial waiver) is met, the sponsor can change planned requests for deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation in the iPSP to planned requests for waiver (or partial waiver). The sponsor should submit these changes as an amendment to an agreed or amended iPSP.

At the time of approval of an application, the FDA may grant a deferral of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation if it finds that: (1) the drug is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (3) there is another appropriate reason for deferral.[53] The planned request for a deferral should list the proposed deferred studies in the same order as they are presented in the table in section 6 of the iPSP.

The planned request for a deferral should include adequate justification and any currently available evidence supporting the justification for a deferral (1 to 2 pages). If the FDA agrees that a plan for a deferral is reasonable early in the preapproval development period (e.g., end-ofphase 1 or end-of-phase 2 meeting), such agreement would reflect the FDA's best judgment at that time.

If the sponsor becomes aware of new or additional information that affects the decision to plan for any deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, the sponsor should reconsider the agreed iPSP and should submit an amended iPSP at the earliest possible time. The FDA may also request that the sponsor amend the iPSP to

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drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." Section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). A molecularly targeted pediatric cancer investigation required under section 505B(a)(1)(B) of the FD&C Act "shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling." Section 505B(a)(3)(A) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A).

[52] See sections 505B(a)(1), 505B(a)(4)(A)(ii)(II), and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(1), 355c(a)(4)(A)(ii)(II), and 355c(e).

[53] See section 505B(a)(4)(A)(i) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(i). In addition, the sponsor must submit: (1) a certification of the grounds for deferring the assessments or reports on the molecularly targeted pediatric cancer investigation; (2) an iPSP; (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and (4) a timeline for the completion of the studies. See section 505B(a)(4)(A)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii).

reflect any new information (see section VI., Relationship of Agreed Initial PSP to the Requirement to Submit a Pediatric Study Plan with an Application).

6. Tabular Summary of Planned Nonclinical and Clinical Development

This section should include a summary in tabular form of all planned: (1) nonclinical development to be conducted in support of the proposed pediatric clinical trials (see also section 8); and (2) clinical pediatric development (categorized by age). The table should include a column to identify whether the sponsor plans to request a deferral of the study (i.e., the sponsor does not plan to submit the data until after FDA approves the application). The table should also include any age groups for which the sponsor plans to request waivers. An example table is included below. The table is provided as an example only. The specific studies planned for a specific drug (e.g., the type of studies, the age groups studied) may differ from those studies listed in the example table.

Case example: Drug X is a new drug under development in adults for disease Y. The sponsor is seeking a partial waiver of pediatric studies required under PREA for patients less than 2 years of age because necessary studies are impossible or highly impracticable. The rarity of the diagnosis in children less than 2 years of age is supported by literature data. The course of disease Y and the effects of drugs in this class are expected to be sufficiently similar in adults and pediatric patients. However, the similarity of the exposure-response relationship between the two populations is not known. Therefore, the sponsor is proposing to include adolescents 12 to less than 17 years of age in the adult trial and is not seeking a deferral request. In patients 2 to less than 12 years of age, the sponsor plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study followed by an efficacy/safety study. The sponsor is proposing stratification by body size in the phase 2 PK/PD study as age is not expected to be a significant covariate for PK or PD for the drug. The sponsor did not propose further stratification by age for the efficacy/safety study in patients 2 to less than 12 years of age. The following is an example table based on this case:

EXAMPLE TABLE: Table of Nonclinical and Clinical Development for Drug X

PLANNED NONCLINICAL DEVELOPMENT*			
Species	**Type of Study (If known, include duration)**	**Comments**	**Deferral Request Planned for the Study (Y/N)****
Rat (or appropriate animal species)	Toxicology study in juvenile animals ages x to xx	To support initiation of clinical studies in children ages x to xx	N
PLANNED PEDIATRIC CLINICAL DEVELOPMENT			
Pediatric PK or PK/PD Studies			
Age Group	**Type of Study (If known, include duration)**	**Comments**	**Deferral Request Planned for the Study (Y/N)**

2 to <12 years	Phase 2 PK/PD study	To determine appropriate dose based on an established PD endpoint	N
Clinical Effectiveness and Safety Evaluation			
Age Group	**Type of Study (If known, include duration)**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
0 to <1 month	Not applicable (plan to request waiver)	Studies are highly impracticable	
1 month to <2 years	Not applicable (plan to request waiver)	Studies are highly impracticable	
2 to <12 years	Efficacy/safety study (R, DB, PC)	Endpoints to be determined	Y
12 to <17 years	Efficacy/safety study (R, DB, PC)	Study to be submitted with initial NDA	N

* May not be applicable for all drugs.
** See section 11 of the Initial Pediatric Study Plan Template.
 PK = pharmacokinetic; PD = pharmacodynamic; R = randomized; DB = double-blind; PC = placebo-controlled

Note: A table generated for a specific drug may not be the same as the sample case above and should be based on the planned studies needed for the drug.

7. Age-Appropriate Formulation Development

If the current formulation is not suitable for all pediatric age groups, sponsors should provide specific plans for the development of an age-appropriate formulation for all pediatric age groups that will be studied. In this section (1 to 3 pages), sponsors should include information regarding planned excipients, to the extent practicable, which will be contained in any pediatric formulation being developed. Sponsors also should provide details of measures taken to ensure appropriate design of a drug formulation, including, to the extent practicable, the design of delivery systems (e.g., capsules, tablets, infusions, devices) to be used in pediatric studies.[54]

8. Nonclinical Studies

[54] For more on considerations for age-appropriate formulations, see the 2014 European Medicines Agency Guideline on Pharmaceutical Development of Medicines for Pediatric Use, available at https://www.ema.europa.eu/en/humanregulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-formulations.

This section should provide a brief summary (1 to 3 pages) of the data from relevant nonclinical studies that support the use of the drug in all pediatric age groups the sponsor will study in the proposed clinical trials. The sponsor should include information that supports the maximum dose and duration of treatment to be used in pediatric studies. If the sponsor has determined that the nonclinical data are sufficient to support the proposed clinical trials and additional nonclinical studies are **not** planned, this summary should include such a statement and justification for this conclusion. If a sponsor plans to conduct a juvenile animal study, we recommend sponsors contact the review division for feedback before initiating this study.

If the existing nonclinical data are not sufficient to support the proposed clinical trials,[55] sponsors should provide a brief description for each of the nonclinical studies they will conduct, including, at a minimum the following:

The species to be studied

The age of animals at the start of dosing

The duration of dosing

The route of administration

The target organ systems of concern with key developmental endpoints to be evaluated, as appropriate

For further information see other guidances, as appropriate.[56]

Sponsors should also list the planned nonclinical studies in the table in section 6 and note (as described in section 11) the timeline for conduct of any such studies.

9. Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients

This section should provide a brief summary (1 to 5 pages) of any clinical data that support the design or initiation of pediatric studies. This section also should include a summary of available data in adult or pediatric patients who have received treatment with the drug (or related drugs) for the proposed indication, for other conditions, or in earlier studies. This section is intended to provide an overview of information already available to support design or initiation of pediatric studies; therefore, a detailed review of available data is not needed in this section.

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[55] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[56] See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006) and the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010).

10. Planned Pediatric Clinical Studies

10.1 Pediatric Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Studies

This section (1 to 10 pages) should provide an outline of each of the pediatric PK/PD studies planned, if applicable.[57] Sponsors should discuss the studies in the order they are presented in the table in section 6. For each study, to the extent practicable, the sponsor should address the following:

The type of study/study design

The objectives of the study

The age group and population in which the study will be conducted

The pediatric formulation(s) to be used in the study

The dose ranges to be used in the PK studies

The endpoints and justification (PK parameters; PD biomarkers)

The existing or planned modeling and simulation to support dose selection and/or study design, data analysis, and interpretation for planned pediatric studies

Any planned pharmacogenomic analyses

Sample size justification

A sponsor must submit full protocols separately to the IND for FDA review and should obtain FDA agreement regarding all full protocols before initiation of pediatric studies outlined in this section.[58]

A dedicated PK study is not always needed in every age group. For example, prior experience with dosing in adolescent patients has demonstrated that knowledge of adult dosing and appropriate dose scaling may be sufficient for some drugs with adequate justification. It may be appropriate for a sponsor to use confirmatory population PK studies to supplement such a program in which a dedicated PK study is not considered essential.[59]

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[57] For further discussion, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.* When final, this guidance will represent the FDA's current thinking on this topic.

[58] See 21 CFR 312.23(a)(6) and 312.30.

[59] For additional information, see the draft guidance for industry, *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.* When final, this guidance will represent the FDA's current thinking on this topic.

10.2 Clinical Effectiveness and Safety Studies

This section should provide a brief outline of each pediatric study planned, discussed in the order each is presented in the table in section 6 (1 to 10 pages). For each study, to the extent practicable, the sponsor should address the following:

The type of study/study design

The objectives of the study

The age group and population in which the study will be conducted

The key inclusion and exclusion criteria for the study

The endpoints (primary and key secondary) to be used

The timing of endpoint assessments

The safety assessments (including timing and length of follow-up)

The statistical approach

The modeling and simulation to be used to optimize the design of planned pediatric studies, when applicable

This section should provide a brief outline of the planned pediatric studies. Therefore, sponsors should not include a detailed protocol and/or statistical analysis plan in the iPSP. Sponsors should be aware that agreement with the outline of planned clinical studies does not constitute agreement with the protocol. Sponsors must submit full protocols separately to their INDs for FDA review and should obtain FDA agreement regarding all full protocols before initiation of pediatric studies outlined in this section. [60] Sponsors should also submit statistical analysis plans separately to their INDs for FDA review and agreement.

11. Timeline of the Pediatric Development Plan

For each study listed in the table in section 6, a general timeline for completion should be included in this section (1 page). A suggested template is provided below. The sponsor should estimate these dates based on current projections for the drug development program. As stated above, the intent of the iPSP is to identify needed pediatric studies early in drug development and to begin planning for these studies. Therefore, the timeline of the pediatric development plan should be based on clinical, scientific, and operational considerations and should be made independent of an anticipated submission date of an application or approval date of a drug. For example, pediatric formulation development can begin before the anticipated submission date of

[60] See 21 CFR 312.23(a)(6) and 312.30.

an application or approval date of a drug. If the dates provided in the iPSP change as drug development proceeds, the sponsor should submit a request to amend the iPSP and include justification for the change.

Formulation development, if applicable

Nonclinical studies, if applicable
− Estimated protocol submission date: No later than ___(month/year) − Estimated study initiation date: No later than ___(month/year) − Estimated study completion date: No later than ___(month/year)
− Estimated final report submission date: No later than ___(month/year)

Clinical studies
PK or PK/PD studies, if applicable:
− Estimated protocol submission date: No later than ___(month/year) − Estimated study initiation date: No later than ___(month/year) − Estimated study completion date: No later than ___(month/year)
− Estimated final report submission date: No later than ___(month/year)

Efficacy/safety and/or dedicated safety studies, if applicable
− Estimated protocol submission date: No later than ___(month/year)
− Estimated study initiation date: No later than ___(month/year)
− Estimated study completion date: No later than ___(month/year)
− Estimated final report submission date: No later than ___(month/year)

Target date of application submission

12. Agreements for Pediatric Studies With Other Regulatory Authorities

It is recommended that sponsors include, if available, a summary (1 to 3 pages) of the most recent agreed pediatric investigation plan with other regulatory authorities (e.g., European Medicines Agency). If negotiations with a regulatory authority are in progress or previous plans are under modification, a sponsor should include a summary of the most recent draft plan. A sponsor should highlight and comment on any differences between the most recent plan with other regulatory authorities and the plan submitted to the FDA. The purpose of including a summary of agreements with other regulatory authorities is to encourage global alignment in pediatric development plans across regulatory authorities when possible.

VI. RELATIONSHIP OF AGREED INITIAL PSP TO THE REQUIREMENT TO SUBMIT A PEDIATRIC STUDY PLAN WITH AN APPLICATION

For NDAs, BLAs, or supplemental applications subject to PREA, sponsors must include an agreed iPSP in the application when a deferral of pediatric studies is requested.[61] In such cases, submission of the iPSP (specifically, the agreed iPSP) fulfills the requirement of the sponsor to submit a pediatric study plan, which must be included in the appropriate section of the application.[62] Failure to fulfill the requirement to submit a pediatric study plan with the application may be grounds for refusal to file an application.[63] Any planned requests for waivers and/or deferrals included in the iPSP serve as the official request with the application submission.[64] The PeRC will review any requests for waivers and/or deferrals and make recommendations as needed to the review division.[65] A final decision about granting or denying such requests is made by the review division at the time of approval of the marketing application.

VII. CONTENT AND TIMING OF REQUESTED AMENDMENT TO AN INITIAL PSP

Sponsors can request an amendment to an agreed iPSP at any time. Requests can include, for example, changing a date listed in section 11 of the iPSP that would significantly delay the initiation and/or completion of pediatric studies (e.g., by more than 12 months), changing planned requests for a deferral to planned requests for a waiver or partial waiver, or changing a planned request for a waiver or partial waiver to a planned request for a deferral. For example, emerging safety data from nonclinical juvenile animal studies and/or adult human clinical trials may support converting a planned request for a deferral to a planned request for a waiver for reasons of safety. Alternatively, the need for additional safety data from adult human clinical trials may support a delay in the initiation of pediatric clinical trials. In addition, formulation data could necessitate a change in a development program. The PeRC will be consulted on the review of significant amendments to an agreed iPSP.[66]

A request for an amendment to an agreed iPSP should include the following:

The requested change(s) supported with a justification

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[61] See sections 505B(a)(4)(A)(ii)(II), 505B(a)(1) and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II), 355c(a)(1), and 355c(e).

[62] See sections 505B(a)(4)(A)(ii)(II) and 505(B)(e)(3) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II) and 355c(e)(3).

[63] See 21 CFR 314.101(d).

[64] See section 505B(e)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B)(ii).

[65] See section 505B(f)(4) of the FD&C Act; 21 U.S.C. 355c(f)(4).

[66] See section 505B(e)(6) of the FD&C Act; 21 U.S.C. 355c(e)(6).

A copy of the agreed iPSP with the requested change(s) tracked and clearly identified

A clean copy of the proposed amended iPSP

Amendments should not be considered agreed upon until the FDA issues a letter stating that the amendments are acceptable.

Once the FDA accepts for filing an application or supplemental application, it is not necessary to submit amendments to the iPSP because changes to the plan for pediatric development can be negotiated during the review cycle as appropriate. For example, a sponsor submits a marketing application with an agreed iPSP, and the review division files the application. The sponsor proposes to modify the timeline for studies after filing the application; in this case, it is not necessary to submit an amended iPSP, but instead the newly proposed timeline can be negotiated with the review division during the review cycle of the application.

The timeline for submission, review, and agreement on an amended iPSP is the same as on an iPSP.[67] (See Section IV., Timing of an Initial PSP Submission). If the FDA does not agree to the amended iPSP, the original agreed iPSP remains in force. If the sponsor submits an amendment to an agreed iPSP within 210 days of the planned submission of an NDA, BLA, or supplement, the amendment may not be considered agreed absent sufficient time for the FDA review. However, the sponsor may submit the NDA, BLA, or supplement with the previously agreed iPSP. FDA intends to, as appropriate, consider changes to the plan for pediatric development during the application review cycle (see section VIII., Non-Agreed Initial PSPs).

However, if, under certain situations, the agreed iPSP included nonclinical and/or pediatric clinical studies that were expected to have been completed before submission of the NDA, BLA, or supplement, failure of the sponsor to complete these agreed studies in a timely manner may result in a refusal to file.[68] In this situation, a sponsor should submit a request for an amendment to the agreed iPSP that includes an updated timeline for the studies and justification for the delay in completing one or more of the agreed pediatric studies. If the FDA considers the justification for the delay to be inadequate and does not agree with the proposed iPSP amendment, the agreed iPSP would remain in force until the FDA and sponsor agree on an amended iPSP (See Section VIII., Non-Agreed Initial PSPs), and the failure of the sponsor to complete the agreed nonclinical and/or pediatric clinical studies in a timely manner still may result in a refusal to file.

VIII. NON-AGREED INITIAL PSPs

If the FDA and the sponsor are unable to reach agreement on an iPSP at the end of the 210-day review period, the FDA intends to issue a letter stating that the iPSP is considered a non-agreed

[67] See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

[68] See section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)), which requires that the assessments or reports on the molecularly targeted pediatric cancer investigation be submitted with the application or supplement to which PREA applies. See also 21 CFR 314.101(d).

iPSP. As discussed in section IX., Reaching Agreement on the Non-Agreed Initial PSP, there is no established timeline for the review and agreement of a non-agreed iPSP. Therefore, sponsors are encouraged to work with FDA to reach agreement during the initial 210-day review period.

If the FDA and the sponsor are unable to reach agreement on the proposed amendments to an agreed iPSP, the FDA intends to issue a letter stating that the amended iPSP is considered a *nonagreed amended iPSP*. Under this circumstance, the agreed iPSP would be considered to be in force until the FDA and sponsor agree on an amended iPSP.

As stated above, for NDAs, BLAs, or supplemental applications subject to PREA, sponsors must include an agreed iPSP in the application when a deferral of pediatric studies is requested, and the failure to submit an agreed iPSP when a deferral is requested may be grounds for refusal to file the application.[69] All correspondence with the FDA regarding any non-agreed amendments should be included in the appropriate section of the application.

IX. REACHING AGREEMENT ON THE NON-AGREED INITIAL PSP

When a sponsor receives a letter of nonagreement, the FDA makes every effort to work with the sponsor and resolve the area(s) of disagreement as quickly as possible; however, no statutory timeline is attached to this process. If the sponsor disagrees with the FDA's recommendations, the sponsor can request a meeting with the FDA. After the sponsor and the FDA have resolved any disagreements, the sponsor should submit the proposed agreed iPSP for FDA review.

APPENDIX: INITIAL PEDIATRIC STUDY PLAN TEMPLATE[70]

When submitting an initial pediatric study plan (iPSP), sponsors should mark the submission "**INITIAL PEDIATRIC STUDY PLAN**" in large, bolded type at the beginning of the title page. For an agreed iPSP or amended iPSP, sponsors should mark the submission "PROPOSED AGREED PEDIATRIC STUDY PLAN" or "AMENDED PEDIATRIC STUDY PLAN," respectively, in large, bolded type at the beginning of the title page.

INITIAL PEDIATRIC STUDY PLAN TITLE PAGE

The proprietary name and the established name of the drug, if any, or, for biological products, the proper name including any appropriate descriptors

Dosage form:

NDA/BLA/IND #:

Drug class:

[69] See sections 505B(a)(4)(A)(ii)(II), 505B(a)(1), and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II), 355c(a)(1), and 355c(e). See also 21 CFR 314.101(d).

[70] This template is also available at https://www.fda.gov/media/84944/download.

Approved indication (if applicable):

Proposed indication (if applicable):

Proposed General Plan: (i.e., full or partial waiver, deferral, and inclusion of a pediatric assessment or molecularly targeted pediatric cancer investigation in the future application)

Cross-reference to other investigational new drug applications for which an iPSP is submitted for this drug development program

OVERVIEW OF THE DISEASE/CONDITION IN THE PEDIATRIC POPULATION (1–3 pages)

OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1–3 pages)

OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS (1–3 pages)

PLANNED REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1–3 pages)

PLANNED REQUEST FOR DEFERRAL(S) OF PEDIATRIC STUDIES (1–2 pages)

TABULAR SUMMARY OF PLANNED NONCLINICAL AND CLINICAL DEVELOPMENT

AGE-APPROPRIATE FORMULATION DEVELOPMENT (1–3 pages)

NONCLINICAL STUDIES (1–3 pages)

CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1–5 pages)

10. PLANNED PEDIATRIC CLINICAL STUDIES

10.1 Pediatric Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Studies (1–10 pages)

10.2 Clinical Effectiveness and Safety Studies (1–10 pages)

11. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1 page)

12. AGREEMENTS FOR PEDIATRIC STUDIES WITH OTHER REGULATORY AUTHORITIES (1–3 pages)

If there is a pending or agreed pediatric investigational plan with EMA (European Medicines Agency), sponsors should provide the corresponding application number (e.g., EMEA-000206PIP01-08).

BEST PHARMACEUTICALS FOR CHILDREN ACT

(see also 42 U.S.C. § 284m to extension of BPCA to biologics)

THE BEST PHARMACEUTICALS FOR CHILDREN ACT AUTHORIZES FDA TO ISSUE WRITTEN REQUESTS FOR VOLUNTARY ROBUST, PEDIATRIC STUDIES. IF THE STUDIES ARE COMPLETED IN SATISFACTION OF THE TERMS OF THE WRITTEN REQUEST, THE SPONSOR IS AWARDED 6 MONTHS MARKETING EXCLUSIVITY, OR PEDIATRIC EXCLUSIVITY, ON ALL INDICATIONS FOR WHICH THE DRUG IS APPROVED.

US CODE

21 U.S.C. §355a. Pediatric studies of drugs

(a) Definitions

As used in this section, the term "pediatric studies" or "studies" means at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies.

(b) Market exclusivity for new drugs

(1) In general

Except as provided in paragraph (2), if, prior to approval of an application that is submitted under section 355(b)(1) of this title, the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), the applicant agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with subsection (d)(4)-

(A)

(i)

(I) the period referred to in subsection (c)(3)(E)(ii) of section 355 of this title, and in subsection (j)(5)(F)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(II) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(E) of such section, and in clauses (iii) and (iv) of subsection (j)(5)(F) of such section, is deemed to be three years and six months rather than three years; and

(ii) if the drug is designated under section 360bb of this title for a rare disease or condition, the period referred to in section 360cc(a) of this title is deemed to be seven years and six months rather than seven years; and

(B)

(i) if the drug is the subject of-

(I) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 355 of this title and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(II) a listed patent for which a certification has been submitted under subsections (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 355 of this title, the period during which an application may not be approved under section 355(c)(3) of this title or section 355(j)(5)(B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(ii) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 355 of this title, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 355(c)(3) of this title or section 355(j)(5)(B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(2) Exception

The Secretary shall not extend the period referred to in paragraph (1)(A) or (1)(B) if the determination made under subsection (d)(4) is made later than 9 months prior to the expiration of such period.

(c) Market exclusivity for already-marketed drugs

(1) In general

Except as provided in paragraph (2), if the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under section 355(b)(1) of this title for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with subsection (d)(4)-

(A)

(i)

(I) the period referred to in subsection (c)(3)(E)(ii) of section 355 of this title, and in subsection (j)(5)(F)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of such section to four years, to forty-eight months, and to seven

and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(II) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(E) of such section, and in clauses (iii) and (iv) of subsection (j)(5)(F) of such section, is deemed to be three years and six months rather than three years; and

(ii) if the drug is designated under section 360bb of this title for a rare disease or condition, the period referred to in section 360cc(a) of this title is deemed to be seven years and six months rather than seven years; and

(B)

(i) if the drug is the subject of-

(I) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 355 of this title and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(II) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 355 of this title, the period during which an application may not be approved under section 355(c)(3) of this title or section 355(j)(5)(B)(ii) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(ii) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 355 of this title, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 355(c)(3) of this title or section 355(j)(5)(B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(2) Exception

The Secretary shall not extend the period referred to in paragraph (1)(A) or (1)(B) if the determination made under subsection (d)(4) is made later than 9 months prior to the expiration of such period.

(d) Conduct of pediatric studies

(1) Request for studies

(A) In general

The Secretary may, after consultation with the sponsor of an application for an investigational new drug under section 355(i) of this title, the sponsor of an application for a new drug under section 355(b)(1) of this title, or the holder of an approved application for a drug under section 355(b)(1) of this title, issue to the sponsor or holder a written request for the conduct of pediatric studies for such drug. In issuing such request, the Secretary shall take into account adequate representation of children of ethnic and racial minorities. Such request to conduct pediatric studies shall be in writing and shall include a timeframe for such studies and a request to the sponsor or holder to propose pediatric labeling resulting from such studies. If a request under this subparagraph does not request studies in neonates, such request shall include a statement describing the rationale for not requesting studies in neonates.

(B) Single written request

A single written request-

(i) may relate to more than one use of a drug; and

(ii) may include uses that are both approved and unapproved.

(2) Written request for pediatric studies

(A) Request and response

(i) In general

If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (b) or (c), the applicant or holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the applicant or holder to act on the request by-

(I) indicating when the pediatric studies will be initiated, if the applicant or holder agrees to the request; or

(II) indicating that the applicant or holder does not agree to the request and stating the reasons for declining the request.

(ii) Disagree with request

If, on or after September 27, 2007, the applicant or holder does not agree to the request on the grounds that it is not possible to develop the appropriate pediatric formulation, the applicant or holder shall submit to the Secretary the reasons such pediatric formulation cannot be developed.

(B) Adverse event reports

An applicant or holder that, on or after September 27, 2007, agrees to the request for such studies shall provide the Secretary, at the same time as the submission of the reports of such studies, with all postmarket adverse event reports regarding the drug that is the subject of such studies and are available prior to submission of such reports.

(3) Action on submissions

The Secretary shall review and act upon a submission by a sponsor or holder of a proposed pediatric study request or a proposed amendment to a written request for pediatric studies within 120 calendar days of the submission.

(4) Meeting the studies requirement

Not later than 180 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 180-day period, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.

(5) Effect of subsection

Nothing in this subsection alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(6) Consultation

With respect to a drug that is a qualified countermeasure (as defined in section 247d–6a of title 42), a security countermeasure (as defined in section 247d–6b of title 42), or a qualified pandemic or epidemic product (as defined in section 247d–6d of title 42), the Secretary shall solicit input from the Assistant Secretary for Preparedness and Response regarding the need for and, from the Director of the Biomedical Advanced Research and Development Authority regarding the conduct of, pediatric studies under this section.

(e) Notice of determinations on studies requirement

(1) In general

The Secretary shall publish a notice of any determination, made on or after September 27, 2007, that the requirements of subsection (d) have been met and that submissions and approvals under subsection (b)(2) or (j) of section 355 of this title for a drug will be subject to the provisions of this section. Such notice shall be published not later than 30 days after the date of the Secretary's determination regarding market exclusivity and shall include a copy of the written request made under subsection (b) or (c).

(2) Identification of certain drugs

The Secretary shall publish a notice identifying any drug for which, on or after September 27, 2007, a pediatric formulation was developed, studied, and found to be safe and effective in the pediatric population (or specified subpopulation) if the pediatric formulation for such drug is not introduced onto the market within one year after the date that the Secretary publishes the notice described in paragraph (1). Such notice identifying such drug shall be published not later than 30 days after the date of the expiration of such one year period.

(f) Internal review of written requests and pediatric studies

(1) Internal review

The Secretary shall utilize the internal review committee established under section 355d of this title to review all written requests issued on or after September 27, 2007, in accordance with paragraph (2).

(2) Review of written requests

The committee referred to in paragraph (1) shall review all written requests issued pursuant to this section prior to being issued.

(3) Review of pediatric studies

The committee referred to in paragraph (1) may review studies conducted pursuant to this section to make a recommendation to the Secretary whether to accept or reject such reports under subsection (d)(4).

(4) Activity by committee

The committee referred to in paragraph (1) may operate using appropriate members of such committee and need not convene all members of the committee.

(5) Documentation of committee action

For each drug, the committee referred to in paragraph (1) shall document, for each activity described in paragraph (2) or (3), which members of the committee participated in such activity.

(6) Tracking pediatric studies and labeling changes

The Secretary, in consultation with the committee referred to in paragraph (1), shall track and make available to the public, in an easily accessible manner, including through posting on the Web site of the Food and Drug Administration-

(A) the number of studies conducted under this section and under section 284m of title 42;

(B) the specific drugs and drug uses, including labeled and off-labeled indications, studied under such sections;

(C) the types of studies conducted under such sections, including trial design, the number of pediatric patients studied, and the number of centers and countries involved;

(D) the number of pediatric formulations developed and the number of pediatric formulations not developed and the reasons such formulations were not developed;

(E) the labeling changes made as a result of studies conducted under such sections;

(F) an annual summary of labeling changes made as a result of studies conducted under such sections for distribution pursuant to subsection (k)(2); and

(G) information regarding reports submitted on or after September 27, 2007.

(7) Informing internal review committee

The Secretary shall provide to the committee referred to in paragraph (1) any response issued to an applicant or holder with respect to a proposed pediatric study request.

(g) Limitations

Notwithstanding subsection (c)(2), a drug to which the six-month period under subsection (b) or (c) has already been applied-

(1) may receive an additional six-month period under subsection (c)(1)(A)(i)(II) for a supplemental application if all other requirements under this section are satisfied, except that such drug may not receive any additional such period under subsection (c)(1)(B); and

(2) may not receive any additional such period under subsection (c)(1)(A)(ii).

(h) Relationship to pediatric research requirements

Exclusivity under this section shall only be granted for the completion of a study or studies that are the subject of a written request and for which reports are submitted and accepted in accordance with subsection (d)(4). Written requests under this section may consist of a study or studies required under section 355c of this title.

(i) Labeling changes

(1) Priority status for pediatric applications and supplements

Any application or supplement to an application under section 355 of this title proposing a labeling change as a result of any pediatric study conducted pursuant to this section-

(A) shall be considered to be a priority application or supplement; and

(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

(2) Dispute resolution

(A) Request for labeling change and failure to agree

If, on or after September 27, 2007, the Commissioner determines that the sponsor and the Commissioner have been unable to reach agreement on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application-

(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

(ii) if the sponsor of the application does not agree within 30 days after the Commissioner's request to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Committee.

(B) Action by the Pediatric Advisory Committee

Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Committee shall-

(i) review the pediatric study reports; and

(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

(C) Consideration of recommendations

The Commissioner shall consider the recommendations of the Pediatric Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

(D) Misbranding

If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

(E) No effect on authority

Nothing in this subsection limits the authority of the United States to bring an enforcement action under this chapter when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

(j) Other labeling changes

If, on or after September 27, 2007, the Secretary determines that a pediatric study conducted under this section does or does not demonstrate that the drug that is the subject of the study is safe and effective, including whether such study results are inconclusive, in pediatric populations or subpopulations, the Secretary shall order the labeling of such product to include information about the results of the study and a statement of the Secretary's determination.

(k) Dissemination of pediatric information

(1) In general

Not later than 210 days after the date of submission of a report on a pediatric study under this section, the Secretary shall make available to the public the medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under subsection (b) or (c).

(2) Dissemination of information regarding labeling changes

Beginning on September 27, 2007, the Secretary shall include as a requirement of a written request that the sponsors of the studies that result in labeling changes that are reflected in the annual summary developed pursuant to subsection (f)(6)(F) distribute, at least annually (or more frequently if the Secretary determines that it would be beneficial to the public health), such information to physicians and other health care providers.

(3) Effect of subsection

Nothing in this subsection alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(l) Adverse event reporting

(1) Reporting in first 18-month period

Beginning on September 27, 2007, during the 18-month period beginning on the date a labeling change is approved pursuant to subsection (i), the Secretary shall ensure that all adverse event

reports that have been received for such drug (regardless of when such report was received) are referred to the Office of Pediatric Therapeutics established under section 393a of this title. In considering the reports, the Director of such Office shall provide for the review of the reports by the Pediatric Advisory Committee, including obtaining any recommendations of such Committee regarding whether the Secretary should take action under this chapter in response to such reports.

(2) Reporting in subsequent periods

Following the 18-month period described in paragraph (1), the Secretary shall, as appropriate, refer to the Office of Pediatric Therapeutics all pediatric adverse event reports for a drug for which a pediatric study was conducted under this section. In considering such reports, the Director of such Office may provide for the review of such reports by the Pediatric Advisory Committee, including obtaining any recommendation of such Committee regarding whether the Secretary should take action in response to such reports.

(3) Preservation of authority

Nothing in this subsection shall prohibit the Office of Pediatric Therapeutics from providing for the review of adverse event reports by the Pediatric Advisory Committee prior to the 18-month period referred to in paragraph (1), if such review is necessary to ensure safe use of a drug in a pediatric population.

(4) Effect

The requirements of this subsection shall supplement, not supplant, other review of such adverse event reports by the Secretary.

(m) Clarification of interaction of market exclusivity under this section and market exclusivity awarded to an applicant for approval of a drug under section 355(j) of this title

If a 180-day period under section 355(j)(5)(B)(iv) of this title overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 355(j) of this title entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from-

(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.

(n) Referral if pediatric studies not submitted

(1) In general

Beginning on September 27, 2007, if pediatric studies of a drug have not been submitted by the date specified in the written request issued or if the applicant or holder does not agree to the request under subsection (d) and if the Secretary, through the committee established under section 355d of this title, determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall carry out the following:

(A) For a drug for which a listed patent has not expired, or for which a period of exclusivity eligible for extension under subsection (b)(1) or (c)(1) of this section or under subsection (m)(2) or (m)(3) of section 262 of title 42 has not ended, make a determination regarding whether an assessment shall be required to be submitted under section 355c(b) of this title.

(B) For a drug that has no unexpired listed patents and for which no unexpired periods of exclusivity eligible for extension under subsection (b)(1) or (c)(1) of this section or under subsection (m)(2) or (m)(3) of section 262 of title 42 apply, the Secretary shall refer the drug for inclusion on the list established under section 284m of title 42 for the conduct of studies.

(C) For a drug that is a qualified countermeasure (as defined in section 247d–6a of title 42), a security countermeasure (as defined in section 247d–6b of title 42), or a qualified pandemic or epidemic product (as defined in section 247d–6d of title 42), in addition to any action with respect to such drug under subparagraph (A) or (B), the Secretary shall notify the Assistant Secretary for Preparedness and Response and the Director of the Biomedical Advanced Research and Development Authority of all pediatric studies in the written request issued by the Commissioner of Food and Drugs.

(2) Public notice

The Secretary shall give the public notice of a decision under paragraph (1)(A) not to require an assessment under section 355c of this title and the basis for such decision.

(3) Effect of subsection

Nothing in this subsection alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(o) Prompt approval of drugs when pediatric information is added to labeling

(1) General rule

A drug for which an application has been submitted or approved under subsection (b)(2) or (j) of section 355 of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent, or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title, clause (iii) or (iv) of section 355(c)(3)(E) of this title, or section

360cc(a) of this title, or by an extension of such exclusivity under this section or section 355f of this title.

(2) Labeling

Notwithstanding clauses (iii) and (iv) of section 355(j)(5)(F) of this title, clauses (iii) and (iv) of section 355(c)(3)(E) of this title, or section 360cc of this title, the Secretary may require that the labeling of a drug approved pursuant to an application submitted under subsection (b)(2) or (j) of section 355 of this title that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include-

(A) a statement that, because of marketing exclusivity for a manufacturer-

(i) the drug is not labeled for pediatric use; or

(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

(B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.

(3) Preservation of pediatric exclusivity and extensions

This subsection does not affect-

(A) the availability or scope of exclusivity under-

(i) this section;

(ii) section 355 of this title for pediatric formulations; or

(iii) section 360cc of this title;

(B) the availability or scope of an extension to any such exclusivity, including an extension under this section or section 355f of this title;

(C) the question of the eligibility for approval under section 355 of this title of any application described in subsection (b)(2) or (j) of such section that omits any other aspect of labeling protected by exclusivity under-

(i) clause (iii) or (iv) of section 355(j)(5)(F) of this title;

(ii) clause (iii) or (iv) of section 355(c)(3)(E) of this title; or

(iii) section 360cc(a) of this title; or

(D) except as expressly provided in paragraphs (1) and (2), the operation of section 355 of this title or section 360cc of this title.

(June 25, 1938, ch. 675, §505A, as added Pub. L. 105–115, title I, §111, Nov. 21, 1997, 111 Stat. 2305 ; amended Pub. L. 107–109, §§2, 4, 5(b)(2), 7–11(a), 18(a), 19, Jan. 4, 2002, 115 Stat. 1408 , 1411, 1413-1415, 1423, 1424; Pub. L. 108–155, §§2(b)(2), 3(a), (b)(1), Dec. 3, 2003, 117 Stat. 1941 ; Pub. L. 108–173, title XI, §1104, Dec. 8, 2003, 117 Stat. 2461 ; Pub. L. 110–85, title V, §502(a)(1), Sept. 27, 2007, 121 Stat. 876 ; Pub. L. 111–148, title VII, §7002(g)(2)(B), Mar. 23, 2010, 124 Stat. 820 ; Pub. L. 112–144, title V, §§501(a), 502(a)(1), (b), 509(a), July 9, 2012, 126 Stat. 1039 , 1040, 1047; Pub. L. 113–5, title III, §307(a), Mar. 13, 2013, 127 Stat. 191 ; Pub. L. 114–255, div. A, title III, §3102(2), Dec. 13, 2016, 130 Stat. 1156 ; Pub. L. 115–52, title V, §505(a)–(b)(2)(A), title VI, §608, Aug. 18, 2017, 131 Stat. 1046 , 1050; Pub. L. 117–9, §1(b)(2), Apr. 23, 2021, 135 Stat. 258 .

21 U.S.C. § 355b. Adverse-event reporting

(a) Toll-free number in labeling. Not later than one year after January 4, 2002, the Secretary of Health and Human Services shall promulgate a final rule requiring that the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355] (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

(b) Drugs with pediatric market exclusivity

(1) In general. During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a], any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 393a of this title. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] in response to the report.

(2) Rule of construction. Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.

42 U.S.C. §284m. Program for pediatric studies of drugs

(a) List of priority issues in pediatric therapeutics

(1) In general

Not later than one year after September 27, 2007, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop and publish a priority list of needs in pediatric therapeutics, including drugs, biological products, or indications that require study. The list shall be revised every three years.

(2) Consideration of available information

In developing and prioritizing the list under paragraph (1), the Secretary-

(A) shall consider-

(i) therapeutic gaps in pediatrics that may include developmental pharmacology, pharmacogenetic determinants of drug response, metabolism of drugs and biologics in children, and pediatric clinical trials;

(ii) particular pediatric diseases, disorders or conditions where more complete knowledge and testing of therapeutics, including drugs and biologics, and identification of biomarkers for such diseases, disorders, or conditions, may be beneficial in pediatric populations; and

(iii) the adequacy of necessary infrastructure to conduct pediatric pharmacological research, including research networks and trained pediatric investigators; and

(B) may consider the availability of qualified countermeasures (as defined in section 247d–6a of this title), security countermeasures (as defined in section 247d–6b of this title), and qualified pandemic or epidemic products (as defined in section 247d–6d of this title) to address the needs of pediatric populations, in consultation with the Assistant Secretary for Preparedness and Response, consistent with the purposes of this section.

(b) Pediatric studies and research

The Secretary, acting through the National Institutes of Health, shall award funds to entities that have the expertise to conduct pediatric clinical trials or other research (including qualified universities, hospitals, laboratories, contract research organizations, practice groups, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct the drug studies or other research on the issues described in paragraphs (1) and (2)(A) of subsection (a). The Secretary may use contracts, grants, or other appropriate funding mechanisms to award funds under this subsection.

(c) Process for proposed pediatric study requests and labeling changes

(1) Submission of proposed pediatric study request

The Director of the National Institutes of Health shall, as appropriate, submit proposed pediatric study requests for consideration by the Commissioner of Food and Drugs for pediatric studies of a specific pediatric indication identified under subsection (a). Such a proposed pediatric study request shall be made in a manner equivalent to a written request made under subsection (b) or (c) of section 505A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a], or section 262(m) of this title, including with respect to the information provided on the pediatric studies to be conducted pursuant to the request. The Director of the National Institutes of Health may submit a proposed pediatric study request for a drug for which-

(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355(j)] or section 262(k) of this title; or

(ii) there is a submitted application that could be approved under the criteria of such section; and

(B) there remains no patent listed pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355(b)(1)], and every three-year and five-year period referred to in subsection (c)(3)(E)(ii), (c)(3)(E)(iii), (c)(3)(E)(iv), (j)(5)(F)(ii), (j)(5)(F)(iii), or (j)(5)(F)(iv) of section 505 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355], or applicable twelve-year period referred to in section 262(k)(7) of this title, and any seven-year period referred to in section 527 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360cc] has ended for at least one form of the drug; and

(C) additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

(2) Written request to holders of approved applications

The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request based on the proposed pediatric study request for the indication or indications submitted pursuant to paragraph (1) (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified under subsection (a) to all holders of an approved application for the drug. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (b) or (c) of section 505A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a] or section 262(m) of this title, including with respect to information provided on the pediatric studies to be conducted pursuant to the request and using appropriate formulations for each age group for which the study is requested.

(3) Requests for proposals

If the Commissioner of Food and Drugs does not receive a response to a written request issued under paragraph (2) not later than 30 days after the date on which a request was issued, the

Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for proposals to conduct the pediatric studies described in the written request in accordance with subsection (b).

(4) Disqualification

A holder that receives a first right of refusal shall not be entitled to respond to a request for proposals under paragraph (3).

(5) Contracts, grants, or other funding mechanisms

A contract, grant, or other funding may be awarded under this section only if a proposal is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

(6) Reporting of studies

(A) In general

On completion of a pediatric study in accordance with an award under this section, a report concerning the study shall be submitted to the Director of the National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study, including a written request if issued.

(B) Availability of reports

(i) In general

Each report submitted under subparagraph (A) shall be considered to be in the public domain (subject to section 505A(d)(4) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a(d)(4)]) and not later than 90 days after submission of such report, shall be-

(I) posted on the internet website of the National Institutes of Health in a manner that is accessible and consistent with all applicable Federal laws and regulations, including such laws and regulations for the protection of-

(aa) human research participants, including with respect to privacy, security, informed consent, and protected health information; and

(bb) proprietary interests, confidential commercial information, and intellectual property rights; and

(II) assigned a docket number by the Commissioner of Food and Drugs and made available for the submission of public comments.

(ii) Submission of comments

An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the submitted comments shall become part of the docket file with respect to each of the drugs.

(C) Action by Commissioner

The Commissioner of Food and Drugs shall take action in a timely and appropriate manner in response to the reports submitted under subparagraph (A), and shall begin such action upon receipt of the report under subparagraph (A), in accordance with paragraph (7).

(7) Requests for labeling change

Within the 180-day period after the date on which a report is submitted under paragraph (6)(A), the Commissioner of Food and Drugs shall-

(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied;

(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner of Food and Drugs determines to be appropriate and requests the holders to make; and

(C)(i) include in the public docket file a reference to the location of the report on the internet website of the National Institutes of Health and a copy of any requested labeling changes; and

(ii) publish through a posting on the Web site of the Food and Drug Administration a summary of the report and a copy of any requested labeling changes.

(8) Dispute resolution

(A) Referral to Pediatric Advisory Committee

If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric Advisory Committee.

(B) Action by the Pediatric Advisory Committee

Not later than 90 days after receiving a referral under subparagraph (A), the Pediatric Advisory Committee shall-

(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

(9) FDA determination

Not later than 30 days after receiving a recommendation from the Pediatric Advisory Committee under paragraph (8)(B)(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

(10) Failure to agree

If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (9), does not agree to make a requested labeling change, the Commissioner of Food and Drugs may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.].

(11) No effect on authority

Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

(d) Authorization of appropriations

(1) In general

There are authorized to be appropriated to carry out this section, $25,000,000 for each of fiscal years 2018 through 2022.

(2) Availability

Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.

(July 1, 1944, ch. 373, title IV, §409I, as added Pub. L. 107–109, §3(3), Jan. 4, 2002, 115 Stat. 1408 ; amended Pub. L. 108–155, §3(b)(6), Dec. 3, 2003, 117 Stat. 1942 ; Pub. L. 109–482, title I, §103(b)(14), Jan. 15, 2007, 120 Stat. 3687 ; Pub. L. 110–85, title V, §502(b), Sept. 27, 2007, 121 Stat. 886 ; Pub. L. 111–148, title VII, §7002(g)(2)(A), Mar. 23, 2010, 124 Stat. 820 ; Pub. L. 112–144, title V, §§507(d), 509(d), July 9, 2012, 126 Stat. 1045 , 1049; Pub. L. 113–5, title III, §307(b), Mar. 13, 2013, 127 Stat. 192 ; Pub. L. 115–52, title V, §501, Aug. 18, 2017, 131 Stat. 1036 .)

QUESTIONS AND ANSWERS

Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)

The following questions and answers have been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on pediatric exclusivity (505A). It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

Q1-Q12: Exclusivity

Exclusivity

Section 505(A) of The Modernization Act enabled FDA to:

- Issue Written Requests for pediatric studies prior to approval of a new drug application if FDA has determined that information related to the use of the drugs in the pediatric population may produce health benefits.
- Issue Written Requests to holders of approved applications for pediatric studies if it has determined that information related to the use of the drug in the pediatric population may produce health benefits.

Section 505(A) also required FDA to develop, prioritize, and publish a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric populations and update it annually.

As an incentive to industry to conduct studies requested by the Agency, Section 505(A) provides for a 6-month period of marketing exclusivity (pediatric exclusivity).

Q1. How does a sponsor or applicant qualify for pediatric exclusivity?

A1. Three essential elements must be in place before an applicant is eligible for pediatric exclusivity. To qualify for pediatric exclusivity, the applicant must meet all of the following conditions:

- Be in receipt of a written request from FDA. FDA issued a Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505(A) if the Federal Food, Drug, and Cosmetic Act [PDF]. The guidance describes what constitutes a Written Request and what it must address. Prior correspondence with applicants regarding clinical trials, agreements at meetings, correspondence describing phase 4 commitments, and other communications with sponsors DO NOT CONSTITUTE a Written Request. The Written Request describes in detail the studies needed and the time frame for their completion; the guidance describes ways in which the Written Request can be amended to revise the study requirements or the specified time frame. The Written Request is the key to whether submitted study reports qualify the applicant for pediatric exclusivity.

- Submit study reports after receipt of the written request. Firms are to submit reports of studies conducted in pediatric populations to the FDA after FDA has issued a Written Request. Under the terms of the statute, FDA must determine whether the studies submitted meet the terms of the Written Request. Submissions of reports should generally be in the form of a new drug application, a supplement to an approved application, or an amendment to a pending application. A firm should, but is not required to, obtain approval of pediatric labeling to qualify for pediatric exclusivity.
- Meet the conditions of the written request. Whether an applicant qualifies for exclusivity for a product after conducting the studies and submitting the reports depends on whether:

  - The submission meets the time frame described in the Written Request, and

  - The studies performed meet the terms specified in the Written Request.

Q2. Can an applicant ask FDA to issue a Written Request for pediatric studies?

A2. Yes. The guidance to industry describes a process in which a sponsor of a new drug or the holder of an application for a product on the list may make a submission to FDA in which it makes a detailed proposal for a Written Request. Where an applicant has more than one product containing the active moiety, the proposal should address each indication that has applicability to pediatric patients and should propose studies in all appropriate age groups. FDA encourages applicants to make such proposals. FDA will review the submitted proposal and MAY issue a Written Request to the applicant based on the applicant's proposal.

Q3. Where should proposals for Written Requests from applicants be sent?

A3. Proposals for Written Requests should be sent to each of the review divisions with regulatory responsibility for any of the applicant's products that contains the same active moiety cited in the Written Request.

Q4. **Does a sponsor HAVE to conduct pediatric studies if it receives a Written Request from FDA?**

A4. No. A company is not required to do the studies requested by FDA in a Written Request if it chooses not to do so. If, however, the applicant decides to conduct studies that differ from those described in the Written Request, the applicant will not qualify for pediatric exclusivity upon submission of the reports thereof. Applicants who choose to deviate from the studies described in the Written Request and who are interested in obtaining pediatric exclusivity should contact the review division and seek to amend the Written Request prior to the conduct of the studies. The applicant must receive an amended Written Request prior to submission of the study reports to NDA.

Q5. Can an applicant obtain exclusivity by submitting an analysis of the literature in response to a Written Request?

A5. Simply compiling the literature on pediatric use of a drug in a given indication will not qualify an applicant for pediatric exclusivity. The generous incentives were made available to stimulate performance of studies necessary to provide useful information on drug use in children.

Q6. Can the applicant for any approved product qualify for pediatric exclusivity?

A6. No. Pediatric exclusivity is an ADD-ON to existing marketing exclusivity or patent protection. In general, products with no patent life or exclusivity remaining cannot qualify. Under certain conditions, however, pediatric exclusivity may be granted to a product without remaining exclusivity IF the supplemental application itself qualifies for a new exclusivity period under the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Amendments). For example, an application to extend an approved adult indication to the pediatric population for a product with no patent life or exclusivity remaining could obtain pediatric exclusivity IF new clinical studies of safety and efficacy are required for approval. In that case, the pediatric supplement would earn 3 years of marketing exclusivity under the 1984 amendments, to which the additional 6 month pediatric exclusivity would be added. A somewhat different situation would be where dosing information was needed in children under 6 years of age that could be based on PK studies. An oral solution dosage form exists but has no marketing exclusivity remaining. However, the firm has a controlled release product containing the same active moiety that is still protected by a 3 year exclusivity period. The controlled release product would not be appropriate for this age group because of the dose delivered. In this situation, PK studies conducted to label the oral solution could be the basis of a 6 month extension of the exclusivity for the controlled release product, provided the terms of the Written Request are met.

Q7. Does Section 505(A) apply to OTC drugs?

A7. Yes. It applies to those OTC drugs that are the subject of approved NDAs.

Q8. For approved drugs, must FDA approve a supplemental application before pediatric exclusivity is granted?

A8. No. The granting of exclusivity is not connected to approval; the pivotal factor is whether the applicant complied with the terms of the Written Request.

Q9. How is pediatric exclusivity different from other exclusivity available under the Waxman-Hatch amendments or the Orphan Drug Act?

A9. Pediatric exclusivity differs from other exclusivity in the following important ways:

- Pediatric exclusivity does not accrue only to the product that was studied in the pediatric population. It attaches to all the applicant's formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety. For example, if a firm markets an oral formulation, a topical cream, and an ophthalmic containing the same active moiety and all the products have remaining marketing exclusivity or patent life, and if the firm conducts studies regarding the active moiety in accordance with a Written Request, 6 months additional exclusivity will be

granted to ALL DOSAGE FORMS AND ALL INDICATIONS with the same active moiety as the drug studied.

- Pediatric exclusivity attaches to the END of all existing marketing exclusivity and patent periods. Waxman-Hatch exclusivity, orphan exclusivity, and patent periods run concurrently.
- Pediatric exclusivity is not tied to approval of labeling containing information on pediatric use based on the studies conducted. It may be granted upon acceptance of the study reports. Acceptance in this context means the Agency has determined that the studies were conducted in accordance with the terms of the Written Request and were reported in accordance with FDA's requirements for filing. Waxman-Hatch and orphan exclusivity are not granted until approval of the application.

Q10. Should a Written Request be issued to the IND or NDA holder?

A10. If an NDA for the drug product exists, the Written Request should be issued to the applicant of the NDA. If no NDA exists for the product, the Written Request should be issued to the IND holder.

Q11. For over-the-counter (OTC) products that are the subject of an NDA, which Office Director should sign Written Requests for pediatric studies?

A11. Consistent with CDER policy for decision making responsibilities on certain other regulatory documents that require Office level sign-off pertaining to OTC drug products subject to NDAs, both the Director of ODE V and the Director of the Office responsible for the specific subject matter review division should sign Written Requests for OTC products.

Q12. Where can I get answers to questions that come up regarding our implementation of the pediatric exclusivity provisions?

A12 Send questions via E-mail to pdit@cder.fda.gov. It is an E-mail account that has been set up by the Pediatric Implementation Team.

CREATING HOPE ACT RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHERS, FDA SAFETY AND INNOVATION ACT (FDASIA), TITLE V

Pursuant to the Creating Hope Act , the FDA may award a sponsor a rare pediatric disease priority review voucher upon award of a pediatric cancer or other pediatric disease drug. The voucher comes with right to faster FDA review for any other drug and any other indication. The voucher may be sold.

US CODE

21 U.S.C. § 360ff. Priority review to encourage treatments for rare pediatric diseases

(a) Definitions

In this section:

(1) Priority review

The term "priority review", with respect to a human drug application as defined in section 379g(1) of this title, means review and action by the Secretary on such application not later than 6 months after receipt by the Secretary of such application, as described in the Manual of Policies and Procedures of the Food and Drug Administration and goals identified in the letters described in section 101(b) of the Prescription Drug User Fee Amendments of 2012.

(2) Priority review voucher

The term "priority review voucher" means a voucher issued by the Secretary to the sponsor of a rare pediatric disease product application that entitles the holder of such voucher to priority review of a single human drug application submitted under section 355(b)(1) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] after the date of approval of the rare pediatric disease product application.

(3) Rare pediatric disease

The term "rare pediatric disease" means 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.

(B) The disease is a rare disease or condition, within the meaning of section 360bb of this title.

(4) Rare pediatric disease product application

The term "rare pediatric disease product application" means a human drug application, as defined in section 379g(1) of this title, that-

(A) is for a drug or biological product that is for the prevention or treatment of a rare pediatric disease;

(B)

(i) is for such a drug-

(I) that contains no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been previously approved in any other application under subsection (b)(1), (b)(2), or (j) of section 355 of this title; and

(II) that is the subject of an application submitted under section 355(b)(1) of this title; or

(ii) is for such a biological product-

(I) that contains no active ingredient that has been previously approved in any other application under section 351(a) or 351(k) of the Public Health Service Act [42 U.S.C. 262(a), 262(k)]; and

(II) that is the subject of an application submitted under section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)];

(C) the Secretary deems eligible for priority review;

(D) that [1] relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;

(E) that [1] does not seek approval for an adult indication in the original rare pediatric disease product application; and

(F) is approved after September 30, 2016.

(b) Priority review voucher

(1) In general

The Secretary shall award a priority review voucher to the sponsor of a rare pediatric disease product application upon approval by the Secretary of such rare pediatric disease product application.

(2) Transferability

(A) In general

The sponsor of a rare pediatric disease product application that receives a priority review voucher under this section may transfer (including by sale) the entitlement to such voucher.

There is no limit on the number of times a priority review voucher may be transferred before such voucher is used.

(B) Notification of transfer

Each person to whom a voucher is transferred shall notify the Secretary of such change in ownership of the voucher not later than 30 days after such transfer.

(3) Limitation

A sponsor of a rare pediatric disease product application may not receive a priority review voucher under this section if the rare pediatric disease product application was submitted to the Secretary prior to the date that is 90 days after July 9, 2012.

(4) Notification

(A) Sponsor of a rare pediatric disease product

(i) In general

Beginning on the date that is 90 days after September 30, 2016, the sponsor of a rare pediatric disease product application that intends to request a priority review voucher under this section shall notify the Secretary of such intent upon submission of the rare pediatric disease product application that is the basis of the request for a priority review voucher.

(ii) Applications submitted but not yet approved

The sponsor of a rare pediatric disease product application that was submitted and that has not been approved as of September 30, 2016, shall be considered eligible for a priority review voucher, if-

(I) such sponsor has submitted such rare pediatric disease product application-

(aa) on or after the date that is 90 days after July 9, 2012; and

(bb) on or before September 30, 2016; and

(II) such application otherwise meets the criteria for a priority review voucher under this section.

(B) Sponsor of a drug application using a priority review voucher

(i) In general

The sponsor of a human drug application shall notify the Secretary not later than 90 days prior to submission of the human drug application that is the subject of a priority review voucher of an

intent to submit the human drug application, including the date on which the sponsor intends to submit the application. Such notification shall be a legally binding commitment to pay the user fee to be assessed in accordance with this section.

(ii) Transfer after notice

The sponsor of a human drug application that provides notification of the intent of such sponsor to use the voucher for the human drug application under clause (i) may transfer the voucher after such notification is provided, if such sponsor has not yet submitted the human drug application described in the notification.

(5) Termination of authority

The Secretary may not award any priority review vouchers under paragraph (1) after September 30, 2024, unless the rare pediatric disease product application-

(A) is for a drug that, not later than September 30, 2024, is designated under subsection (d) as a drug for a rare pediatric disease; and

(B) is, not later than September 30, 2026, approved under section 355(b)(1) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)].

(c) Priority review user fee

(1) In general

The Secretary shall establish a user fee program under which a sponsor of a human drug application that is the subject of a priority review voucher shall pay to the Secretary a fee determined under paragraph (2). Such fee shall be in addition to any fee required to be submitted by the sponsor under subchapter VII.

(2) Fee amount

The amount of the priority review user fee shall be determined each fiscal year by the Secretary, based on the difference between-

(A) the average cost incurred by the Food and Drug Administration in the review of a human drug application subject to priority review in the previous fiscal year; and

(B) the average cost incurred by the Food and Drug Administration in the review of a human drug application that is not subject to priority review in the previous fiscal year.

(3) Annual fee setting

The Secretary shall establish, before the beginning of each fiscal year beginning after September 30, 2012, the amount of the priority review user fee for that fiscal year.

(4) Payment

(A) In general

The priority review user fee required by this subsection shall be due upon the notification by a sponsor of the intent of such sponsor to use the voucher, as specified in subsection (b)(4)(A). All other user fees associated with the human drug application shall be due as required by the Secretary or under applicable law.

(B) Complete application

An application described under subparagraph (A) for which the sponsor requests the use of a priority review voucher shall be considered incomplete if the fee required by this subsection and all other applicable user fees are not paid in accordance with the Secretary's procedures for paying such fees.

(C) No waivers, exemptions, reductions, or refunds

The Secretary may not grant a waiver, exemption, reduction, or refund of any fees due and payable under this section.

(5) Offsetting collections

Fees collected pursuant to this subsection for any fiscal year-

(A) shall be deposited and credited as offsetting collections to the account providing appropriations to the Food and Drug Administration; and

(B) shall not be collected for any fiscal year except to the extent provided in advance in appropriations Acts.

(d) Designation process

(1) In general

Upon the request of the manufacturer or the sponsor of a new drug, the Secretary may designate-

(A) the new drug as a drug for a rare pediatric disease; and

(B) the application for the new drug as a rare pediatric disease product application.

(2) Request for designation

The request for a designation under paragraph (1) shall be made at the same time a request for designation of orphan disease status under section 360bb of this title or fast-track designation under section 356 of this title is made. Requesting designation under this subsection is not a prerequisite to receiving a priority review voucher under this section.

(3) Determination by Secretary

Not later than 60 days after a request is submitted under paragraph (1), the Secretary shall determine whether-

(A) the disease or condition that is the subject of such request is a rare pediatric disease; and

(B) the application for the new drug is a rare pediatric disease product application.

(e) Marketing of rare pediatric disease products

(1) Revocation

The Secretary may revoke any priority review voucher awarded under subsection (b) if the rare pediatric disease product for which such voucher was awarded is not marketed in the United States within the 365-day period beginning on the date of the approval of such drug under section 355 of this title or section 351 of the Public Health Service Act [42 U.S.C. 262].

(2) Postapproval production report

The sponsor of an approved rare pediatric disease product shall submit a report to the Secretary not later than 5 years after the approval of the applicable rare pediatric disease product application. Such report shall provide the following information, with respect to each of the first 4 years after approval of such product:

(A) The estimated population in the United States suffering from the rare pediatric disease.

(B) The estimated demand in the United States for such rare pediatric disease product.

(C) The actual amount of such rare pediatric disease product distributed in the United States.

(f) Notice and report

(1) Notice of issuance of voucher and approval of products under voucher

The Secretary shall publish a notice in the Federal Register and on the Internet Web site of the Food and Drug Administration not later than 30 days after the occurrence of each of the following:

(A) The Secretary issues a priority review voucher under this section.

(B) The Secretary approves a drug pursuant to an application submitted under section 355(b) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] for which the sponsor of the application used a priority review voucher under this section.

(2) Notification

If, after the last day of the 1-year period that begins on the date that the Secretary awards the third rare pediatric disease priority voucher under this section, a sponsor of an application submitted under section 355(b) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] for a drug uses a priority review voucher under this section for such application, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a document-

(A) notifying such Committees of the use of such voucher; and

(B) identifying the drug for which such priority review voucher is used.

(g) Eligibility for other programs

Nothing in this section precludes a sponsor who seeks a priority review voucher under this section from participating in any other incentive program, including under this chapter, except that no sponsor of a rare pediatric disease product application may receive more than one priority review voucher issued under any section of this chapter with respect to the drug for which the application is made..[2]

(h) Relation to other provisions

The provisions of this section shall supplement, not supplant, any other provisions of this chapter or the Public Health Service Act [42 U.S.C. 201 et seq.] that encourage the development of drugs for tropical diseases and rare pediatric diseases.

(i) GAO study and report

(1) Study

(A) In general

Beginning on the date that the Secretary awards the third rare pediatric disease priority voucher under this section, the Comptroller General of the United States shall conduct a study of the effectiveness of awarding rare pediatric disease priority vouchers under this section in the development of human drug products that treat or prevent such diseases.

(B) Contents of study

In conducting the study under subparagraph (A), the Comptroller General shall examine the following:

(i) The indications for which each rare disease product for which a priority review voucher was awarded was approved under section 355 of this title or section 351 of the Public Health Service Act [42 U.S.C. 262].

(ii) Whether, and to what extent, an unmet need related to the treatment or prevention of a rare pediatric disease was met through the approval of such a rare disease product.

(iii) The value of the priority review voucher if transferred.

(iv) Identification of each drug for which a priority review voucher was used.

(v) The length of the period of time between the date on which a priority review voucher was awarded and the date on which it was used.

(2) Report

Not later than 1 year after the date under paragraph (1)(A), the Comptroller General shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate, a report containing the results of the study under paragraph (1).

(June 25, 1938, ch. 675, §529, as added Pub. L. 112–144, title IX, §908, July 9, 2012, 126 Stat. 1094 ; amended Pub. L. 114–113, div. A, title VII, §765, Dec. 18, 2015, 129 Stat. 2286 ; Pub. L. 114–229, §2(a), Sept. 30, 2016, 130 Stat. 943 ; Pub. L. 114–255, div. A, title III, §3013(a), Dec. 13, 2016, 130 Stat. 1093 ; Pub. L. 116–159, div. C, title I, §2105, Oct. 1, 2020, 134 Stat. 729 ; Pub. L. 116–215, div. B, title II, §1211, Dec. 11, 2020, 134 Stat. 1045 ; Pub. L. 116–260, div. BB, title III, §321, Dec. 27, 2020, 134 Stat. 2932 ; Pub. L. 117–9, §1(a)(4), Apr. 23, 2021, 135 Stat. 257 .)

DRAFT GUIDANCE

Rare Pediatric Disease

Priority Review Vouchers

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OOPD) Aaron Friedman at 301–796–2989, or (CBER) Stephen Ripley at 240-402-7911, or (CDER) Althea Cuff at 301-796-4061, or (OPT) Terrie Crescenzi at 301-796-8646.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Office of Orphan Products Development (OOPD)
Office of Pediatric Therapeutics (OPT)

July 2019

Revision 1

Rare Pediatric Disease Priority Review Vouchers Guidance for Industry

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U.S. Department of Health and Human Services
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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information on the implementation of section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA),[71] which added section 529 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act).[72] Under section 529, FDA[73] 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.[74] 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;[75] programs that encourage or require the study of drugs used in pediatric populations under the Best 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

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

[72] 21 U.S.C. 360ff. Unless otherwise noted, references to "sections" in this guidance are to sections of the FD&C Act.

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

[74] 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).

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

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 Act8) 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 Act9 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

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).
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/cellul arandgenetherapy/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.
The statutory definition for the term "human drug application" is "an application for--
approval of a new drug submitted under section 355(b) of this title, or
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.
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].[76]

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 lifethreatening 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].

[76] 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.

Serious or life-threatening manifestations primarily affect children

Of note, section 529 describes the pediatric population as from birth through 18 years.[77][78] 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.[79] 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.[80]

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).

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[77] We interpret "from birth to 18 years" as including all individuals less than 19 years of age (i.e., as from 0 through [78] 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).

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

[80] 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 lifethreatening 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.[81] 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,[82] 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.

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.[83]

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

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[81] 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).
[82] 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.
[83] *See* section 529(a)(4).

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[84]:

− For prevention or treatment[85] 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.[86]

Is submitted under section 505(b)(1) of the FD&C Act[87] 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).[88]

Q3. What does it mean to be "for" prevention or treatment of a rare pediatric disease?[89]

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:

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[84] See footnote 8.
[85] See footnote 15.
[86] 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).
[87] See footnote 9.
[88] 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.
[89] *See* Section 529(a)(4)(A)(i).

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).

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).[90] Indeed, studies using novel therapies should generally be conducted in young adults (18 to 21 years of age) prior to exposing 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.[91] 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

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[90] *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.

[91] 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.

application for FDA's review.[92] 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.[93] 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?

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.[94]

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."

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[92] 21 CFR 314.50(d)(5)(iv); 21 CFR 601.2; 21 U.S.C. 379h.
[93] 21 U.S.C. 379h. [28] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf .
[94] Section 529(e)(2).

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.[95]

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[96] or a request for fast track designation under section 506.[97] 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:

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.[98]

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 preNDA/BLA meeting

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[95] 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.

[96] 21 U.S.C. 360bb.

[97] 21 U.S.C. 356.

[98] 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.

because many of the features of fast track designation will no longer be applicable after that time.[99][100]

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.[101] 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 order to be eligible to receive a voucher.[102] 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:

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;

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[99] 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/ucm128

[100] .htm.

[101] 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).

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

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;

The proposed dosage form and route of administration;

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;

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;

An explanation of the mechanism of action, with supportive data, suggesting that the drug may be effective in the rare pediatric disease;[103]

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

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[103] 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.

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.[104] 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 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."[105] 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

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[104] 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.

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

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,[106] 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:

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.[107]

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 nonrare 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 lifethreatening 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;

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[106] 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.
[107] Section 529(b)(4)(A)(i).

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.

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,[108] 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

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

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.[109] 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?

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).

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[109] *Id*.

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.[110] 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[111] 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.

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[110] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf.
[111] See footnote 9.
[48] See footnote 9.

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 Act48 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").[112] This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric 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.[113]

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.[114]

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.[115] 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.[116]

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.[117] 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

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[112] Section 529(b)(4)(B)(i).
[113] *Id*.
[114] *Id*.
[115] Section 529(b)(2).
[116] Section 529(b)(4)(B)(ii).
[117] Section 529(b)(2)(B).

in response to Question 19). A complete record of transfer must be made available to FDA in order to redeem a transferred voucher.[118]

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.[119] 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.[120] Payment of this 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.[121]

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.[122] 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.[123]

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,[124] 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?

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[118] *Id*. *See also* section 529(b)(4)(B).
[119] Section 529(c)(1).
[120] Section 529(c)(2).
[121] Section 529(c)(4)(C).
[122] Section 529(c)(4)(A).
[123] Section 529(c)(4)(B).
[124] See footnote 45.

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 been approved in any other application under section 505(b) of the FD&C Act.[125] 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.[126]

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.

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[125] 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.

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

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).[127]

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

Q31. Will a drug that receives rare pediatric disease designation also qualify for orphandrug 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.[128] 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 orphandrug 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.[129] 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.

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[127] Section 529(b)(3).
[128] Section 529(a)(3)(B). *See also* section 526.
[129] See 21 CFR 316.25(a)(2).

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 301796-7900.

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[130] 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.

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

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).

Q34. Whom should I contact if I have questions about a rare pediatric disease product application?

Sponsors with questions not addressed in this guidance should contact OOPD for questions related to designation as a rare disease, OPT for questions related to designation as a rare pediatric disease, and the appropriate review division or office within CDER or CBER for questions related to rare pediatric disease product applications. CDER and CBER encourage early interaction with potential sponsors on these issues (e.g., in a pre-IND meeting or early in the clinical development program).

ORPHAN DRUG ACT

THE ORPHAN DRUG ACT AIMS TO ENCOURAGE DRUG DEVELOPMENT FOR RARE DISEASES. IT PROVIDES FINANCIAL INCENTIVES SUCH AS A SEVEN-YEAR PERIOD OF MARKET EXCLUSIVITY FOR A DRUG APPROVED TO TREAT AN ORPHAN DISEASE, A TAX CREDITS OF UP TO 50% FOR RESEARCH AND DEVELOPMENT EXPENSES FOR THE FIRST INDICATION AND A WAIVER OF USER FEES FOR DRUG APPLICATIONS.

US CODE

21 U.S.C. § 360aa. Recommendations for investigations of drugs for rare diseases or conditions

(a) Request by sponsor; response by Secretary. The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before—
(1) it may be approved for such disease or condition under section 355 of this title, or
(2) if the drug is a biological product, it may be licensed for such disease or condition under section 262 of title 42.
If the Secretary has reason to believe that a drug for which a request is made under this section is a drug for a disease or condition which is rare in the States, the Secretary shall provide the person making the request written recommendations for the non-clinical and clinical investigations which the Secretary believes, on the basis of information available to the Secretary at the time of the request under this section, would be necessary for approval of such drug for such disease or condition under section 355 of this title or licensing of such drug for such disease or condition under section 262 of title 42.
(b) Regulations. The Secretary shall by regulation promulgate procedures for the implementation of subsection (a) of this section.

21 U.S.C. § 360bb. Designation of drugs for rare diseases or conditions
(a) Request by sponsor; preconditions; "rare disease or condition" defined
(1) The manufacturer or the sponsor of a drug may request the Secretary to designate the drug as a drug for a rare disease or condition. A request for designation of a drug shall be made before the submission of an application under section 355(b) of this title for the drug, or the submission of an application for licensing of the drug under section 262 of title 42. If the Secretary finds that a drug for which a request is submitted under this subsection is being or will be investigated for a rare disease or condition and—
(A) if an application for such drug is approved under section 355 of this title, or
(B) if a license for such drug is issued under section 262 of title 42,
the approval, certification, or license would be for use for such disease or condition, the Secretary shall designate the drug as a drug for such disease or condition. A request for a designation of a drug under this subsection shall contain the consent of the applicant to notice being given by the Secretary under subsection (b) of this section respecting the designation of the drug.
(2) For purposes of paragraph (1), the term "rare disease or condition" means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.
(b) Notification of discontinuance of drug or application as condition. A designation of a drug under subsection (a) of this section shall be subject to the condition that—
(1) if an application was approved for the drug under section 355(b) of this title or a license was issued for the drug under section 262 of title 42, the manufacturer of the drug will notify the

Secretary of any discontinuance of the production of the drug at least one year before discontinuance, and
(2) if an application has not been approved for the drug under section 355(b) of this title or a license has not been issued for the drug under section 262 of title 42 and if preclinical investigations or investigations under section 355(i) of this title are being conducted with the drug, the manufacturer or sponsor of the drug will notify the Secretary of any decision to discontinue active pursuit of approval of an application under section 355(b) of this title or approval of a license under section 262 of title 42.
(c) Notice to public. Notice respecting the designation of a drug under subsection (a) of this section shall be made available to the public.
(d) Regulations. The Secretary shall by regulation promulgate procedures for the implementation of subsection (a) of this section.

21 U.S.C. § 360cc. Protection for drugs for rare diseases or conditions
(a) Exclusive approval, certification, or license
Except as provided in subsection (b), if the Secretary-
(1) approves an application filed pursuant to section 355 of this title, or
(2) issues a license under section 262 of title 42

for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title or issue another license under section 262 of title 42 for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. Section 355(c)(2) [1] of this title does not apply to the refusal to approve an application under the preceding sentence.
(b) Exceptions
During the 7-year period described in subsection (a) for an approved application under section 355 of this title or license under section 262 of title 42, the Secretary may approve an application or issue a license for a drug that is otherwise the same, as determined by the Secretary, as the already approved drug for the same rare disease or condition if-
(1) the Secretary finds, after providing the holder of exclusive approval or licensure notice and opportunity for the submission of views, that during such period the holder of the exclusive approval or licensure cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated; or
(2) the holder provides the Secretary in writing the consent of such holder for the approval of other applications or the issuance of other licenses before the expiration of such seven-year period.

(c) Condition of clinical superiority
(1) In general
If a sponsor of a drug that is designated under section 360bb of this title and is otherwise the same, as determined by the Secretary, as an already approved or licensed drug is seeking exclusive approval or exclusive licensure described in subsection (a) for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already approved or licensed drug that is the same drug.

(2) Definition
For purposes of paragraph (1), the term "clinically superior" with respect to a drug means that the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.
(3) Applicability
This subsection applies to any drug designated under section 360bb of this title for which an application was approved under section 355 of this title or licensed under section 262 of title 42 after August 18, 2017, regardless of the date on which such drug was designated under section 360bb of this title.
(d) Regulations
The Secretary may promulgate regulations for the implementation of subsection (c). Beginning on August 18, 2017, until such time as the Secretary promulgates regulations in accordance with this subsection, the Secretary may apply any definitions set forth in regulations that were promulgated prior to such date, to the extent such definitions are not inconsistent with the terms of this section, as amended by such Act.
(e) Demonstration of clinical superiority standard
To assist sponsors in demonstrating clinical superiority as described in subsection (c), the Secretary-
(1) upon the designation of any drug under section 360bb of this title, shall notify the sponsor of such drug in writing of the basis for the designation, including, as applicable, any plausible hypothesis offered by the sponsor and relied upon by the Secretary that the drug is clinically superior to a previously approved drug; and
(2) upon granting exclusive approval or licensure under subsection (a) on the basis of a demonstration of clinical superiority as described in subsection (c), shall publish a summary of the clinical superiority findings.

21 U.S.C. § 360dd. Open protocols for investigations of drugs for rare diseases or conditions
If a drug is designated under section 360bb of this title as a drug for a rare disease or condition and if notice of a claimed exemption under section 355(i) of this title or regulations issued thereunder is filed for such drug, the Secretary shall encourage the sponsor of such drug to design protocols for clinical investigations of the drug which may be conducted under the exemption to permit the addition to the investigations of persons with the disease or condition who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs.

21 U.S.C. § 360ee. Grants and contracts for development of drugs for rare diseases and conditions

(a) Authority of Secretary
The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in (1) defraying the costs of developing drugs for rare diseases or conditions, including qualified testing expenses, (2) defraying the costs of developing medical devices for rare diseases or conditions, and (3) defraying the costs of developing medical foods for rare diseases or conditions.
(b) Definitions
For purposes of subsection (a):

(1) The term "qualified testing" means-
(A) human clinical testing-
(i) which is carried out under an exemption for a drug for a rare disease or condition under section 355(i) of this title (or regulations issued under such section); and
(ii) which occurs before the date on which an application with respect to such drug is submitted under section 355(b) of this title or under section 262 of title 42;

(B) preclinical testing involving a drug for a rare disease or condition which occurs after the date such drug is designated under section 360bb of this title and before the date on which an application with respect to such drug is submitted under section 355(b) of this title or under section 262 of title 42; and
(C) prospectively planned and designed observational studies and other analyses conducted to assist in the understanding of the natural history of a rare disease or condition and in the development of a therapy, including studies and analyses to-
(i) develop or validate a drug development tool related to a rare disease or condition; or
(ii) understand the full spectrum of the disease manifestations, including describing genotypic and phenotypic variability and identifying and defining distinct subpopulations affected by a rare disease or condition.

(2) The term "rare disease or condition" means (1) in the case of a drug, any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug, (2) in the case of a medical device, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical device for such disease or condition will be developed without assistance under subsection (a), and (3) in the case of a medical food, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance under subsection (a). Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under section 360bb of this title is made.
(3) The term "medical food" means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
(c) Authorization of appropriations
For grants and contracts under subsection (a), there is authorized to be appropriated $30,000,000 for each of fiscal years 2018 through 2022.

GUIDANCE

FDA GUIDANCE FOR INDUSTRY: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases: (December 2017)

SAFEGUARDS FOR CHILDREN IN CLINICAL INVESTIGATIONS: IRB AND CONSENTS

REGULATIONS

Subpart D - Additional Safeguards for Children in Clinical Investigations

§ 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in § 50.51, § 50.52, or § 50.53 and the conditions of all other applicable sections of this subpart D.

§ 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that:

(a) No greater than minimal risk to children is presented; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in § 50.55.

[78 FR 12951, Feb. 26, 2013]

§ 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of § 50.51, § 50.52, or § 50.53, the clinical investigation may proceed only if:

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of § 50.51, § 50.52, or § 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine, in accordance with and to the extent that consent is required under part 50, that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations to be conducted under § 50.51 or § 50.52.

(2) Where clinical investigations are covered by § 50.53 or § 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased,

unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by § 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under § 50.53 or § 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

GUIDANCE

Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA Under 21 CFR 50.54. Additional Safeguards for Children in Clinical Investigations

Additional copies are available from:
Office of Policy, Office of the Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301)827-3360 http://www.fda.gov/

U.S. Department of Health and Human Services
Food and Drug Administration
December 2006
Final Guidance

Contains Nonbinding Recommendations

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GUIDANCE FOR CLINICAL INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS AND SPONSORS

Process for Handling Referrals to FDA Under 21 CFR 50.54
Additional Safeguards for Children in Clinical Investigations

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, Institutional Review Boards (IRBs), sponsors, and other interested parties in understanding the Food and Drug Administration's (FDA or agency) process for handling clinical investigations that include children as subjects and that have been referred to FDA for review under 21 CFR 50.54. This guidance describes the procedures FDA generally intends to follow in handling such clinical investigations and in reaching final determinations pursuant to that regulation. It is based in part on FDA's experience to date with such referrals. The Department of Health and Human Services (HHS) has human subject protection regulations that also govern research involving children and supported or conducted by HHS. (See 45 CFR Part 46 Subpart D.) This guidance also addresses situations in which a clinical investigation is subject to both 21 CFR 50.54 and 45 CFR 46.407.[131]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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

FDA adopted 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations", as an interim final rule in April 2001 (21 CFR Part 50, Subpart D) (Subpart D) (See 66 FR 20598, April 24, 2001). Under these regulations an IRB must review clinical investigations that involve children as subjects and are covered by Subpart D and must approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52 or 50.53, and the conditions of all other applicable sections of Subpart D. If an IRB does not believe that a clinical investigation within the scope described in 21 CFR 50.1 and 56.101 and

[131] The HHS Subpart D regulations are implemented and interpreted by HHS's Office for Human Research Protections (OHRP) and are nearly identical to FDA's regulations. OHRP has posted on its website information pertaining to its process for handling clinical protocols that are subject to 45 CFR 46.407, and to 45 CFR 46.407 as well as FDA's Subpart D regulations. See www.hhs.gov/ohrp/children/guidance_407process.html.

involving children as subjects meets the requirements of 21 CFR 50.51, 50.52 or 50.53, the clinical investigation may proceed only if:
The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
The Commissioner of Food and Drugs (Commissioner), after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: - The clinical investigation in fact satisfies 21 CFR 50.51, 50.52 or 50.53, or - The following three conditions described in 21 CFR 50.54 are met:
The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
The clinical investigation will be conducted in accordance with sound ethical principles; and
Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55.

III. REVIEW PROCESS

In FDA-regulated clinical investigations involving children, the agency makes every effort to protect the rights, safety, and welfare of those children. In addition, the agency strives to achieve the basic goals of adherence to sound ethical principles, transparency through public and expert input, efficiency, timeliness, clarity, and consistency. These goals are also endorsed by the Subcommittee on Research Involving Children of the Secretary's Advisory Committee on Human Research Protections (SACHRP).[132] FDA believes that these goals are best served by having a clear, efficient, and comprehensive process for referrals by IRBs under 21 CFR 50.54.

A. Overview of Process

FDA will use its advisory committee process to evaluate clinical investigations referred for review under 21 CFR 50.54. This process will provide transparency and help ensure expert input as well as public participation. When FDA receives a referral from an IRB, the agency will determine if the clinical investigation described in the protocol is regulated by FDA as described in 21 CFR 50.1(a). If so, the agency will determine whether the referral is complete and can be accepted for processing. If the referral is accepted, the agency generally will call a meeting of the Pediatric Ethics Subcommittee (the Subcommittee) of the Pediatric Advisory Committee (PAC) and present the referral to the Subcommittee for its consideration. At the next open meeting of the PAC, the Subcommittee chair (or another member of the Subcommittee, if the chair is unavailable) will present to the PAC the Subcommittee's recommendation(s) regarding the referred clinical investigation. After discussion and deliberation, the PAC will make its recommendation(s) regarding the referral to the Commissioner of Food and Drugs. The Commissioner will then make the final determination as to whether the clinical investigation meets the requirements of FDA's Subpart D regulations. This process is discussed in greater detail below.

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[132] See Recommendations for OHRP/FDA Harmonization Subcommittee on Research Involving Children of SACHRP, January 29, 2004 minutes, page 9.

B. Public Participation

Public review and comment is required under 21 CFR 50.54. Furthermore, FDA believes that public participation is important to help ensure the comprehensiveness and integrity of the review of clinical investigations referred under that regulation and the protection of the children who may be enrolled in the investigations. In order to encourage public participation, FDA intends to establish an agency docket for each accepted referral and solicit public comment on the proposed investigation. The materials in the docket for each investigation will include the referral documents sent by the IRB, related agency correspondence, public comments on the referral, the transcripts of both the Subcommittee meeting and the PAC meeting, and the final determination of the Commissioner regarding the referral under 21 CFR 50.54. Materials submitted to the docket will be available through FDA's Division of Dockets Management or through FDA's Division of Freedom of Information.

In addition, the Subcommittee and PAC meetings will be open to the public. At the Subcommittee meeting, the chair will also present a summary of the public comments received.

C. Scheduling the Subcommittee and Advisory Committee Meetings

When FDA receives an appropriate and complete referral[133] from an IRB under 21 CFR 50.54, the Office of Pediatric Therapeutics (OPT) will coordinate with the Executive Secretary[134] of the PAC regarding the scheduling of the Subcommittee and PAC meetings. FDA generally expects to schedule Subcommittee meetings directly preceding a PAC meeting. The PAC is currently scheduled to meet approximately three times per year, but FDA will consider calling additional meetings as necessary.

D. Submitting a Referral

The agency encourages IRBs considering referring a clinical investigation under § 50.54 first to discuss with the sponsor whether there are appropriate modifications to the protocol that would allow the clinical investigation to be approved under another provision of Subpart D.

IRBs should send referrals under 21 CFR 50.54 of clinical investigations regulated by FDA, as described in 21 CFR 50.1(a), to FDA's OPT at opt@fda.gov, or Office of Pediatric Therapeutics, Office of the Commissioner, FDA, 5600 Fishers Lane, RM 13B-45, HFG-2, Rockville, MD 20857. FDA may also receive copies of referrals from OHRP in situations where an IRB has referred a clinical investigation to OHRP but not to FDA. Similarly, if an IRB submits a clinical investigation to FDA but not to OHRP, FDA will usually send it to OHRP so that OHRP can determine whether the clinical investigation is also subject to HHS jurisdiction. If a clinical investigation is subject to both HHS and FDA jurisdiction, then, as discussed below in Section III.O., the referral process will be conducted jointly by FDA and OHRP under 21 CFR 50.54 and 45 CFR 46.407.

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[133] See discussion of the joint review process with OHRP in section III.O

[134] The Executive Secretary is the Designated Federal Official (DFO) who coordinates the activities of the advisory committee and serves as the link between committee members, FDA, industry and the public.

E. Documents to Include in the Referral

If an IRB decides to refer a clinical investigation for consideration under 21 CFR 50.54, the IRB should submit its finding (required under 21 CFR 50.54(a)) that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

The referral should also include the following:
An explanation as to why the IRB does not believe that the clinical investigation meets the requirements of 21 CFR 50.51, 50.52, or 50.53. FDA believes that in most cases this probably will be explained in the IRB's minutes from its discussions of the protocol at issue.
The research protocol and, if the clinical investigation is being conducted under an Investigational New Drug application (IND) or Investigational Device Exemption (IDE), the IND or IDE number assigned by FDA;
All informed consent documents, including the parental permission form and, if being used, the assent forms and/or a description of the assent process; and
Any other informative supporting documents, such as IRB minutes pertinent to the clinical investigation, correspondence between the IRB and the investigator, product labeling, and the investigator's brochure.

In addition, the IRB should ensure that the submitted documents consistently describe the clinical investigation**. We strongly encourage IRBs to submit electronic versions of all documents.**

These documents are needed to allow FDA to complete its initial assessment of the clinical investigation to determine if the study is subject to FDA jurisdiction, and to provide the Subcommittee and the PAC with complete information regarding the referral. The referring IRB should provide these documents in a form the IRB would find approvable, but for the issue(s) that prompted the referral under 21 CFR 50.54. Providing these documents in "IRB-approvable" condition will allow the Subcommittee and the PAC to focus on the issue(s) that prompted the referral, and not on other matters that the IRB is able to resolve itself.

When OPT receives a referral, it will contact the referring IRB to confirm receipt of the referral. This will begin the process of exchanging information about the referral process between OPT, the IRB, and the investigator. Either in that initial contact or subsequently, OPT will advise the IRB as to whether the clinical investigation is subject to FDA jurisdiction and, if it is, whether the referral is complete, and thus acceptable for review, or whether any information is missing from the submission. Depending on the circumstances of the research, OPT may ask for additional information, which may include, for example, information regarding the past use of the investigational article in children or adults, documents regarding continuing review, drug preparation protocol, or the certificate of analysis for the chemical being studied. During this exchange OPT will explain the procedures the agency intends to follow and will encourage the IRB to ask any questions it might have about the requirements of 21 CFR 50.54.

Following this exchange, the IRB may decide to withdraw the referral from consideration. The reasons for withdrawal could include, for example, a misunderstanding of the requirements of the Subpart D regulations and the applicability of 50.54 to the clinical investigation at issue, i.e., a determination by the IRB after further analysis that the clinical investigation can in fact

proceed under another provision in the Subpart D regulations. The agency encourages the IRB to document the reasons for withdrawal of the referral in its request to do so. FDA suggests that an IRB in doubt about whether to refer a clinical investigation under 50.54 consult with OPT as soon as possible via email at opt@fda.gov.

F. Assessment of Referral

Following receipt of the referral, FDA will determine whether the protocol is FDA-regulated (generally within 2 weeks after receipt) and inform the referring IRB in writing of the determination. If the clinical investigation was referred to FDA by OHRP, FDA will also inform OHRP of that determination.

The considerations under FDA's IND regulations (see 21 CFR Part 312) and IDE regulations (see 21 CFR Part 812) that are used to determine whether an IND or IDE can go into effect are related to, but distinct from, the considerations under Part 50 regarding the protection of human subjects. Therefore, IRBs should note that, although some clinical investigations are exempt from the requirement that they need be conducted under an IND (see 21 CFR 312.2(b)), those that are exempt are still subject to 21 CFR Parts 50 and 56 and thus may trigger the Subpart D process under section 50.54. Similarly, a clinical investigation of a medical device may be exempt under 21 CFR 812.2(c) from the requirement that it be conducted under an IDE, but the clinical investigation may still be subject to the Subpart D process. Furthermore, as indicated in 21 CFR 50.1(a), Part 50 also applies to certain investigations that are not subject to sections 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (21 USC §§ 355(i), 360j(g)).

G. Acceptance of Referral

Following receipt of the referral, OPT will then ask the referring IRB for any other relevant documents and inform the IRB that FDA intends to post the documents in the docket created for the referral, and on the agency's website. If the IRB believes that any documents it has included in its referral may be considered confidential by the sponsor, the IRB will be responsible for obtaining any necessary permission from the sponsor to post the documents. If an IRB (or sponsor) objects to the public posting of the documents, the agency will be unable to proceed with the referral.

H. Multi-Site Clinical Investigations

In some circumstances clinical investigations referred for review under 21 CFR 50.54 may be conducted at multiple sites. In the event that an IRB at one or more of the clinical sites refers the investigation for review, it should notify the sponsor. In such a situation, FDA strongly encourages the sponsor to notify the IRB(s) and investigator(s) at all of the other sites of the referral. Once an IRB has made a referral under 50.54, pursuant to that regulation the investigation may not proceed (i.e., no subjects may be recruited or enrolled in the investigation) at any site for which that IRB has responsibility.

Once IRBs at other sites have been notified by the sponsor of the referral, they may choose to allow the clinical investigation to proceed at their sites, or they may choose to await the outcome of the 50.54 referral. In making this determination, FDA encourages IRBs to consider the implications of continuing the investigation during the pendency of the review and determination

under 21 CFR 50.54. For example, at the conclusion of the review, it is possible that the Commissioner could determine that the investigation cannot proceed because one or more of the criteria in 21 CFR 50.54(b) are not met. Alternatively, the Commissioner might determine that the investigation can proceed but only with modifications of the protocol or the informed consent documents and procedures. At the sites where the clinical investigation goes forward, the IRBs of record retain all normal responsibilities for review and oversight.

I. Federal Register Notices

Following a referral, FDA generally will issue three Federal Register notices:
A solicitation of public comments on the referral, along with background information for the referral, notice of the establishment of a docket for the referral, and directions for how to access the docket. Generally, FDA will provide approximately 4 weeks for submission of comments to the docket;
The announcement of the Pediatric Ethics Subcommittee meeting; and
The announcement of the Pediatric Advisory Committee meeting.

J. Composition of the Pediatric Ethics Subcommittee

FDA will select the members of the Subcommittee in accordance with 21 CFR 50.54(b) and other relevant federal laws, including the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2)(1972). The Subcommittee will include at least two members of the PAC. Whenever possible, the selected members of the PAC will have clinical expertise relevant to the subject matter under discussion. FDA will also invite individuals to serve on the Subcommittee who have expertise and/or experience relevant to the clinical investigation being discussed. As a general matter, OPT will make these selections in collaboration with the relevant FDA Center(s) and review division(s). Additional individuals will be invited according to the principles set forth in 21 CFR 50.54(b), such that the Subcommittee consists of a "panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law)" (21 CFR 50.54(b)). As a general matter, FDA also believes that usually it will be helpful to include a patient advocate/community representative and a statistician on the Subcommittee.

The agency notes that there will be no cap on the number of members of the Subcommittee, and the agency will include as many members as necessary to ensure that the relevant expertise is represented.

K. The Subcommittee Meeting

FDA intends to invite a representative of the referring IRB (to be selected by the IRB) and the investigator to attend the Subcommittee meeting and to make a presentation to the Subcommittee regarding the referred protocol. The agency encourages the IRB representative and the investigator to attend the meeting to help the Subcommittee understand the clinical investigation and basis for the referral. One or more representatives from the FDA review division responsible
for reviewing the clinical investigation may also attend to answer questions from the Subcommittee. As appropriate, the agency may invite additional individuals to make presentations to the Subcommittee regarding either the referred protocol or issues raised in it (for example, the sponsor of the clinical investigation, or, in a situation involving a multi-site trial, a

representative from an IRB that has approved the protocol). Although a referral may be made because of a particular aspect of the clinical investigation, the Subcommittee and the PAC, as well as FDA (and OHRP if they are involved[135]), usually will consider the clinical investigation in its entirety.

FDA anticipates that a Subcommittee meeting usually will last for one day and a typical agenda will include:
Call to order
Meeting statement
Description of Subpart D expert panel process
Overview, charge to panel
Background of clinical investigation and protocol-specific scientific/medical issues
Investigator comments
IRB comments, including identification of specific ethical issues which led to the referral
Summary of public comments
Open public hearing
Presentation of questions
Expert panel discussion
Discussion, agreement, and vote on recommendation(s) (summary of deliberations) that will be presented to PAC.

The Subcommittee will operate by majority vote. Meeting transcripts and recommendations from the Subcommittee meeting will be made available to the public in the docket established for the referral and on the agency's website.

L. PAC Meeting

At the next meeting of the PAC (usually shortly after the Subcommittee meeting), the chair of the Subcommittee (or another member of the Subcommittee, if the chair is unavailable) will present the Subcommittee's recommendation(s) regarding whether the clinical investigation meets the requirements of Subpart D and other relevant requirements of Part 50. The agency also encourages the IRB representative and the investigator to attend the PAC meeting such that they are available to answer questions about the referred protocol. After discussion of the clinical investigation and the recommendation(s), the PAC will vote on its recommendation(s) to the Commissioner regarding whether the proposed clinical investigation may proceed under 21 CFR Part 50 Subpart D. The PAC's recommendations may include changes that the PAC believes are necessary for the clinical investigation to proceed as well as other suggested changes to improve the investigation. In cases where FDA and OHRP are working jointly to review a clinical investigation subject to both FDA's and HHS' regulations, the PAC recommendation(s) also will be made to the Secretary. (See Section III.O., for more details on studies subject to joint FDA-HHS reviews.)

The PAC will operate by majority vote. Meeting transcripts and recommendation(s) from the PAC meeting will be made available to the public in the docket established for the referral and on the agency's website. After the PAC meeting, the chair will usually summarize the recommendation(s) of the PAC in a letter to OPT.

[135] See discussion of joint review process with OHRP in section III.O.

M. Transmittal Memorandum

OPT will draft and send a transmittal memorandum to the Commissioner outlining the PAC and Subcommittee recommendation(s), and including any recommendations/comments that FDA may have. The transmittal memorandum also will include any other necessary supporting documentation. The transmittal memorandum will request that the Commissioner make a final determination as to whether, and if so, under what provisions of Subpart D, the clinical investigation may proceed. After the Commissioner has made a final determination, OPT will forward that determination to the referring IRB and will post it in the docket created for the referral and on the agency's website.

N. Referral Process Timing

OPT projects that this referral process will take approximately six months to complete; complex submissions may take longer to process (e.g., protocols involving a joint referral with OHRP).

O. FDA-DHHS joint review under 21 CFR 50.54 and 45 CFR 46.407

In light of the need for both consistency and efficiency, the process for IRB referrals of proposed clinical investigations that are both HHS-conducted or supported and FDA-regulated will function in essentially the same manner as the process for FDA-only referrals. In such cases:
HHS, through OHRP, will participate in the selection of members for the Subcommittee.
After the Subcommittee makes a recommendation to the PAC, the PAC will make its recommendation(s) to both the Secretary of HHS and the Commissioner of Food and Drugs.
OPT will forward the Commissioner's determination to OHRP.
OHRP will send a transmittal memo with its recommendation, the Commissioner's determination, and all supporting documents, including the recommendation(s) of the PAC and the summary of the Subcommittee meeting, to the Secretary for a determination as to whether the clinical investigation may be conducted or supported by HHS.

ELIGIBILITY REGARDING CHILDREN ON ADULT CANCER STUDIES

Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th
Floor Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2019
Clinical/Medical

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Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials
Guidance for Industry[136]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

INTRODUCTION

The purpose of this guidance is to provide the pharmaceutical industry, clinical investigators, and institutional review boards with information to facilitate the inclusion of adolescent patients (for purposes of this guidance, defined as ages 12 to 17) in relevant adult oncology clinical trials. FDA recommends the inclusion of adolescent patients in disease- and target-appropriate adult oncology clinical trials to enable earlier access to investigational and approved drugs[137] for adolescent patients with cancer. Topics that are discussed in this guidance include the following:

Appropriate criteria for the inclusion of adolescent patients in adult oncology clinical trials at various stages of drug development

Dosing and pharmacokinetic and pharmacodynamic evaluations

Safety monitoring

Ethical considerations

The information in this guidance is meant to serve as a general guideline for sponsors considering this approach. Because specific details of an adult oncology drug development program that includes adolescent patients will vary depending on the characteristics and development stage of the drug and disease(s) under evaluation, sponsors are encouraged to

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[136] This guidance has been prepared by the Divisions of Hematology and Oncology Products and Clinical Pharmacology V in the Center for Drug Evaluation and Research and the Oncology Center of Excellence (OCE) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

contact the responsible FDA review division to discuss details of the program before implementation.

In addition, enrolling adolescent patients in adult oncology clinical trials may contribute toward addressing pediatric regulatory requirements under section 505A or 505B of the Federal Food, Drug, and Cosmetic Act. Details of these requirements should be discussed with the responsible FDA review division.

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.

BACKGROUND

Cancers in young pediatric patients are often different from those in adult patients and require unique treatment approaches; however, some cancers found in adolescent patients—such as some soft tissue and bone sarcomas, central nervous system tumors, leukemias and lymphomas, and melanoma—are similar in histology and biologic behavior to those found in adults. Adolescent patients, because of their age, have historically been ineligible for enrollment in adult oncology clinical trials, and the initial pediatric trials for many drugs are conducted years later, often after the drug is approved in adults. As a result, adolescent patients may have delayed access to potentially effective therapies. In addition, accrual of adolescent patients to pediatric trials evaluating approved drugs may be difficult because patients can receive the drug through off-label use.

CRITERIA INCLUDING ADOLESCENT PATIENTS IN ADULT FOR ONCOLOGY CLINICAL TRIALS

Adolescent patients should be eligible for enrollment in adult oncology clinical trials at all stages of drug development when the histology and biologic behavior of the cancer under investigation is the same in, or the molecular target of the drug is relevant to, cancers in both adult and adolescent patients.

The following are recommendations regarding including adolescent patients by stage of drug development:

First-in-human or dose-escalation trials:

– Adolescent patients may be enrolled after some initial adult pharmacokinetic and toxicity data are obtained. The sponsor should consult with the responsible FDA review division to determine the amount and type of adult data needed before enrolling adolescent patients.

– In general, adolescent patients enrolled in these early phase trials should have cancers that are relapsed after or refractory to standard therapy with no curative options or for which no standard therapies with curative intent exist.

Activity-estimating or confirmatory trials:

– Adolescent patients can be enrolled simultaneously with adults

DOSE SELECTION FOR ADOLESCENT PATIENTS IN ADULT ONCOLOGY CLINICAL TRIALS

Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on pharmacokinetics. Selection of an appropriate dose for adolescent patients in clinical trials should be based on pharmacokinetic and/or pharmacodynamic characteristics of the investigational drug with consideration of body size effect on drug exposure, toxicity, and activity data (if available); the therapeutic index of the drug; and dose- and exposure-response relationships in adults.[138]

The following are recommendations for dosing based on how the drug is dosed in adults:

For drugs with **body size-adjusted dosing** for adults, adolescent patients should receive the same body size-adjusted dose (mg/kg or mg/m^2) that is administered in adults.

For drugs administered as a **fixed dose** based on data showing no clinically meaningful body size effect on drug exposure and toxicity in adults, a minimum body weight threshold should be defined to prevent adolescent patients who have a lower body weight than average from exceeding adult exposures.

– An FDA analysis of adult population pharmacokinetics of oncology drugs suggested that 40 kg (the approximate median body weight of a 12-year-old[139]) is generally the lower end of the body weight range that has no clinically relevant effect on drug pharmacokinetics or safety. (This cutoff may change based on the characteristics of the drug, including the effect of body size on pharmacokinetics, the therapeutic index, and dose- and exposure-response relationships.)

– In general, adolescent patients who weigh at least 40 kg can receive the same fixed dose administered in adults.

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[138] Selection of an appropriate dose for adolescent patients may be more complex for certain biological products that are regulated by CBER. Sponsors of such products should consult with the relevant review division in CBER to determine if there are specific considerations they should take into account with respect to their products.

[139] See the Clinical Growth Charts web page under National Center for Health Statistics at the Centers for Disease Control and Prevention website (https://www.cdc.gov/growthcharts/clinical_charts.htm).

– In general, adolescent patients who weigh less than 40 kg should switch to a body weight (mg/kg) or body surface area (mg/m^2) adjusted dose. This adjusted dose should be based on an adult reference body size (e.g., the average adult body weight of 70 kg or median body weight or surface area of the adult patient population determined from existing data).

Pharmacokinetic and/or pharmacodynamic (if available) samples should be collected from adolescent patients included in the adult oncology drug development program.

SAFETY MONITORING

Safety data collected during the trial should be examined for any age-related differences.

The evaluation of developmental toxicities (e.g., growth derangements, fertility issues) that require a long duration of follow-up may not be possible in the context of early phase trials; however, the sponsor should develop a plan for longitudinal evaluation of potential developmental toxicities when it is feasible, particularly in trials enrolling patients in earlier lines of therapy.

Adolescent patients enrolled in adult oncology clinical trials should have access to appropriate care providers and facilities necessary to address the clinical management of potentially unique toxicities in this patient population, which may require pediatric oncology expertise.

Juvenile animal studies are not routinely needed before the enrollment of adolescent patients in adult oncology clinical trials, unless clinical and/or nonclinical data do not provide sufficient information on toxicities.[140]

ETHICAL CONSIDERATIONS

Under 21 CFR 50.50, institutional review boards reviewing adult oncology clinical trials that allow for the enrollment of adolescent patients must ensure that the provisions of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, and, specifically, 21 CFR 50.52, Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects, are satisfied before approving the studies. Considerations should include disease and/or molecular target, available therapeutic options, and dose level for first-in-human trials.

Enrollment of appropriately selected adolescent patients in relevant adult oncology clinical trials with appropriate dose considerations and adequate safety monitoring is justified given the severe and life-threatening nature of their disease.

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[140] Leighton, JK, Saber H, Reaman G, and Pazdur R, 2016, An FDA Oncology View of Juvenile Animal Studies in Support of Initial Pediatric Trials for Anticancer Drugs, Regul Toxicol Pharmacol, Aug; 79:142–143.

COMBINATION STUDIES

GUIDANCES

Contains Nonbinding Recommendations

Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research Food and Drug Administration 10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714 druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)

June 2013 Clinical Medical

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Guidance for Industry[141]

Codevelopment of Two or More New Investigational Drugs for Use in Combination

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors in the codevelopment[142] of two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition. For purposes of this guidance, these not-previously-developed drugs are referred to as *new investigational drugs*. The guidance provides recommendations and advice on how to address certain scientific and regulatory issues that may arise during codevelopment of two or more new investigational drugs. It is not intended to apply to development of fixed combinations of previously approved drugs or to development of a single new investigational drug to be used in combination with a previously approved drug or drugs. FDA believes the recommendations in this guidance relevant to demonstrating the contribution of the individual new investigational drugs to the effect(s) of the combination are consistent with the requirements of 21 CFR § 300.50, "fixed-combination prescription drugs for humans." This guidance applies only to drugs and biological products regulated by the Center for Drug Evaluation and Research.[143] The guidance is not intended to apply to biological products regulated by the Center for Biologics Evaluation and Research or medical devices.

FDA's guidance documents, including this guidance, 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

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[141] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[142] The term *codevelopment* as used in this guidance refers to the concurrent development of two or more new investigational drug products that are intended to be used in combination to treat a disease or condition. A sponsor may elect to codevelop two or more new investigational drug products to be marketed as individual agents intended to be used in combination as a fixed-combination or co-packaged drug.

[143] For purposes of this guidance, the term *drug* includes therapeutic biological products that are regulated by CDER. Consult the Therapeutic Biologics Web page for further information on the types of biological products to which this guidance applies, on the Internet at

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Combination therapy is an important treatment modality in many disease settings, including cancer, cardiovascular disease, and infectious diseases. Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus to develop new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response, minimize development of resistance, or minimize adverse events. In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of new investigational drugs.

Because existing developmental and regulatory pathways focus primarily on assessment of the safety and effectiveness of a single new investigational drug acting alone, or in combination with a previously approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more new investigational drugs. Although interest in codevelopment has been most prominent in oncology and infectious disease settings, codevelopment also has potential application in other therapeutic settings. Therefore, this guidance is intended to describe a high-level, generally applicable approach to codevelopment of two or more new investigational drugs. It describes the criteria for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.

III. DETERMINING WHETHER CODEVELOPMENT IS AN APPROPRIATE DEVELOPMENT OPTION

Codevelopment generally will provide less information about the clinical safety and effectiveness and dose-response of the individual new investigational drugs intended to be used in combination than would be obtained if the individual drugs were developed alone. How much less information will vary depending on a variety of factors, including the stage of development at which the individual new investigational drugs cease to be studied independently. For example, in codevelopment scenarios in which rapid development of resistance to monotherapy is a major concern, it may not be possible or appropriate to obtain clinical data for each drug in the combination beyond phase 1 testing. Because co-development generally will provide less information about the individual new investigational drugs, it may present greater risk compared

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplicati ons/TherapeuticBiologicApplications/default.htm.

to clinical development of an individual drug. Given this concern, FDA believes that codevelopment should ordinarily be reserved for situations that meet all of the following criteria:

The combination is intended to treat a serious disease or condition.[144]

There is a strong biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway or steps in disease pathogenesis, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity).

A full nonclinical characterization of the activity of both the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents[145] A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.

There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., monotherapy for the disease of interest leads to resistance, one or both of the agents would be expected to have very limited activity when used as monotherapy).

FDA recommends that sponsors consult with FDA on the appropriateness of codevelopment before initiation of clinical development of a combination.

IV. NONCLINICAL CODEVELOPMENT

A. Demonstrating the Biological Rationale for the Combination

The biology of the disease, pathogen, or tumor type should be sufficiently understood to provide a plausible biological rationale for the use of combination therapy to treat the disease or condition. For example, in an oncology setting, the biological rationale may be to intervene at different steps in the cell proliferation pathway. The biological rationale for a combination antiinfective therapy may be to target different metabolic pathways or different steps in the replication cycle of the pathogen to reduce the chance of developing resistance to the therapy or

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[144] For purposes of this guidance, the term *serious disease or condition* refers to a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. This definition is consistent with various statutory and regulatory provisions concerning the use of FDA-regulated medical products to treat serious or life-threatening diseases and conditions. See, e.g. § 561 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC § 360bbb) and corresponding regulations (21 CFR part 312 subpart I) regarding expanded access to unapproved therapies and diagnostics; § 505-1 of the FD&C Act (21 USC § 355-1) regarding Risk Evaluation and Mitigation Strategies; FDA regulations at 21 CFR part 314 subpart H and 21 CFR part 601 subpart E regarding accelerated approval; and § 506 of the FD&C Act (21 USC 356 regarding fast track development and designation.

[145] For purposes of this guidance, the term "available therapy" is interpreted as it is described in the guidance for industry on *Available Therapy*. This guidance is available on the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

increase efficacy in treating disease caused by resistant organisms (e.g., multidrug-resistant tuberculosis).

Sponsors should develop evidence to support the biological rationale for the combination in an in vivo (preferable) or in vitro model relevant to the human disease or condition the product is intended to treat. The model should compare the activity of the combination to the activity of the individual drugs. The model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), and/or a better toxicity profile than the individual new investigational drugs. In addition to valuable activity data, a relevant model may provide information about the relative doses of the individual new investigational drugs.

B. Nonclinical Safety Characterization

For detailed recommendations regarding nonclinical safety characterization for two or more new investigational drugs to be used in combination, sponsors should consult the International Conference on Harmonisation (ICH) guidance on nonclinical safety studies (ICH M3(R2)).[146] Section XVII of ICH M3(R2) (Combination Drug Toxicity Testing) includes a discussion of nonclinical safety studies appropriate in a combination drug development setting involving two early stage entities. ICH M3(R2) defines early stage entities as compounds with limited clinical experience (i.e., phase 2 studies or less), so the discussion is specifically applicable to the type of development described in this guidance. In situations in which it is possible to obtain only limited clinical data for the individual new investigational drugs, additional nonclinical data for the individual drugs or combination may be needed before beginning human studies with the combination (e.g., see section V.A.1 below). For codevelopment of anticancer combinations, sponsors should consult the guidance for industry ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*.[147]

V. CLINICAL CODEVELOPMENT

This section provides a general roadmap and guiding principles for concurrent clinical development of two or more new investigational drugs to be used in combination. It includes recommendations for characterizing the clinical safety and effectiveness of the combination and, to the extent needed or possible, the individual drugs in the combination.

Note: The appropriate review division should be consulted on the specifics of a given clinical development program.

A. Early Human Studies (Phase 1)

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[146] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization* at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. ICH M3(R2) is a revision of the 1997 ICH guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.*

[147] See the ICH guidance for industry ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm085389.pdf

The main objectives of early studies in humans are to characterize the safety and pharmacokinetics of both the individual new investigational drugs and the combination and to provide data to support appropriate dosing for the combination in phase 2 testing.

1. Safety of the Individual New Investigational Drugs

Whenever possible, the safety profile of each individual new investigational drug should be characterized in phase 1 studies in the same manner as would be done for the development of a single drug, including determination of the maximum tolerated dose (MTD), the nature of the dose limiting toxicity (DLT), and pharmacokinetic parameters. If there is a useful measure (e.g., biomarker) of pharmacologic activity, it will also be important to determine dose-response for that measure. If testing in healthy volunteers is not possible (e.g., if nonclinical data suggest a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers), the safety profile of the individual drugs should be evaluated in patients with the disease of interest. These safety data will guide decisions in later studies about starting doses, dose escalation increments, and final dose selection.

If it is not possible to characterize the safety of the individual new investigational drugs in humans (e.g., where drug toxicity prevents use of healthy volunteers and even short duration monotherapy would be unethical in patients with the disease of interest), the sponsor should conduct nonclinical studies of the combination to support initial dosing of the combination in humans. The nonclinical data for the combination should include pharmacokinetic (absorption, distribution, metabolism, and excretion) and toxicokinetic data and appropriate biomarker/target interaction data, if relevant.

2. Safety and Dosing of the Combination

For initial human effectiveness studies of the combination, the combination starting dose, dosing escalation intervals, and doses to be used in dose-response studies should be determined primarily from the phase 1 safety data for the individual new investigational drugs, if available. If phase 1 safety data for the individual drugs are unavailable, nonclinical data for the combination may be needed to determine the initial combination dose in humans (see previous section). Phase 1 safety studies of the combination may also be important in some cases because of the potential for additive toxicity. One study design that could be used is sequential testing in which subjects get drug A, then drug B, then A and B together.

B. Clinical Pharmacology

The sponsor should conduct the same clinical pharmacology studies for each of the individual new investigational drugs in the combination as would be done if the drugs were being developed separately — including assessment of bioavailability, characterization of pharmacokinetics, and mass balance. Studies to evaluate the effects of intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors on pharmacokinetics and pharmacodynamics, and exposure-response could be conducted either with the individual drugs or the combination. The role of pharmacogenomics should be investigated and incorporated into the combination drug development plan to identify potential sources of pharmacokinetic or pharmacodynamic variability.

The evaluation of drug interaction potential should follow the same sequence as is used in other development programs; results of in vitro drug metabolism and drug transporter studies would inform the need for in vivo drug interaction studies.

If feasible, dose-response should be evaluated for each individual new investigational drug in the combination. The results of such studies should be used to determine doses at which to further explore the combination. If the individual new investigational drugs cannot be administered alone, various doses of each drug administered in combination should be assessed. If one drug has no activity or minimal activity when used alone, dose-response should be assessed when the individual drugs are administered in combination using a number of different doses of both the active drug and the inactive drug. A similar approach should be used to evaluate dose-response where each drug in the combination has minimal activity when used alone.

Response should also be evaluated with respect to systemic drug concentration to provide insight into efficacy and safety as a function of drug exposure. Concentration-response assessments should be done in phase 2 and phase 3 trials. In phase 3 trials, use of more than one dose of each of the drugs in the combination should be considered to increase exposure ranges and further assess dose-response.

C. Proof of Concept Studies (Phase 2)

In general, phase 2 testing should accomplish the following for a given combination:

Further demonstrate the contribution of each individual new investigational drug in the combination to the extent possible and needed (i.e., to the extent not sufficiently established by existing data);
Provide evidence of the effectiveness of the combination; and
Optimize the dose or doses of the combination for phase 3 trials.

The amount and types of clinical data needed and appropriate study designs will vary depending on the nature of the combination being developed, the disease or condition the combination is intended to treat, and other factors. A factorial study designed to assess the effects attributable to each drug in the combination is generally the preferred design to support combination use. However, there may be circumstances in which it would be inappropriate to use one or more of the drugs in the combination as monotherapy in studies of the disease or condition of interest, or it would only be possible to administer the individual drugs in the combination as monotherapy for short durations. In these circumstances, a factorial design will have limited utility.

The following scenarios illustrate possible phase 2 study designs for combinations of two new investigational drugs in different situations. Scenario 1 includes a discussion of a standard factorial design as well as an adaptive factorial design that could be used if there is uncertainty about using the individual drugs as monotherapy. Scenario 2 describes an alternative design that may be useful when the drugs in the combination cannot be administered as monotherapy. Scenario 3 describes a design that might be used when one drug in the combination has minimal or no activity and is intended primarily to enhance the activity of the other drug.

<u>Scenario 1: Each new investigational drug alone has activity and they can be administered separately</u>

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that each new investigational drug has some activity, but the combination appears to have greater activity, and rapid development of resistance is not a concern, a four-arm, phase 2 trial in the disease or condition of interest comparing the combination to each drug alone and to placebo or standard of care (SOC) (AB v. A v. B v. SOC or placebo[148]) should be used to demonstrate the contribution of the individual drugs to the combination and proof of concept. If SOC is a known effective therapy (not solely palliative), a study design in which each of the arms is added to SOC could be used (AB + SOC v. A + SOC v. B + SOC v. placebo + SOC).

An adaptive trial design[149] with the same four treatment arms might also be used where appropriate, initially using the treatment arms described above and terminating the singledrug arms early if it becomes clear that the single agents have much less activity than the combination. Such a design may demonstrate the contribution of each drug to the activity of the combination without exposing the large number of patients typically required for phase 3 trials to therapeutic products with inadequate activity. When determining whether to terminate monotherapy treatment arms early, it may be necessary to use endpoints that provide evidence of treatment effect more readily than endpoints that would be used in confirmatory phase 3 trials to minimize the amount of time subjects may be exposed to a low activity drug. For example, it may be preferable to use viral load, response rate, or a persuasive pharmacodynamic or other biomarker rather than survival or cure rate.

Scenario 2: The individual new investigational drugs in the combination cannot be administered separately

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that the individual new investigational drugs in the combination cannot be administered separately in clinical trials in the disease of interest (e.g., because such testing would involve administering treatment known to be ineffective as monotherapy), or cannot be administered as monotherapy for the duration needed to evaluate effectiveness (e.g., because of rapid development of resistance), proof-of-concept evidence for the combination ordinarily should come from a study directly comparing the combination (AB) to SOC. Alternatively, if SOC is known effective therapy (not solely palliative), an add-on design could be used comparing the combination plus SOC to placebo plus SOC.

In some resistance scenarios, it may be possible to administer the individual drugs in the combination as monotherapy for a short duration, but long enough to establish proof of concept in humans. For example, direct-acting antivirals (DAAs) to treat chronic hepatitis C virus infection could be administered as monotherapy for 3 days to establish antiviral activity and for initial dose exploration. For DAA studies of longer duration, the combination should be used or the individual drugs should be added to an active control.[150]

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[148] Note that in this scenario the placebo arm is intended to show the effect size compared to no treatment, not to show the contribution of each drug.

[149] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics.* This draft guidance is available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf.

[150] See the draft guidance for industry *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral*

Scenario 3: When administered separately, one new investigational drug in the combination is active and one is inactive

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies suggest that one of the new investigational drugs in the combination is inactive or minimally active and one drug is modestly active, but the combination has substantial activity, the more active drug generally will require greater scrutiny and should ordinarily be studied as a single drug in a phase 2 study. The minimally active drug generally would not require study as a single drug beyond initial phase 1 safety studies. In this scenario, proof of concept and the contribution of each new investigational drug could be demonstrated using a three-arm comparison of the active drug alone, the combination, and SOC (A v. AB v. SOC), or the combination and the individual drug added to SOC where SOC is a known effective therapy (AB + SOC v. A + SOC v. placebo + SOC).

If the inactive drug in a combination contributes to the activity of the combination only by increasing the systemic concentrations of the active drug, human pharmacokinetic data may provide adequate evidence to support the contribution of the inactive drug. A confirmatory study of the combination would usually be needed to provide evidence of effectiveness for the combination (see section V.D).

Dose Finding — Dose-finding studies could be very important to refine the combination dose or doses and select doses for phase 3 trials. Depending on the role of each new investigational drug, it may be useful to test multiple doses of both drugs to establish the optimal combination dose in terms of risks and benefits. If one new investigational drug in a two-drug combination is more active than the other, it may be more important to study multiple doses of the more active drug (as part of the combination). For the same reason, it may be more important to study multiple doses of a drug that is significantly more toxic than the other drug in the combination. Other study designs and types of studies also may be appropriate.

D. Confirmatory Studies (Phase 3)

The appropriate phase 3 study design generally will be a case-by-case determination based on what has been previously demonstrated about the effects of the combination and the individual new investigational drugs, the feasibility of monotherapy and SOC alone treatment arms, and other factors. For example:

If findings from in vivo or in vitro models and/or phase 2 trials adequately demonstrate the contribution of each new investigational drug to the combination, phase 3 trials comparing the combination to SOC or placebo generally will be sufficient to establish effectiveness.

If the contribution of the individual new investigational drugs is not clear and it is ethically feasible to use one or more of the individual drugs as monotherapy in a study arm, the contribution of the individual drugs could be demonstrated using a factorial design (see Scenario

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Agents for Treatment (section III.A.4.b – Phase 1b (proof-of-concept) trials)) or consult the Division of Antiviral Drug Products in CDER for more specific recommendations. This draft guidance is available on the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

1 in section V.C). It may be possible to do a factorial study using only active drug treatment arms (AB v. A v. B). This design would be adequate to demonstrate the contribution of each new investigational drug, but would not be able to directly measure the overall treatment effect. However, if the effect of SOC is wellestablished and known to be small, it may be possible to estimate the treatment effect of the combination without a concurrent SOC or placebo arm.

If phase 2 data do not provide sufficient evidence of the contribution of each new investigational drug in a two-drug combination, but do provide strong evidence that the combination is superior to one of the drugs alone, a two-arm design comparing the combination to the more active drug alone (AB v. A) may be needed to demonstrate that the less active drug (B) contributes to the activity of the combination. In this situation, it may be useful to study more than one dose of the more active drug.

Unexpected toxicity (e.g., serious adverse events observed at higher than expected rates) in phase 2 trials is a potential complication for development of a combination and progressing to phase 3 trials. If the toxicity can be attributed to one drug in the combination, it may be possible to conduct phase 3 trials with the combination using a lower dose or doses of the more toxic drug.
If the toxicity cannot be attributed to an individual drug in the combination, additional studies may be needed to identify the more toxic drug and appropriate dosing for the combination before initiating phase 3 trials. The specifics of any phase 3 design should be discussed with the appropriate FDA review division at an end-of-phase 2 meeting.

VI. REGULATORY PROCESS ISSUES IN CODEVELOPMENT

Sponsors should consider a number of regulatory issues when planning the codevelopment of two or more new investigational drugs for use in combination. Key issues are outlined below.

A. Early Interaction with FDA

Sponsors are encouraged to communicate as early as possible (e.g., pre-IND meeting) with the appropriate CDER review division when considering codevelopment. Sponsors also are encouraged to consult FDA as needed throughout the development process. We expect that such communication will help facilitate development of the combination therapy.

B. Investigational New Drug Applications (INDs)

1. INDs for the Combination and the Individual New Investigational Drugs

Decisions about IND submissions required under 21 CFR part 312 for the combination and individual new investigational drugs in the combination will depend on the development objectives and the timing of the decision to pursue codevelopment. The following general principles apply:

If a sponsor intends to undertake codevelopment as described in this guidance, there should be one IND for the combination that covers all of the drugs in the combination at the point in time at which the sponsor initiates clinical studies of the combination.

If a sponsor is undecided about development of a combination, it may be appropriate to conduct preliminary proof-of-concept clinical studies for the combination under an IND for one of the drugs in the combination, provided that there is a single agent IND in effect for each drug in the combination (i.e., provided FDA has the information required under the IND regulations for each of the drugs). If the sponsor then decides to pursue development of the combination, it could do so under the single agent IND (which will become the combination IND) or submit a new IND for the combination.

If a sponsor intends to develop a combination and develop one or more of the drugs in the combination for use as a single agent, there should be a separate IND for the combination and each of the individual drugs being developed.

If the individual drugs in a combination would be reviewed by different review divisions within FDA, the combination IND should be submitted to the division that has jurisdiction over the indication for the combination.

Decisions about IND submissions for codevelopment scenarios that are not covered by these general principles will be determined on a case-by-case basis in consultation with the appropriate review division(s).

When submitting an IND for a combination, sponsors may cross-reference existing INDs for the individual drugs in the combination. If the sponsor of the combination IND is not the sponsor of the IND for one of the drugs used in the combination, the sponsor of the combination IND must obtain written authorization to cross-reference any content in the other sponsor's IND that is used to support the combination IND (§ 312.23(b)).

2. IND Safety Reports

In cases in which there is an active IND for the combination and active INDs for one or more of the individual drugs in the combination, IND safety reports required under § 312.32(c) for adverse events that occur in studies of the combination should be submitted to the IND for the combination and all INDs for the individual drugs in the combination. If a reportable adverse event occurs in a study of one of the individual drugs in the combination, the report should be submitted to the IND for that individual drug and to the IND for the combination.

The IND safety report submitted to the IND for the study in which the adverse event occurred is considered the original report. Reports submitted to other INDs should be clearly identified as duplicates to ensure that the same adverse event is not counted more than once. If a report is submitted to multiple INDs, each IND safety report should identify all INDs to which the report is submitted.

3. IND Annual Reports

There must be separate IND annual reports (21 CFR 312.33) for the combination IND and any individual drug INDs. The reports should cross-reference each other. Each annual report should identify all INDs to which the report is cross-referenced.[151]

4. Other IND Submissions

Where there is a combination IND and INDs for one or more individual drugs, sponsors should consider whether the information in a planned IND submission is relevant to only one IND or to multiple INDs. Consider the following examples:

A protocol submission for a study of the combination should be submitted only to the combination IND.

Chemistry, manufacturing, and controls for the combination should be submitted only to the combination IND.

A nonclinical information amendment describing carcinogenicity studies with the combination should be submitted to the combination IND and any INDs for the individual drugs in the combination.

Where information is relevant to more than one IND, the information can be submitted in its entirety to each IND or can be submitted to one IND and cross-referenced in the other INDs.

C. Marketing Applications

In general, decisions about the type or types of marketing application(s) to be submitted for a drug-drug combination (e.g., combination application, individual drug applications) will depend on how the applicant intends to market the combination and the individual drugs, as well as the data submitted in support of the application. We anticipate that applications will be submitted and user fees assessed consistent with FDA's user fee bundling policy (see Guidance for Industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*). The following examples illustrate how we anticipate applications may be submitted for different types of combinations, but FDA should be consulted prior to making any of the submissions discussed in this section:

Example 1: If the individual drugs in the combination will be marketed as distinct products (separate packaging), a separate marketing application for each drug in the combination should be submitted.

Example 2: In Example 1, if the applicant also intends to market one or more of the drugs in the combination for use as monotherapy, the same marketing application can be used for the combination and monotherapy uses.

[151] Also see the ICH guidance for industry *E2F Development Safety Update Report*, section II.E, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Example 3: If the drugs in the combination will be marketed as a combination drug product (i.e., either a co-packaged or a fixed-combination drug), a single marketing application for the combination should be submitted.

Example 4: In Example 3, if the applicant also intends to market one or more of the drugs in the combination for use as monotherapy, a separate marketing application should be submitted for the individual drug(s) for monotherapy use.

Example 5: If the individual drugs in a combination drug product are marketed first as a co-packaged drug, an application for a corresponding fixed-combination drug may be submitted as a supplement to the co-packaged drug application.

Other examples not listed here should be discussed with FDA.

If an application cross-references any information in an IND or marketing application not owned by the applicant that is needed to support approval of the marketing application, the application must contain a written authorization to cross-reference such information (21 CFR 314.50(g)(1)).

D. Labeling

Decisions about how to meet the labeling requirements in 21 CFR 201.57 will also depend on how the applicant intends to market the combination.

If the individual drugs in the combination will be marketed together as a combination drug product (either a fixed-combination or co-packaged drug), the prescribing information for the combination should be a single document describing use of the combination.

If the individual drugs in the combination will be marketed as distinct products intended for use in combination, there should be separate prescribing information for each distinct product. The prescribing information for each drug should include pertinent information concerning the safe and effective use of the combination, reference the labeling of the other product(s), and state that the drug was developed and studied for use in combination with the other drug(s).

There are a range of other potential scenarios in which one or more of the drugs in a combination may be limited to combination use only, or may be indicated for combination use, monotherapy, and/or in combination with drugs other than those with which the drug was codeveloped. It is advisable for applicants to consult FDA concerning their specific circumstances.

Decisions about how to provide patient-directed information such as a Medication Guide or administration instructions should be made on a case-by-case basis in consultation with FDA.

E. Postmarketing Safety Monitoring Considerations

Postmarketing safety monitoring should consider additional postmarketing risks that may be presented by initial marketing of two or more new investigational drugs for use in combination as compared to the risks associated with marketing a single new investigational drug. Risks will vary depending on the nature of the combination and how the combination is marketed. Applicants should consider potential postmarketing risks from, among other things:

Potential for use of each drug individually;
Potential for use of any of the drugs in the combination with marketed drugs other than those with which the drugs were codeveloped; and
Other drugs likely to be co-administered with the combination.

FDA encourages sponsors to consult with the appropriate FDA divisions to discuss their proposed approach to postmarketing safety monitoring.

Cross Labeling Oncology Drugs in Combination Regimens Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th
Floor Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Rm.
3128 Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Cross Labeling Oncology Drugs in Combination Regimens Guidance for Industry[152]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

INTRODUCTION

Drug approvals in oncology often build on treatment effects by adding drugs[153] to current regimens or by combining investigational drug products in a combination regimen, creating new regimens with greater efficacy. For the purpose of this guidance, a *combination regimen* refers to two or more drugs that are marketed separately, where at least one of the drugs has an approved indication for the combination based upon one or more adequate and well-controlled clinical trials. *Cross labeling* is defined as inclusion of information in approved product labeling of two or more oncology drug products approved in a combination regimen for a specific indication.

The purpose of this guidance is to describe the Food and Drug Administration's (FDA's) current recommendations about including relevant information in labeling for oncology drugs[154] approved for use in a combination regimen, including important considerations for cross labeling of these drugs. This guidance does not address all issues that might arise relating to labeling for oncology drugs for use in a combination regimen. Applicants proposing cross labeling for oncology drug combination regimens should contact the review division for information on cross labeling of their individual products. This guidance also does not address circumstances in which a drug product and a biological product packaged separately constitute a cross-labeled combination product as defined in 21 CFR 3.2(e).

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[152] This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[153] For the purposes of this guidance, all references to *drug* or *drugs* include both human drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and therapeutic biological products licensed under section 351 of the Public Health Service Act. For the purposes of this guidance, codevelopment of two or more new investigational drugs for use in combination has the meaning described in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.

[154] For the purpose of this guidance, *oncology drugs* refer to drugs indicated for the treatment of malignant disease or diseases.

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.

BACKGROUND AND SCOPE

Cross labeling of two or more drugs administered in a combination regimen can provide clear, consistent, and accessible information to guide the safe and effective use of the cross-labeled drugs in a regimen for oncological disease or diseases. The intent of cross labeling is to provide information in product labeling for the drugs used in a combination regimen that is complementary and consistent; the intent is not to include all of the same information in labeling for each drug in the combination regimen.

The scope of this guidance is limited to oncology drugs for which (1) the applicant owns or has a right of reference[155,156] to the data demonstrating the safety and effectiveness of the new combination regimen for treatment of an oncological disease, (2) the applicant submits an application to FDA that includes labeling for the use of the drug in this new combination regimen, and (3) the application provides evidence to support the contribution of the applicant's drug to the overall treatment effect of the combination regimen.

The recommendations in this guidance are not intended for drugs outside its scope. Applicants in non-oncology therapeutic areas should contact the applicable review division if they wish to discuss whether cross labeling may be appropriate for their application.

PROCEDURES FOR CROSS LABELING APPLICATION SUBMISSIONS

A. Timing for Cross Labeling Regulatory Submissions

Applicants should discuss the proposed content of the planned application, including the evidence establishing the contribution of each drug in the combination regimen, in their proposal for cross labeling a new oncology drug combination regimen in a pre-new drug application/biologics license application meeting or a pre-supplemental new drug application/biologics license application meeting.

[155] *Right of reference* has the same meaning as defined in 21 CFR 314.3.

[156] This guidance does not address use of the pathway described by section 505(b)(2) of the FD&C Act, which could facilitate cross labeling of two or more drug products regulated under the FD&C Act that are administered in a combination regimen. See the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent the Agency's current thinking on this topic. There are certain regulatory considerations (e.g., patents and exclusivity) for applications submitted through the 505(b)(2) pathway, but discussion of those considerations is beyond the scope of this guidance.

Ideally, cross labeling for each drug identified in the combination regimen will occur at the same time. However, approval of separate applications for cross-labeled drugs may occur in sequence, as applicants may have different timelines for submitting their applications.

B. Regulatory Submissions

Each applicant seeking cross labeling for a drug used in a combination regimen with one or more other drugs must submit an original application or efficacy supplement for cross labeling.[157]

Applicants seeking cross labeling may reference another application's data that demonstrate the treatment effect of the combination regimen if the applicant is the application holder for each drug in the combination regimen or if the applicant obtains a letter of authorization authorizing a right of reference from the appropriate application holder.

The application that is being referenced by the applicant should already be filed by FDA.[158]

Applicants should annotate each section in their application that is being crossreferenced to another application.

CONTENT OF LABELING

This section of the guidance summarizes cross labeling considerations for selected sections in the Full Prescribing Information. This section is not intended to be exhaustive. An applicant that wishes to submit an application for cross labeling of an oncology drug approved for use in a combination regimen should consult with the appropriate oncology prescription drug review division about the specific issues raised by the application. For recommendations for specific sections and subsections of labeling, applicants should refer to FDA's Prescription Drug Labeling Resources website.[159]

For each new drug submitted in an original application as a separately packaged product intended for use in a combination regimen with one or more new drugs or with one or more approved drugs, the new drug's labeling should include information on the safe and effective use

[157] See 21 CFR 314.50, 314.70, 601.2, and 601.12.

[158] See, for example, 21 CFR 314.101, CBER SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA).

[159] See https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

of the combination regimen, as noted below, as well as information that would be limited to the individual drug.[160]

For an approved drug, proposed changes to the approved labeling should include information on the safe and effective use of the drug in combination with the other drug or drugs in the combination regimen.

In general, the brand or trade name should be used for the applicant's drug that is the subject of the original application, and the established name (for a biological product, the proper name) should be used for the other products in the combination regimen.

Below are recommendations that an applicant should consider when submitting an application for cross labeling.

INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES sections:

INDICATIONS AND USAGE section: The indication for the combination regimen should be the same for all drugs approved for use in the combination regimen, except that (1) the applicant's drug should be listed first in the combination regimen and (2) the established name (for a biological product, the proper name) should be used for the other drugs in the combination regimen. This order and naming format should be used in all combination regimen-related labeling text, as appropriate.

DOSAGE AND ADMINISTRATION section:

Although this section should identify the other drug or drugs in the combination regimen,[161] in general, information should be limited to the recommended dosage for the applicant's drug as used in the combination regimen. Dosage information for other drugs in the combination regimen should be provided by statements that refer the reader to the Prescribing Information for the other drugs, as appropriate; however, if the combination regimen dosing is complex or if the Prescribing Information for the other drugs does not contain the necessary dosing information, the recommended dosages of each drug in the combination regimen should be specified in this section.

Dosage modification instructions generally should be limited to the applicant's drug unless there are adverse reactions *associated with the combination regimen* that would require dosage modifications for the other drug or drugs in the combination regimen that are not described in the Prescribing Information for the other drug or drugs.

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[160] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

[161] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010).

The preparation and administration information generally should be included only for the applicant's drug.

– CLINICAL STUDIES section: The clinical trial descriptions and results for the combination regimen should be consistent in the Prescribing Information for each cross-labeled drug in the combination regimen.

Safety information about the other drug or drugs in the combination regimen should be included in both the applicant drug's labeling and the labeling for the other drug or drugs in the regimen when the combination regimen raises significant new safety issues that were not seen with the use of the applicant's drug alone. Examples include but are not limited to the following:

WARNINGS AND PRECAUTIONS section: This section should include information unique to the combination regimen, based on the potentiation or development of novel clinically significant adverse reactions and/or risks. Information about warnings and precautions attributed solely to the other drug or drugs in the combination regimen should ordinarily not be included in the applicant's drug labeling.

ADVERSE REACTIONS section: The *Clinical Trials Experience* subsection should include adverse reactions observed in the trial or trials supporting approval of the cross-labeled combination regimen. In general, the percentage of subjects with a serious adverse reaction or fatal adverse reaction should be reported for those subjects treated with the combination regimen. The percentage of subjects treated with the combination regimen who required permanent discontinuation, dosage interruption, or dosage reduction should be reported, including specific information for the applicant's drug when dosage modification and data collection methodologies permit these determinations.

PATIENT COUNSELING INFORMATION section: Information regarding the combination regimen that a health care provider should convey to patients or caregivers should be limited to unique toxicities and unique preparation and administration instructions relevant to the combination regimen.

The following sections generally should include only information relevant to the applicant's drug (and not the other drug or drugs used in the combination regimen); however, there may be exceptions (e.g., when the pharmacokinetics of one drug in a combination regimen are altered by another drug in the regimen).

BOXED WARNING (if applicable)
DOSAGE FORMS AND STRENGTHS
CONTRAINDICATIONS
DRUG INTERACTIONS
USE IN SPECIFIC POPULATIONS
OVERDOSAGE
DESCRIPTION
CLINICAL PHARMACOLOGY

GIVE KIDS A CHANCE ACT:

One pager:

GIVE KIDS A CHANCE ASK
Give Kids a Chance Act will save lives of children with cancer with combinations of drugs

Despite scientific advances in precision medicines, to get to cures, cancer patients still often require combinations of drugs. As a result, there are now thousands cancer trials studying combinations of novel drugs for adults. However, there are only a handful of cancer trials studying combinations of novel drugs for kids.

The Solution:

The Give Kids a Chance Act amends the RACE for Children Act to provide for pediatric studies of combinations of novel cancer drugs. The Give Kids a Chance Act would not cost taxpayers anything.

Pursuant to the Give Kids a Chance Act, a drug company with an original new drug application submitted to FDA for a new active ingredient to treat an adult cancer may be directed to conduct a pediatric investigation of either a single drug or of a combination of drugs. If the company is directed to conduct a study of a combination of drug, the other drug of a combination can only be one of the following: 1) An already-approved generic or biosimilar drug that is the standard of care for a pediatric cancer, or 2) an already-approved drug to treat an adult cancer which is in the company's pipeline (e.g. for which the 505B(a)(1)(B) applicant is the sponsor), subject to FDA finding that the molecular target of that drug is substantially relevant to a pediatric cancer.

This means that investigating the combination drug does not present any intellectual property issues.

Legislative History:

The Give Kids a Chance Act was passed in the House of Representatives in the 117th Congress as Section 714 of HR 7667, the PDUFA bill. We ask the 118th Congress pass this exact same language.

Draft text:

THE GIVE KIDS A CHANCE ACT,
passed in the House of Representatives as HR 7667, SEC. 714.
RESEARCH INTO PEDIATRIC USES OF DRUGS; ADDITIONAL AUTHORITIES OF FOOD AND DRUG ADMINISTRATION REGARDING MOLECULARLY TARGETED CANCER DRUGS.

(a) In General.—

(1) ADDITIONAL ACTIVE INGREDIENT FOR APPLICATION DRUG; LIMITATION REGARDING NOVEL-COMBINATION APPLICATION DRUG.—Section 505B(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(a)(3)) is amended—

(A) by redesignating subparagraphs (B) and (C) as subparagraphs (C) and (D), respectively; and

(B) by striking subparagraph (A) and inserting the following:

"(A) IN GENERAL.—For purposes of paragraph (1)(B), the investigation described in this paragraph is (as determined by the Secretary) a molecularly targeted pediatric cancer investigation of—

"(i) the drug or biological product for which the application referred to in such paragraph is submitted; or

"(ii) such drug or biological product in combination with—

"(I) an active ingredient of a drug or biological product—

"(aa) for which an approved application under section 505(j) under this Act or under section 351(k) of the Public Health Service Act is in effect; and

"(bb) that is determined by the Secretary to be the standard of care for treating a pediatric cancer; or

"(II) an active ingredient of a drug or biological product—

"(aa) for which an approved application under section 505(b) of this Act or section 351(a) of the Public Health Service Act to treat an adult cancer is in effect and is held by the same person submitting the application under paragraph (1)(B); and

"(bb) that is directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.

(4) CONFORMING AMENDMENTS.—Section 505B(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(a)) is amended—

(A) in paragraph (3)(C), as redesignated by paragraph (1)(A) of this subsection, by striking "investigations described in this paragraph" and inserting "investigations referred to in subparagraph (A)"; and

(B) in paragraph (3)(D), as redesignated by paragraph (1)(A) of this subsection, by striking "the assessments under paragraph (2)(B)" and inserting "the assessments required under paragraph (1)(A)".

(b) Guidance.—The Secretary shall—

(1) not later than 12 months after the date of enactment of this Act, issue draft guidance on the implementation of the requirements in subsection (a); and

(2) not later than 12 months after closing the comment period on such draft guidance, finalize such guidance.

(c) Applicability.—The amendments made by this section apply with respect to any application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and any application under section 351(a) of the Public Health Service Act (42 U.S.C. 262), that is submitted on or after the date that is 3 years after the date of enactment of this Act.

(d) Reports To Congress.—

(1) SECRETARY OF HEALTH AND HUMAN SERVICES.—Not later than 2 years after the date of enactment of this Act, the Secretary of Health and Human Services shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report on the Secretary's efforts, in coordination with industry, to ensure implementation of the amendments made by subsection (a).

(2) GAO STUDY AND REPORT.—

(A) STUDY.—Not later than 3 years after the date of enactment of this Act, the Comptroller General of the United States shall conduct a study of the effectiveness of requiring assessments and investigations described in section 505B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C.355c), as amended by subsection (a), in the development of drugs and biological products for pediatric cancer indications.

(B) FINDINGS.—Not later than 7 years after the date of enactment of this Act, the Comptroller General shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions

of the Senate a report containing the findings of the study conducted under subparagraph (A).

“(B) ADDITIONAL REQUIREMENTS.—

“(i) DESIGN OF INVESTIGATION.—A molecularly targeted pediatric cancer investigation referred to in subparagraph (A) shall be designed to yield clinically meaningful pediatric study data that is gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.

“(ii) LIMITATION.—An investigation described in subparagraph (A)(ii) may be required only if the drug or biological product for which the application referred to in paragraph (1)(B) contains either—

“(I) a single new active ingredient; or

“(II) more than one active ingredient, if an application for the combination of active ingredients has not previously been approved but each active ingredient has been previously approved to treat an adult cancer.

“(iii) RESULTS OF ALREADY-COMPLETED PRECLINICAL STUDIES OF APPLICATION DRUG.—The Secretary may require that reports on an investigation required pursuant to paragraph (1)(B) include the results of all preclinical studies on which the decision to conduct such investigation was based.

“(iv) RULE OF CONSTRUCTION REGARDING INACTIVE INGREDIENTS.—With respect to a combination of active ingredients referred to in subparagraph (A)(ii), such subparagraph shall not be construed as addressing the use of inactive ingredients with such combination.”.

(2) DETERMINATION OF APPLICABLE REQUIREMENTS.—Section 505B(e)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(e)(1)) is amended by adding at the end the following: “The Secretary shall determine whether subparagraph (A) or (B) of subsection (a)(1) shall apply with respect to an application before the date on which the applicant is required to submit the initial pediatric study plan under paragraph (2)(A).”.

(3) CLARIFYING APPLICABILITY.—Section 505B(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(a)(1)) is amended by adding at the end the following:

“(C) RULE OF CONSTRUCTION.—No application that is subject to the requirements of subparagraph (B) shall be subject to the requirements of subparagraph (A), and no application (or supplement to an application) that is subject to the requirements of subparagraph (A) shall be subject to the requirements of subparagraph (B).”.