Dockets Management Branch
Food and Drug Administration
April 12, 2006

Attachment 3

Guidance for Industry (Draft): 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DRAFT GUIDANCE

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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

Guidance for Industry

How to Comply with the Pediatric Research Equity Act

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA).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).

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

[2] 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,[3] 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.[4]

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[5] issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

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[3] 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.

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

[5] 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

1. 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.)

2. 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."[6] 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).

3. 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.

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

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:

- 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 well-controlled 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 life-threatening 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[7] 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

[7] 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.

(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).

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:

(a) 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.

(b) 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).

(c) 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:

(a) 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).

(b) 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).

(c) 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).

(d) 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).

2. 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

3. 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.[8]

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*[9] or should contact the relevant review division.

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

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

IX. ADDITIONAL INFORMATION

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.)

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

2. 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
   _____ Alzheimer's disease
   _____ Amyotrophic lateral sclerosis
   _____ Arteriosclerosis
   _____ Infertility
   _____ Menopause symptoms
   _____ Osteoarthritis
   _____ Parkinson's disease
   _____ Other (please state and justify)

   _____ Basal cell and squamous cell cancer
   _____ Breast cancer
   _____ Colorectal cancer
   _____ Endometrial cancer
   _____ Hairy cell cancer
   _____ Lung cancer (small cell and non-small cell)
   _____ Oropharynx cancers (squamous cell)
   _____ Ovarian cancer (non-germ cell)
   _____ Pancreatic cancer
   _____ Prostate cancer
   _____ Renal cell cancer
   _____ Uterine cancer

   (b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
   (c) 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.
   (d) 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.

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

4. 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.)

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

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

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

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

4. 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):

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

5. 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.

6. 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