Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling

Guidance for Industry

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)

March 2019
Labeling

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Contains Nonbinding Recommendations

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

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

This guidance is intended to assist applicants in determining the appropriate placement and content of pediatric information in human prescription drug and biological product[2] labeling as described in the regulations for the content and format of labeling for human prescription drug and biological products.[3,4,5]

The goal of this guidance is to provide recommendations to help ensure that information on the use of prescription drugs in pediatric populations (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labeling so that the information is clear and accessible to health care providers.

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

[1] This guidance has been prepared by the Division of Pediatrics and Maternal Health and the Labeling Development Team in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research 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 (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) that are regulated as drugs.

[3] 21 CFR 201.56(d) and 21 CFR 201.57.

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

[5] FDA intends to issue additional guidance specific to biological products licensed under section 351(k) of the PHS Act on the content of pediatric use information in the *Pediatric Use* subsection of labeling, including examples of pediatric use statements for the labeling of such products.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. FDA Pediatric Labeling Initiatives

Until the early 1990s, the majority of drug labeling contained minimal or no pediatric use information to guide safe and effective use 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. This regulation was intended to promote the inclusion of pediatric information from new clinical studies, previously published pediatric studies, and case reports in an effort to provide pediatric dosing and monitoring information in labeling. It also required drug manufacturers to examine existing data and determine whether those data were sufficient to support additional pediatric use information in a drug's labeling.[6] Subsequent pediatric legislation included the Best Pharmaceuticals for Children Act (BPCA)[7] and the Pediatric Research Equity Act (PREA).[8] The BPCA contains economic incentives for conducting pediatric studies of drugs and biological products, and PREA establishes requirements for studies of certain drugs and biological products that may be used in pediatric patients. The BPCA and PREA were made permanent in 2012 with the passage of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144).

[6] 59 FR 64240 (December 13, 1994).

[7] Pub. L. 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a). Although section 505A has been amended since the passage of the BPCA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, the BPCA. We adopt that convention in this guidance.

[8] Pub. L. 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, PREA. We adopt that convention in this guidance.

Data submitted in response to a written request[9] under the BPCA and assessments[10] submitted in response to a PREA study requirement must be described in labeling whether findings are positive, negative, or inconclusive.[11] Pediatric information in the labeling must not be false or misleading in any particular.[12]

B. Pediatric Age Groups

For prescription drug labeling, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research generally define *pediatric population(s)* and *pediatric patient(s)* as ages birth to 16 years (i.e., younger than 17 years old), and these phrases include the subpopulation age groups of neonates, infants, children, and adolescents.[13] The FDA generally recommends using the phrases "pediatric patients X to Y years old," "pediatric patients aged X to Y years," or "pediatric patients aged X years and older" (or similar phrases)[14] when describing a specific age group(s) or pediatric subpopulation in labeling. However, the use of another description to define the pediatric population in labeling will be considered on a case-by-case basis if there is a valid scientific rationale for an alternative approach (e.g., post-menarche).

III. PLACEMENT OF PEDIATRIC INFORMATION IN HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCT LABELING

In general, pediatric use information should be discussed in the *Pediatric Use* subsection and included in other sections of labeling as appropriate. When studies are waived under PREA because evidence strongly suggests that a drug would be ineffective or unsafe in a specific

[9] A written request (WR) is a specific document issued by FDA requesting submission of a certain study or studies to determine whether the use of a drug could provide a meaningful health benefit in the pediatric population. The WR specifies the elements of the study or studies that a sponsor or application holder must fulfill to obtain pediatric exclusivity. The FDA can issue a WR at the request of an interested person or on its own initiative. Issuance of a WR to a sponsor or application holder does not require the recipient to conduct the pediatric study or studies described in the WR. It is the recipient's decision whether to conduct the study or studies and possibly obtain pediatric exclusivity.

[10] 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 505B(a)(2)(A) of the FD&C Act).

[11] Sections 505A(j) and 505B(g)(2) of the FD&C Act.

[12] See, e.g., section 505(d), 505(e) of the FD&C Act.

[13] 21 CFR 201.57(c)(9)(iv)(A).

[14] In labeling and in this guidance, the term *pediatric population(s)* (e.g., drugs approved to reduce the risk of disease in healthy children) can be used instead of *pediatric patients*.

pediatric age group(s), the safety concern or lack of efficacy must be described in labeling[15] (i.e., *Pediatric Use* subsection and summarized in other sections as appropriate).

The content of the pediatric use information should be based on the type of information being conveyed, which can be characterized as follows:

- Scenario 1: The evidence supports the safety and effectiveness of a drug for an indication in pediatric patients (either all pediatric patients or in a specific pediatric age group(s))

- Scenario 2: The evidence does not support the safety and effectiveness of a drug for an indication in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) because results of studies conducted in that population were either negative (i.e., data from studies strongly suggest that the drug would be ineffective or unsafe) or inconclusive

- Scenario 3: There is no evidence available to support safety and effectiveness of an indication in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) because studies have not been conducted or are ongoing in that population and/or studies in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) have been waived under PREA

- Scenario 4: Based on available evidence, the drug is contraindicated for use in all pediatric patients, a specific pediatric age group(s), or a specific subgroup of pediatric patients

The following sections provide more detailed descriptions of each of these four scenarios.

A. Evidence Supports Safety and Effectiveness of a Drug for an Indication in Pediatric Patients (Scenario 1)

When data support the use of a drug for a pediatric indication, pediatric use information must be placed in relevant sections of labeling.[16]

- **INDICATIONS AND USAGE:** All approved pediatric indications should be included in the INDICATIONS AND USAGE section.[17] If the drug is indicated for use in the

[15] Section 505B(a)(5)(D) and 505B(b)(2)(D) of the FD&C Act.

[16] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[17] See 21 CFR 201.57(c)(2) and 21 CFR 201.57(c)(9)(iv)(B).

entire pediatric population, the term pediatric patients or pediatric population should be incorporated into the indication statement.[18] For example:

> "DRUG X is indicated for the treatment of Indication Y in adult and pediatric patients."

However, if a drug's pediatric indication is only for use in a specific pediatric age group, the indication statement should specify the ages of the indicated pediatric age group. For example:

> "DRUG X is indicated for the treatment of Indication Y in adults and pediatric patients aged 6 years and older."

- **DOSAGE AND ADMINISTRATION:** This section must include the recommended dosage in pediatric patients for all approved pediatric indications.[19] This section must also include important preparation and administration instructions pertinent to pediatric use (e.g., directions on dilution and/or reconstitution) and storage conditions for stability of the prepared drug.[20,21] If an approved age-appropriate formulation for a drug approved under an NDA is not commercially marketed, but can be prepared by a licensed pharmacist in a licensed pharmacy, the labeling should include detailed preparation instructions for the pharmacist (e.g., including information on suspending and sweetening agents).[22]

- **ADVERSE REACTIONS:** Details of pediatric adverse reaction data from clinical studies or postmarketing data must be included in the ADVERSE REACTIONS section.[23] Special attention should be given to highlighting adverse reactions that are novel or unique in pediatric patients or that occur at a different frequency or severity (greater or lesser) than in adults.

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[18] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). 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 guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[19] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[20] 21 CFR 201.57(c)(3)(iv)).

[21] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[22] See also the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the FDA's current thinking on this topic.

[23] 21 CFR 201.57(c)(7) and the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

- **USE IN SPECIFIC POPULATIONS, *Pediatric Use*:** The *Pediatric Use* subsection must include a required regulatory statement (pediatric use statement)[24] or reasonable alternative statement[25] when a drug is approved in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) for an indication that is the same as an approved indication in adults.[26] For a consistent approach for this subsection, a pediatric use statement is recommended when a drug is approved in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) for an indication that is different from those approved in adults.[27] The pediatric use statement generally should be the first sentence in the *Pediatric Use* subsection. The following is an example of a pediatric use statement:

  > "The safety and effectiveness of DRUG X (for Indication Y) have been established in pediatric patients aged 6 years and older."

  When a drug is approved for pediatric use based on adequate and well-controlled studies in adults (i.e., extrapolation of effectiveness) with other information supporting pediatric use, this subsection must include (a summary of) the basis of approval.[28] In the following example, the basis of approval appears after the pediatric use statement:

  > "The safety and effectiveness of DRUG X (for Indication Y)[29] have been established in pediatric patients aged 6 months and older. Use of DRUG X for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 6 months and older *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*."

  If a drug is approved in adults and also is approved in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) based on adequate and well-controlled studies in pediatric patients, the basis of approval can be included in this subsection (e.g., a summary of the pediatric study designs, the number of patients in each designated age group exposed to the drug) with cross-references to the appropriate section(s) or subsection(s) of labeling that provide more detailed information.

[24] 21 CFR 201.57(c)(9)(iv)(C) and (D).

[25] 21 CFR 201.57(c)(9)(iv)(G).

[26] 21 CFR 201.57(c)(9)(iv)(C) and (D).

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

[28] 21 CFR 201.57(c)(9)(iv)(D).

[29] To improve clarity, the pediatric use statement can include the approved pediatric indication.

When a drug is approved for use only in pediatric patients, and not in adult patients, the entire labeling should provide information essential for the safe and effective use in pediatric patients. Only a summary statement of the approved pediatric indication (pediatric use statement), and any limitations on the pediatric indication should be described in the *Pediatric Use* subsection. For example:

> "The safety and effectiveness of DRUG X have been established in pediatric patients aged 6 years and older (for Indication Y) and the information on this use is discussed throughout the labeling. The safety and effectiveness of DRUG X have not been established in pediatric patients younger than 6 years old."

The *Pediatric Use* subsection must also include the following information, as applicable, when related to the safe and effective pediatric use of the drug and should include cross-references to other sections or subsections of labeling as appropriate:[30]

- Specific risks or safety concerns (hazards) associated with the use of the drug in pediatric patients or in any specific pediatric age group (e.g., neonates) and/or the need for specific monitoring.

- Any limitations on the pediatric indication. If the approved indication(s) does not include all pediatric age groups, an appropriate pediatric use statement about the unapproved pediatric age groups must be included (e.g., "The safety and effectiveness of DRUG X have not been established in pediatric patients younger than 6 months of age").[31]

- Any differences between pediatric and adult responses to the drug (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data).

The FDA may permit use of alternative statements in the *Pediatric Use* subsection if it determines that none of the statements described above (and the statements in Scenarios 2, 3, and 4 described in section III.B., C., and D. of this guidance) are appropriate or relevant to the drug's labeling and if the alternative statements are accurate and appropriate.[32]

- **CLINICAL PHARMACOLOGY:** Detailed descriptions of pediatric pharmacokinetic, pharmacodynamic, and/or pharmacogenomic study data; relevant data obtained from modeling, simulation, or bridging studies; and dose response information should be included in the CLINICAL PHARMACOLOGY section.[33]

[30] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[31] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[32] 21 CFR 201.57(c)(9)(iv)(G).

[33] See 21 CFR 201.57(c)(13); see also the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).

- **CLINICAL STUDIES:** Detailed descriptions of studies that provide substantial evidence of effectiveness for use in pediatric patients or populations (e.g., study design(s), population(s), endpoints, and results and limitations of the study design or evidence) should be provided in the CLINICAL STUDIES section.[34]

B. Evidence Does Not Support Safety and Effectiveness of a Drug for an Indication in Pediatric Patients (Scenario 2)

When it is determined that available evidence regarding safety or effectiveness does not support a pediatric indication, relevant pediatric information related to the unapproved use that is included in labeling generally should be placed only in the *Pediatric Use* subsection. Negative studies and inconclusive studies should be briefly summarized in this subsection, and not elsewhere in the labeling, to avoid the implication that a drug is safe and effective in pediatric patients.[35]

An appropriate pediatric use statement must appear in the *Pediatric Use* subsection,[36] before the summary of the available evidence, to clarify that safety and effectiveness in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) have not been established for the unapproved indication discussed so that an unapproved indication or use is not implied or suggested.[37] For example:

> "The safety and effectiveness of DRUG X have not been established in pediatric patients (for Indication Y). Effectiveness was not demonstrated in two adequate and well-controlled studies conducted in 120 DRUG X-treated pediatric patients, aged 6 to younger than 17 years for Indication Y."

If the use of the drug for an indication not approved in pediatric patients is associated with a risk or safety concern (hazard) in pediatric patients, the risk or safety concern must be described in the *Pediatric Use* subsection and must be stated in other sections of labeling as appropriate (e.g., BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections). A cross-reference from the *Pediatric Use* subsection to the applicable section or subsection that states the risk must be included.[38]

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[34] See 21 CFR 201.57(c)(15); see also the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

[35] A drug is deemed to be misbranded if pediatric information in the labeling is false or misleading in any particular (21 U.S.C 352(a)).

[36] 21 CFR 201.57(c)(9)(iv)(E) or (F).

[37] See 21 CFR 201.57(c)(2)(iv) and (v).

[38] 21 CFR 201.57(c)(9)(iv)(E) or (F).

Furthermore, when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the *Pediatric Use* subsection.

C. No Evidence to Support Safety and Effectiveness of a Drug for an Indication in Pediatric Patients (Scenario 3)

When there is no evidence to support the safety and effectiveness of a drug for an indication in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) because studies have not been conducted or are ongoing, an appropriate pediatric use statement must be placed in the *Pediatric Use* subsection to state that safety and effectiveness in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) have not been established.[39] Examples of such statements include:

> "The safety and effectiveness of DRUG X have not been established in pediatric patients."
>
> "The safety and effectiveness of DRUG X have not been established in pediatric patients younger than 6 years old."

In addition to the pediatric use statement, if there is evidence strongly suggesting that a drug would be ineffective or unsafe (e.g., if studies are waived under PREA for this reason), the information must be included in the *Pediatric Use* subsection and if appropriate, must be stated in other sections of labeling (e.g., BOXED WARNING, CONTRAINDICATIONS, and/or the WARNINGS AND PRECAUTIONS sections).[40] A cross-reference from the *Pediatric Use* subsection to the applicable section or subsection that states the risk must be included.[41] For example:

> "The safety and effectiveness of DRUG X (for Indication Y) have not been established in pediatric patients aged 6 months and older. DRUG X is not recommended for use in patients younger than 6 months of age because of the potential for increased systemic absorption of drug name due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier *[see Warnings and Precautions (5.X)]*."

D. Contraindicated for Use in Pediatric Patients (Scenario 4)

If a drug is contraindicated in all pediatric patients, in a specific pediatric age group(s), or in a subgroup of pediatric patients, the contraindication and reason for the contraindication should be

[39] 21 CFR 201.57(c)(9)(iv)(E) or (F).

[40] Section 505B(a)(5)(D) and 505B(b)(2)(D) of the FD&C Act.

[41] 21 CFR 201.57(c)(9)(iv)(E) and (F).

stated first in the *Pediatric Use* subsection as well as in the CONTRAINDICATIONS section. When a drug is contraindicated in all pediatric patients, the contraindication statement in the *Pediatric Use* subsection should be used as an alternative pediatric use statement instead of stating that safety and effectiveness have not been established in pediatric patients.[42] If the contraindication arose from a study conducted in pediatric patients, a brief description of the study should follow the contraindication statement in the *Pediatric Use* subsection. When a contraindication in pediatric patients applies only to a specific pediatric age group(s) or subgroup(s) of pediatric patients, an additional pediatric use statement, as appropriate, should be added to the *Pediatric Use* subsection to describe the evidence or lack of evidence to support use in the remaining pediatric age group(s). Examples of such Pediatric Use statements are:

Example 1:

> "DRUG X is contraindicated in pediatric patients because of deaths observed in a juvenile animal study with administration of drug name to juvenile rats at clinically relevant doses *[see Contraindications (4) and Warnings and Precautions (5.X)]*." *(Include a brief description of the data that support the contraindication.)*

Example 2:

> "DRUG X is contraindicated in pediatric patients younger than 1 year of age because of an increased risk of systemic toxicity, including marked increases in blood pressure *[see Contraindications (4) and Warnings and Precautions (5.X)]*.
>
> The safety and effectiveness of DRUG X in pediatric patients aged 1 year and older have been established." *(See USE IN SPECIFIC POPULATIONS, Pediatric Use, in section III.A. of this guidance.)*

The contraindicated use must be described in the CONTRAINDICATIONS section,[43] and risk information associated with the contraindicated use should also be summarized in other sections of labeling as appropriate (i.e., BOXED WARNING and WARNINGS AND PRECAUTIONS section).

IV. INACTIVE INGREDIENTS

If a drug contains one or more inactive ingredients that may be associated with a significant safety concern in pediatric patients (all pediatric patients, specific pediatric age group(s), or subgroup(s)) (e.g., benzyl alcohol toxicity in neonates or infants), the risk must be described in

[42] 21 CFR 201.57(c)(9)(iv)(G): "If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate."

[43] 21 CFR 201.57(c)(5).

labeling.[44] The significant safety risk related to an inactive ingredient generally should be summarized in the BOXED WARNING, CONTRAINDICATIONS, and/or WARNINGS AND PRECAUTIONS section, and should also be described in the *Pediatric Use* subsection.

V. JUVENILE ANIMAL DATA

Nonclinical toxicity studies in juvenile animals can provide useful information concerning the safety profile of a drug in immature systems and a drug's potential effects on the growth and development of pediatric patients.[45,46] A concise summary of clinically relevant nonclinical toxicology studies in juvenile animal models should be described in the *Pediatric Use* subsection, following the information required in the *Pediatric Use* subsection,[47] under the heading Juvenile Animal Toxicity Data. In general, juvenile animal data should not be included in labeling when the data do not suggest an adverse signal.

Juvenile animal study data should be summarized in the *Pediatric Use* subsection when the data suggest an adverse signal(s) that has not been previously assessed in a pediatric clinical study (e.g., information on long-term safety, either for growth or neurocognitive development; or in cases where the juvenile animal studies have addressed safety concerns in an age group not studied in a pediatric study). Generally, only information that may have clinical relevance should be summarized. The summary should be discussed in clinically relevant terms, such as:

- Human equivalent dose exposures
- Ages of animals studied and how they correlate with approximate human ages
- Organ systems affected (e.g., "central nervous system" instead of describing "excessive grooming" or "hindlimb splay")
- Duration of treatment of animals and relationship to clinical use
- Reversibility of the adverse effect
- Developmental delay, if applicable

In general, pediatric clinical data are more directly relevant than juvenile animal data. Therefore, in situations in which the pediatric clinical data and nonclinical data suggest a similar risk, the

[44] 21 CFR 201.57(c)(9)(iv)(H).

[45] See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006).

[46] We support the principles of the 3Rs (replacement/reduction/refinement) 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 such an alternative method is adequate to meet a nonclinical regulatory purpose.

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

clinical data should be used to discuss key details and clinical implications of the risk, while the nonclinical data should be briefly summarized, if appropriate.

As described above, a summary of all clinically relevant juvenile animal data necessary for prescribing decisions should be concisely stated in the *Pediatric Use* subsection. Therefore, in general, there is no need to include a description of the juvenile animal studies in the NONCLINICAL TOXICOLOGY section.