Guidance for Industry and Review Staff

Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling

Good Review Practice

DRAFT GUIDANCE

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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)

February 2013
Labeling

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Guidance for Industry and Review Staff[1] Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 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 applicants and review staff at the Food and Drug Administration (FDA) in determining the appropriate placement and content of pediatric information in human prescription drug and biological products labeling in accordance with the final rule amending the requirements for content and format of labeling (71 FR 3922, January 24, 2006).[2]

This guidance does not provide format recommendations for pediatric information in labeling. Format requirements are described in the final rule amending the requirements for content and format of labeling for human prescription drug and biological products (71 FR 3922, January 24, 2006).[3]

The goal of this guidance is to help ensure that all useful information on the use of drugs and biological products in the pediatric population (whether positive, negative, or inconclusive) is

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] 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 products licensed under section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

[3] See the draft guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

consistently placed in the proper sections within labeling so that the information is clear and accessible to health care providers.

This guidance provides recommendations on the following:

- Placement and content of pediatric information in human prescription drug and biological products labeling when available data support a pediatric indication

- Placement and content of pediatric information in human prescription drug and biological products labeling when available data do not support a pediatric indication (i.e., data are negative or inconclusive)

This guidance does not pertain to labeling for nonprescription drug products.[4]

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. Although guidance documents do not legally bind FDA, review staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

II. BACKGROUND

A. History of FDA Pediatric Labeling Initiatives

Up until the early 1990s, the majority of drug labeling contained minimal or no pediatric use information to inform the safe and effective use of these drugs in the pediatric population. In 1994, the FDA began the first of several initiatives to improve pediatric use information in drug labeling by issuing a final rule revising the requirements for the *Pediatric Use* subsection of labeling (59 FR 64242, December 13, 1994). This regulation was designed to promote the inclusion of pediatric information from new clinical trials as well as from previously published pediatric studies and case reports in an effort to provide pediatric dosing and monitoring information in labeling, and it required drug manufacturers to survey existing data and determine whether those data were sufficient to support additional pediatric use information in a drug's labeling. On December 2, 1998 (63 FR 66632), the FDA issued the final rule "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (the pediatric rule). The pediatric rule was suspended by court order on October 17, 2002.

[4] See the guidance for industry *Labeling OTC Human Drug Products — Questions and Answers*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Section 111 of Title I of the Food and Drug Administration Modernization Act, enacted November 21, 1997, created section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355a) that contained economic incentives for pediatric studies of approved drugs, including the 6-month period of pediatric exclusivity to be added to existing exclusivity and patent protection on a drug if studies *fairly respond* to a pediatric Written Request even if the data submitted are inconclusive or do not support a labeling change. This program expired January 1, 2002, and on January 4, 2002, it was reauthorized in the Best Pharmaceuticals for Children Act (BPCA) (21 U.S.C. 355a). The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A of the FD&C Act and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct at their own expense.[5] Title V of the Food and Drug Administration Amendments Act of 2007 (FDAAA), signed into law on September 27, 2007 (21 U.S.C. 355a), reauthorized the BPCA, section 505A of the FD&C Act. The BPCA was made permanent in 2012 with passage of the Food and Drug Administration Safety and Innovation Act (FDASIA).

The Pediatric Research Equity Act (PREA), originally enacted on December 3, 2003 (Public Law 108-155), codified many of the elements of the pediatric rule, and established requirements for studies of certain drugs and biological products used in pediatric patients. PREA (section 505B of the FD&C Act, 21 U.S.C. 355c), reauthorized by FDAAA, as Title IV, on September 27, 2007 (21 U.S.C. 355c) and made permanent in 2012 with the passage of FDASIA, requires pediatric studies for certain drugs and biological products. Specifically, PREA requires applications (or supplements to applications) under section 505 of the FD&C Act or section 351 of the Public Health Service Act (PHSA), respectively, 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 FD&C Act).

PREA also authorizes the FDA to require holders of applications for previously approved marketed drugs approved under section 505 of the FD&C Act and biological products licensed under section 351 of the PHSA, who are not seeking approval for one of the changes specified above, to submit a pediatric assessment under certain circumstances (section 505B(b) of the FD&C Act). Pediatric assessments "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 505(B)(a)(2) of the FD&C Act).

The goal of both BPCA and PREA is to provide pediatric information in drug labeling to encourage the appropriate use of drugs in treating pediatric patients.

[5] In the BPCA, the term *sponsor* refers to an entity that has submitted an investigational new drug application or a new drug application before the new drug application is approved. The term *holder of an approved application* refers to a company holding an approved new drug application to market a drug product containing the drug at issue (21 U.S.C. 355a(b), (c), and (d)).

B. Pediatric Age Categories

The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research generally define the pediatric population in the following manner:[6]

- Neonates: birth up to 1 month
- Infants: 1 month up to 2 years
- Children: 2 years up to 12 years
- Adolescents: 12 years to younger than 17 years

The ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* includes preterm infants as a pediatric population age group, and uses different terms and age ranges for other categories.

- Preterm newborn infants
- Term newborn infants: 0 to 27 days
- Infants and toddlers: 28 days to 23 months
- Children: 2 to 11 years
- Adolescents: 12 to 16-18 years (dependent on region)

The use of age categories depends on the indication and drug being studied and may be modified if there is a valid scientific rationale for an alternate approach (e.g., Tanner staging).

C. Data From BPCA and PREA Studies and Waiver

Data submitted in response to a Written Request[7] under the BPCA and assessments submitted in response to a PREA study requirement must be described in labeling whether findings are positive, negative, or inconclusive (sections 505A(j) and 505B(g)(2) of the FD&C Act). These pediatric data should be placed in the labeling as described in section III., Placement of Pediatric Data in Human Prescription Drug and Biological Products Labeling.

When pediatric studies under PREA are fully or partially waived by the FDA because there is evidence that a drug would be ineffective or unsafe in a pediatric population or pediatric subpopulation, the safety concern or lack of efficacy must be described in labeling (section 505B(a)(4)(D) and 505B(b)(2)(D) of the FD&C Act (21 U.S.C. 355(c))).

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

[7] A Written Request is a specific document from the FDA, generally signed by the applicable office director(s) or authorized delegate, requesting submission of a certain study or studies to determine whether the use of a drug (active moiety) could provide a meaningful health benefit in the pediatric population. The Written Request specifies the elements of the study or studies that the FDA expects a sponsor or application holder to include to earn pediatric exclusivity. The FDA can issue a Written Request at the request of an interested person or on its own initiative. Issuance of a Written Request to a sponsor or holder of an approved application does not require the recipient to conduct the pediatric studies described in the Written Request. It is the recipient's decision whether to conduct the studies and possibly obtain pediatric exclusivity.

D. Extrapolation

Under PREA (section 505B(a)(2)(B) of the FD&C Act), if the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be extrapolated from adult data. Thus, a drug may be considered to be effective in the pediatric population when it has been demonstrated to be effective in adults, if the disease process and the benefits of the drug are expected to be the same in the pediatric population when compared to adults. Considerations for demonstrating that the disease process is similar between adults and the pediatric population include the pathophysiology, natural history of the disease, and maturity of the target organ(s) in the pediatric population. Considerations for concluding that the beneficial effects of the drug are expected to be similar in adults and pediatric patients include mechanism of action and maturity of receptors and enzyme systems in the pediatric population, among others. Decisions regarding whether and when to extrapolate efficacy from adults to pediatric patients are made on a case-by-case basis.

Extrapolation of data from adults to the pediatric population under PREA generally refers only to efficacy and not to safety or dosing. Because pediatric patients may be more or less prone to drug toxicities based on immaturity or developmental changes, the safety of a drug generally should be studied in pediatric patients directly. In addition, the pharmacokinetics of a drug in the pediatric population usually cannot be predicted from that in adults. Therefore, pharmacokinetic studies, when feasible, or pharmacodynamic studies or efficacy clinical trials should be conducted to identify the appropriate pediatric dosing. Scientific data supporting the decision to extrapolate efficacy should be discussed with the appropriate review division during the early stages of drug development, and documentation of these data should be submitted with the protocol and/or final study reports.

PREA further provides for extrapolation from one pediatric age group to another pediatric age group. It states, "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 FD&C Act). Whether or not pediatric studies in more than one age group are necessary depends on the expected therapeutic benefit and use in each age group, and on whether effectiveness data from one age group can be extrapolated to other age groups. As with the use of the adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant pediatric age groups. In some cases (e.g., with some preventive vaccines), it may be appropriate to extrapolate safety and effectiveness from one pediatric age group to another pediatric age group. Decisions about whether and when to extrapolate between pediatric age groups are made on a case-by-case basis.

E. Categories of Pediatric Data for Decision Making

Pediatric data used to make a decision about whether or not a drug will be approved for a pediatric indication generally fall into two major categories: (1) sufficient to support safety and effectiveness in the pediatric population (or one or more relevant pediatric subpopulations); and (2) insufficient to support safety and effectiveness in the pediatric population (or one or more relevant pediatric subpopulations). A pediatric subpopulation is a specifically described group of pediatric patients, generally characterized by age group (21 CFR 201.57(c)(9)(iv)), physiological

stage such as puberty, or disease-related. A pediatric labeling decision tree is available to help facilitate this decision making (see the Appendix: Pediatric Data and Labeling Decision Tree).

1. Substantial Evidence of Effectiveness and Sufficient Evidence to Support Safety

Section 505(d) of the FD&C Act defines substantial evidence of effectiveness as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[8] Sufficient evidence to support safety in the pediatric population usually should be assessed in each pediatric age group studied (section 505B(a)(2)(B)(i) of the FD&C Act).

Use of a drug in the pediatric population, or in one or more relevant pediatric subpopulations, (a pediatric indication) can be supported by available data in the following ways:

- **Studies in the pediatric population (or one or more relevant pediatric subpopulations) only:** All available data for the drug come from a pediatric study or studies, either because the indication studied is unique to the pediatric population or the drug has been studied only in the pediatric population. The study or studies provide substantial evidence of effectiveness, such as in dose-ranging and dose-response studies or adequate and well-controlled studies and there are sufficient data from controlled and uncontrolled studies or other sources to adequately assess safety.

- **Studies in both adults and the pediatric population (or one or more relevant pediatric subpopulations):** A drug is indicated for both adult and pediatric populations based on adequate and well-controlled clinical efficacy trials conducted in each population. The data from each population support the use in the other population for the specific indication, allowing a conclusion that there is substantial evidence of effectiveness and sufficient evidence of safety in both populations.

- **Studies in adults with supporting data in the pediatric population that allow extrapolation of effectiveness to the pediatric population or studies in a pediatric population that allow extrapolation of effectiveness to another pediatric population:** A drug is indicated in both adults and the pediatric population, but effectiveness in pediatric population is extrapolated (see below) from adult data or from data in another pediatric population. That is, the substantial evidence of effectiveness is based on adequate and well-controlled clinical trials in adults (or in other pediatric patients), with additional supporting data in the specific pediatric population, typically including

[8] For biological products approved under section 351 of the PHSA (42 U.S.C. 262), licenses are issued upon showing that the products meet standards to ensure "continued safety, purity and potency." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). Substantial evidence of effectiveness is required to support an indication (21 CFR 201.27(c)(2)(v)); the quality of evidence is described in the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*

pharmacokinetic and sometimes pharmacodynamic data. In general, safety cannot be extrapolated and would need to be assessed in each pediatric population studied.[9]

Where data other than pharmacokinetic data are needed, a pediatric indication can be supported by data demonstrating a pharmacologic effect in the pediatric population, even if the effect cannot be a basis for approval in the absence of other data. In this case, pharmacologic effect data may support approval in a pediatric population if the particular endpoint was available for adults and the pharmacologic effect was also present in adults. For example, where a pediatric population cannot perform the exercise tests needed for approval of drugs indicated for heart failure or pulmonary hypertension in adults, hemodynamic effects similar to those seen in adults might support approval for a pediatric population.

When efficacy studies are not ethical or feasible in the pediatric population (e.g., countermeasures for exposure to lethal or permanently disabling biological, chemical, radiological, or nuclear substances), data from adequate and well-controlled studies in animals may be used to provide substantial evidence of effectiveness (see the animal efficacy rule (21 CFR part 314, subpart I)).[10] Safety would need to be assessed in the pediatric population.

2. Insufficient Evidence to Support Safety and Effectiveness

In this category, use of a drug in a pediatric population (a pediatric indication) is not supported by available data or no data are available. The following are two examples under this category.

- **Studies in the pediatric population, but effectiveness and/or safety not established**

  – Effectiveness is not established because either the drug was found to be ineffective in pediatric patients studied or the clinical efficacy data are inconclusive.

  – Pediatric pharmacokinetic studies were conducted with the intention that they would support extrapolation of effectiveness from adult data; however, because of inadequacies in dose selection, results do not allow extrapolation of effectiveness from adult data.

  – Safety is not established because the drug was found to be unsafe in the pediatric population, the safety data are inconclusive, or a unique safety concern exists in pediatric patients.

[9] In some cases (e.g., with some preventive vaccines), it may be appropriate to extrapolate safety and effectiveness from one pediatric age group to another pediatric age group.

[10] See the draft guidance for industry *Animal Models — Essential Elements to Address Efficacy Under the Animal Rule*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- **No studies are available in any pediatric population and extrapolation of adult effectiveness data to the pediatric population is not possible**

III. PLACEMENT OF PEDIATRIC DATA IN HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS LABELING

Sections 505A(j) and 505B(g)(2) of the FD&C Act require that data submitted in response to a Written Request under the BPCA and assessments submitted in response to a PREA study requirement be described in labeling whether findings are positive, negative, or inconclusive.

The *Pediatric Use* subsection should provide useful information that is clear and accessible to health care providers and should describe what is known and unknown about use of the drug in the pediatric population (e.g., if studies have been done or not, explanation of why the available evidence does not support a pediatric approval) and must highlight any differences in effectiveness or safety in the pediatric population versus the adult population (21 CFR 201.57(c)(9)(iv)(B)).

All data summarized in the *Pediatric Use* subsection should be discussed in further detail in other labeling sections, as appropriate (21 CFR 201.57(c)(9)(iv)(B)). Appropriate labeling cross-references should be used when pediatric data are summarized in one section of labeling and discussed in more detail in another section of labeling.

When a pediatric indication is supported by available data, the pediatric information must be placed in the labeling as required by regulation (21 CFR 201.57(c)(9)(iv)). Recommendations are further described in section III.A., Sufficient Evidence to Support Safety and Effectiveness for a Pediatric Indication.

When a pediatric indication is **not** supported by available data, the *Pediatric Use* subsection must contain a statement explaining that safety and effectiveness have not been established in the relevant pediatric population(s) (21 CFR 201.57(c)(9)(iv)(F). In such cases, the pediatric information pertaining to the unapproved use (including a description of the clinical trial(s), dosing, and pharmacokinetic information) generally should appear only in USE IN SPECIFIC POPULATIONS, *Pediatric Use*, to avoid the impression that the drug has an approved pediatric use (see section III.B., Insufficient Evidence to Support Safety and Effectiveness for a Pediatric Indication). If a specific risk has been identified for pediatric patients, this risk information must be described in the *Pediatric Use* subsection and, if appropriate, placed in the CONTRAINDICATIONS section or WARNINGS AND PRECAUTIONS section. In such cases, the *Pediatric Use* subsection must refer to the risk information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, as required by regulation (21 CFR 201.57(c)(9)(iv)(B), (E), and (F)).

If required studies under PREA are waived because of evidence that a drug would be ineffective or unsafe, the safety or effectiveness concern must be described in the labeling (section 505B(a)(4)(D) and 505B(b)(2)(D) of the FD&C Act).

A. Sufficient Evidence to Support Safety and Effectiveness for a Pediatric Indication

When data support the use of a drug in a pediatric population for a particular indication, pediatric use information must be placed in relevant sections of labeling, as applicable, as described below (21 CFR 201.57(c)(9)(iv)(B), (C), and (D)). The information contained in the following bulleted list is intended for the full prescribing information as described in 21 CFR 201.57(c). In the prescribing information for human prescription drugs and biological products, the Highlights of Prescribing Information, USE IN SPECIFIC POPULATIONS, *Pediatric Use*, should contain a concise summary of any clinically significant differences in response or use of a drug in a pediatric population.

- **INDICATIONS AND USAGE:** All indications should be described, including those that are the same for adults and the pediatric population and any pediatric indications that differ from those approved for adults. If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the pediatric population, the ages should be specified in this section of labeling.

- **DOSAGE AND ADMINISTRATION:** Appropriate pediatric dosing information must be included for all indications for which the drug is approved in the pediatric populations. If an extemporaneously prepared formulation is the appropriate pediatric dosage form, instructions for extemporaneous preparation by a pharmacist or patient should be provided.

- **CONTRAINDICATIONS:** Any pediatric age group or setting in which the drug should not be used in pediatric patients because the risk of use outweighs any potential benefit should be described.

- **WARNINGS AND PRECAUTIONS:** Clinically significant pediatric adverse reactions, potential safety risks, and any limitations imposed on pediatric use because of adverse reactions or potential safety risks must be included. For the most serious safety concerns in pediatric patients, a boxed warning should be considered.

- **ADVERSE REACTIONS:** Details of appropriate pediatric adverse reaction data from clinical studies or postmarketing data must be included. Special attention should be given to highlighting adverse reactions that are novel in pediatric patients or that occur at different frequency or severity (greater or lesser) than in adults. A summary of these adverse reactions should also be included in the *Pediatric Use* subsection.

- **USE IN SPECIFIC POPULATIONS, *Pediatric Use*:** The *Pediatric Use* subsection should provide useful information that is clear and accessible to health care providers and should describe what is known and unknown about use of the drug in the pediatric population. The subsection must also emphasize any differences in effectiveness or safety in the pediatric population versus the adult population. When all available data supporting approval of the drug come solely from a pediatric study or studies, the information must be placed in the labeling as required by regulation (21 CFR

201.57(c)(9)(iv)), and only a concise summary statement, rather than redundant information, should be placed in the *Pediatric Use* subsection.

– When approval for use in a pediatric indication(s) is based on adequate and well-controlled pediatric studies, the following information should be described or summarized briefly:

  - The number of pediatric patients studied and the number of patients in each designated pediatric age group
  - Any specific statements regarding the basis of the pediatric indication(s) if the drug is also approved for the same indication(s) in adults (e.g., the data that support effectiveness or extrapolation)
  - Any limitations on the pediatric indication or pediatric use
  - The need for specific monitoring
  - The specific risks associated with the use of the drug in any subsets of the pediatric population (e.g., neonates)
  - Any significant differences between pediatric and adult responses to the drug (e.g., pharmacodynamic/pharmacokinetic data)
  - Other information related to the safe and effective pediatric use of the drug

– When approval for use in a pediatric indication is based on extrapolation from adequate and well-controlled studies in adults (or from data in younger or older pediatric patients) with additional data supporting pediatric use, the following statement or a reasonable alternative that adequately conveys the required information must be included:

> "The safety and effectiveness of (*drug name*) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*)."
> (21 CFR 201.57(c)(9)(iv)(D)(1))

In addition, data summarized in the above statement must be discussed in more detail in the appropriate section of labeling. Any significant differences between pediatric and adult responses, a need for specific monitoring, dosing adjustments, and any other information related to the safe and effective use of the drug in pediatric patients must be cited briefly in the *Pediatric Use* subsection (21 CFR 201.57(c)(9)(iv)(D)(2)),

and a more detailed discussion should be included in the appropriate section of labeling.

- **CLINICAL PHARMACOLOGY, *Pharmacodynamics* and *Pharmacokinetics*:** A more detailed discussion of the pharmocodynamic, pharmacokinetic, and pharmacogenomic data summarized in the *Pediatric Use* subsection should be provided. Relevant pediatric pharmacokinetic and/or pharmacodynamic study data and dose response information should be included.

- **CLINICAL STUDIES:** A more detailed discussion of the pediatric clinical data summarized in the *Pediatric Use* subsection should be provided.

- **PATIENT COUNSELING INFORMATION:** If appropriate, necessary information for safe and effective use of a drug for prescribers to convey to pediatric patients or caregivers should be provided.

Appropriate labeling cross-references should be used when pediatric data are summarized in one section of labeling and discussed in more detail in another section of labeling.

B. Insufficient Evidence to Support Safety and Effectiveness for a Pediatric Indication

When it is determined that evidence is insufficient to support a pediatric indication, all relevant pediatric information related to the unapproved use should be placed **only** in USE IN SPECIFIC POPULATIONS, *Pediatric Use*, except where required by law, so as not to imply an approved pediatric indication. As noted above, any negative or inconclusive study that satisfies a Written Request under the BPCA or a PREA assessment (sections 505A(j) and 505B(g)(2) of the FD&C Act) must be described in this subsection, as well as any safety concerns or differences in the safety profile in the pediatric population versus the adult population. Pharmacokinetic data, in the absence of efficacy data, should only be included in this subsection when the data reflect a safety concern related to dosing (e.g., the clearance of the drug is low, resulting in higher exposure). Additionally, if a specific risk has been identified for pediatric patients, the risk information must be placed in the *Pediatric Use* subsection or, if appropriate, in the CONTRAINDICATIONS section or the WARNINGS AND PRECAUTIONS section and the *Pediatric Use* subsection must refer to the information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, as required by regulation (21 CFR 201.57(c)(9)(iv)(E)).

Contextual language may be appropriate to clarify that the inclusion of certain pediatric information in the *Pediatric Use* subsection does not imply FDA approval for this use. The following examples illustrate how pediatric information that is insufficient to support approval should be presented in the *Pediatric Use* subsection.

- When substantial evidence does **not** exist to support an indication in a **particular** pediatric population, or the drug has not been studied in a particular pediatric population, an appropriate statement must be included (21 CFR 201.57(c)(9)(iv)(E)), such as "*Safety*

and effectiveness in pediatric patients below the age of (__) have not been established." The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval in those patients).

- When substantial evidence does **not** exist to support a new use (a new indication) in the pediatric population, or the drug has not been studied in the pediatric population for additional labeled adult indication(s), an appropriate statement must be included (21 CFR 201.57(c)(9)(iv)(E)), such as "*Safety and effectiveness have not been established in pediatric patients for indications other than XXX*." The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval for the new use).

- When substantial evidence does **not** exist to support an indication in **any** pediatric population, or the drug has not been studied in any pediatric population, the following statement (or a reasonable alternative) must be included (21 CFR 201.57(c)(9)(iv)(F)): "*Safety and effectiveness in pediatric patients have not been established.*" The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval).

- If a risk is associated with the use of the drug in a particular pediatric population (e.g., preterm or neonatal infants), the risk must be described in the *Pediatric Use* subsection or, if appropriate, described in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section and referenced in the *Pediatric Use* subsection (21 CFR 201.57(c)(9)(iv)).

C. Inactive Ingredients

If a drug contains one or more inactive ingredients that present an increased safety risk (toxic effects) to a pediatric population, a special note of the risk must be provided in labeling. A special note of the risk must be placed in the CONTRAINDICATIONS section (21 CFR 201.57(c)(5)) and/or WARNINGS AND PRECAUTIONS section (21 CFR 201.57(c)(6)), and also briefly summarized in the *Pediatric Use* subsection (21 CFR 201.57(c)(9)(iv)).

D. Juvenile Animal Data

If nonclinical toxicology studies in a juvenile animal model have been conducted to support clinical pediatric trials, these studies should be noted in the *Pediatric Use* subsection. A concise summary of the juvenile animal data, including the human dose exposure equivalents used in the study as well as pertinent study endpoints, should be described.

505 **APPENDIX:**
506 **PEDIATRIC DATA AND LABELING DECISION TREE**
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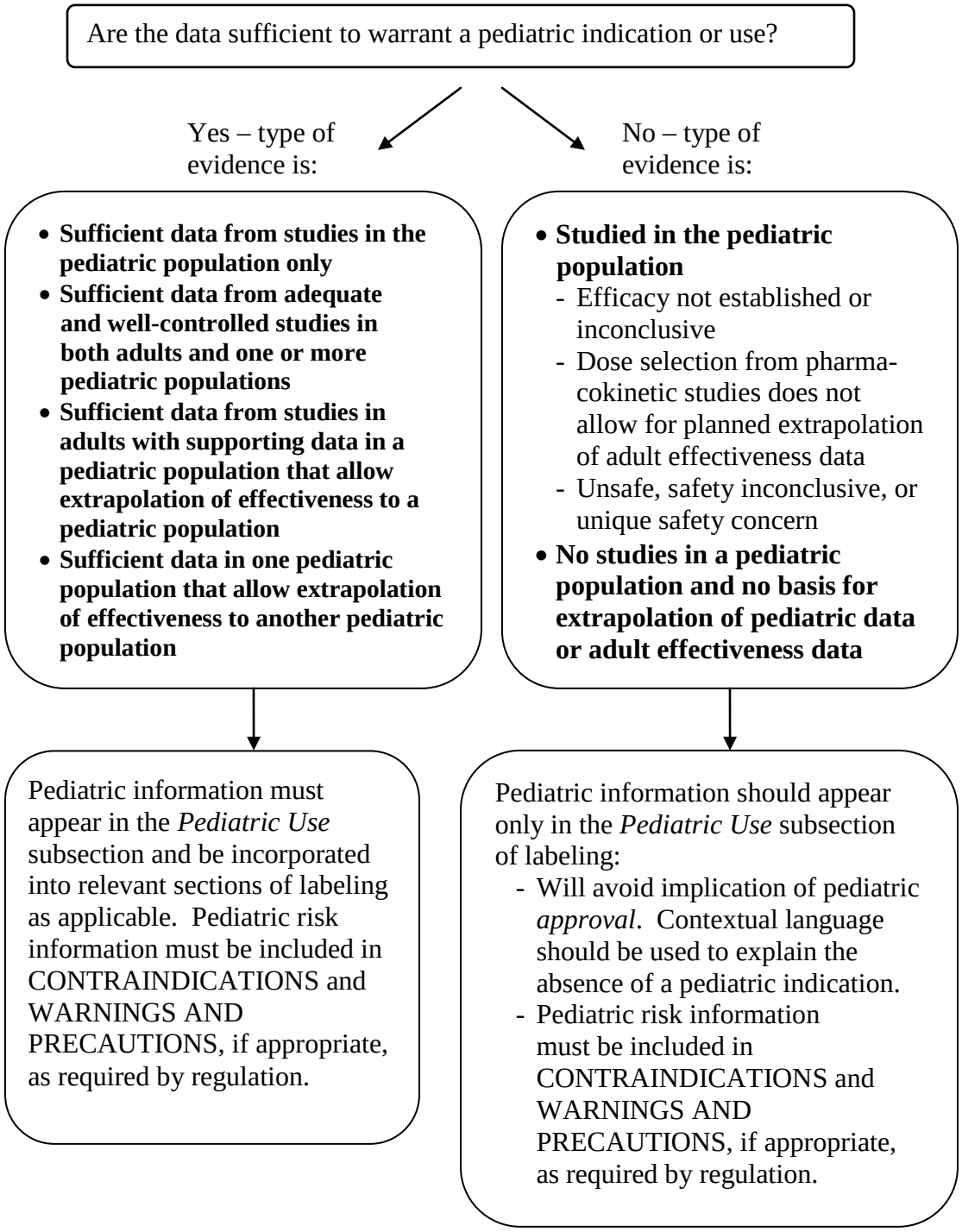

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