

Pediatric Information In Prescribing Information

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- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
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Learning Objectives



- Discuss how stakeholder input concerning pediatric use information in labeling informed the development of the Pediatric Labeling Guidance¹
- Discuss the key concepts in the Pediatric Labeling Guidance¹
 - Four pediatric use scenarios
 - How to include juvenile animal toxicity data in labeling

¹ In this presentation, the phrase “Pediatric Labeling Guidance” refers to the guidance for industry: [Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling](#) (March 2019)

Example 1: DRUG-X Is Approved in Which Pediatric Age Group?



(Years of Age: 1 to 17?, 2 to 17?, 4 to 17?, or Other?)

8 USE IN SPECIFIC POPULATIONS

No required pediatric usage statement

8.4 Pediatric Use

DRUG-X was studied in 150 pediatric patients aged 1 to 17 years old. There were insufficient number of pediatric patients below 2 years old to assess the safety of DRUG-X. Efficacy was lower in pediatric patients younger than 4 years old than in those 4 to 17 years old.

Example 2: DRUG-X Is Approved in Which Pediatric Age Group? (Years of Age: Birth to 17?, 13 to 17?, or Other?)

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of **patients** with Disease-A.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of DRUG-X for Indication-A have been established in **adolescents**. Use of DRUG-X for this indication is supported by evidence from adequate and well-controlled studies in adults **and pediatric patients aged 13 to 17 years old** [see *Clinical Studies (14.1, 14.2)*].

Pediatric Labeling Guidance: Four Pediatric Use Scenarios



Four Scenarios for Including Pediatric Use Information in Labeling



- Evidence supports safety and effectiveness of drug for a pediatric indication (**Scenario 1**)
- Evidence does **not** support safety and effectiveness of a drug for a pediatric indication:
 - Results of pediatric studies were negative or inconclusive (**Scenario 2**)
 - No evidence available because studies have not been conducted or are ongoing (**Scenario 3**)
 - Drug is contraindicated in pediatric patients (**Scenario 4**)

Scenario 1: Evidence Supports Safety and Effectiveness of Drug for a Pediatric Indication



Scenario 1: Drug Has a Pediatric Indication



- **INDICATIONS AND USAGE Section:** Should include all approved pediatric indications.¹ For example:
 - “DRUG-X is indicated for the treatment of Indication-A in adults and **pediatric patients aged 6 years and older.**”
- **DOSAGE AND ADMINISTRATION Section:** Must include recommended pediatric dosage for all approved pediatric indications and important preparation, administration, and storage instructions pertinent to pediatric use²

¹ See 21 CFR 201.57(c)(2), 21 CFR 201.57(c)(9)(iv)(B), and draft guidance for industry: [Indications and Usage Section of Labeling – Content and Format](#) (July 2018). When final, this guidance will represent FDA’s current thinking on this topic.

² See 21 CFR 201.57(c)(9)(iv)(B), (C), and (D); 21 CFR 201.57(c)(3)(iv)); and guidance for industry [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format](#) (March 2010).

Scenario 1: Drug Has a Pediatric Indication



- **ADVERSE REACTIONS Section:** Must include details of pediatric adverse reactions (AR).¹ Should highlight novel or unique AR in pediatric patients or those that occur at a different frequency or severity than in adults
- **CLINICAL PHARMACOLOGY Section:** Should include:²
 - Details of pediatric PK, PD, and/or pharmacogenomic data
 - Relevant data from modeling, simulation, or bridging studies

AR = Adverse Reactions; PK = pharmacokinetic; PD = pharmacodynamic

¹ See 21 CFR 201.57(c)(7) and guidance for industry: [Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format](#) (January 2006).

² See 21 CFR 201.57(c)(13) and guidance for industry: [Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format](#) (December 2016).

Scenario 1: Drug Has a Pediatric Indication



CLINICAL STUDIES Section:

Should include detailed description and results of studies that provide substantial evidence of effectiveness for use in pediatric patients¹



¹ See 21 CFR 201.57(c)(15) and guidance for industry: [Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format](#) (January 2006)

Scenario 1: Drug Has a Pediatric Indication

Pediatric Use Subsection: *Pediatric Use Statement*

Pediatric use statement¹ should generally be the first sentence in *Pediatric Use* subsection and:

- Must be included when pediatric and adult indications are the same²
- Should be included when the pediatric and adult indications are different

¹ A reasonable alternative statement may be included [see 21 CFR 201.57(c)(9)(iv)(G)]

² See 21 CFR 201.57(c)(9)(iv)(C) and (D)

Scenario 1: Drug Has a Pediatric Indication

Pediatric Use Subsection: Basis of Approval



When a drug is approved for pediatric use based on adequate and well-controlled studies:

- In pediatric patients - include a basis of approval statement¹
- In adults (based on extrapolation) - must include a basis of approval statement²

Avoid terminology “based on clinical experience” when describing the basis of approval

¹ Basis of approval statement in this situation may include a summary of pediatric study designs, number of patients in each designated age group exposed to the drug; ² 21 CFR 201.57(c)(9)(iv)(D)(1)

Scenario 1: Drug Has a Pediatric Indication

Pediatric Use Subsection



Pediatric Use Statement



8.4 Pediatric Use

The safety and effectiveness of DRUG-X (for Indication-A) have been established in pediatric patients aged 6 years 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 years and older [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1)*].

Basis of Approval Statement

Scenario 1: Drug Only Approved in Pediatric Patients (not adults) - *Pediatric Use Subsection*

Should only include a pediatric use statement and any limitations on the pediatric indication(s), e.g.,:

Pediatric Use Statement

8.4 Pediatric Use

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

Limitations

Scenario 1: Drug Has a Pediatric Indication

Pediatric Use Subsection



Must include the following, as applicable:¹

- Specific risks or safety concerns in pediatric patients and/or need for specific monitoring
- Any limitations on the pediatric indication
- Any differences between pediatric and adult responses (e.g., adverse reactions, PK/PD data)

Scenarios 2, 3, and 4: Evidence Does Not Support Safety and Effectiveness of Drug for a Pediatric Indication

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Scenario 2: No Pediatric Indication Because Pediatric Study Results Are Negative or Inconclusive

Pediatric Use Subsection

- Must include an appropriate pediatric use statement¹
- Must avoid implication that drug is safe and effective in pediatric patients²

Pediatric Use Statement



8.4 Pediatric Use

The safety and effectiveness of DRUG-X have not been established in pediatric patients (for Indication-A). 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-A.



¹ See 21 CFR 201.57(c)(9)(iv)(E) or (F); ² See 21 CFR 201.57(c)(2)(iv) and (v)

Summary of negative study

Scenario 2: No Pediatric Indication Because Pediatric Study Results Are Negative or Inconclusive

If the unapproved use in pediatric patients is associated with a risk or safety concern must:¹

- Describe in *Pediatric Use* subsection
- State in other sections of labeling as appropriate
- Include a cross-reference from the *Pediatric Use* subsection to the applicable section(s)/subsection(s) that states the risk or safety concern



¹ See 21 CFR 201.57(c)(9)(iv)(E) or (F)

Scenario 3: No Pediatric Indication Because Studies Have Not Been Conducted or Are Ongoing

Pediatric Use Subsection (1 of 2)

Must include an appropriate pediatric use statement¹ such as:

- “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.”

Scenario 3: No Pediatric Indication Because Studies Have Not Been Conducted or Are Ongoing

Pediatric Use Subsection (2 of 2)

If there is evidence strongly suggesting that drug would be unsafe or ineffective must include in *Pediatric Use* subsection and if appropriate in BW, W&P, and/or CONTRAINDICATIONS sections¹

8.4 Pediatric Use

The safety and effectiveness of DRUG X (for Indication-A) 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 the potential for an immature skin barrier [see *Warnings and Precautions (5.X)*].

Scenario 4: Drug Is Contraindicated in Pediatric Patients – *Pediatric Use* Subsection



Should state contraindication and reason for contraindication in beginning of the *Pediatric Use* subsection, e.g.,:

8.4 Pediatric Use

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)*]. *[[include pediatric use statement for pediatric patients greater than 1 year of age and older]]*

Pediatric Use Statements



“Pediatric Use Statements”



- Generally “pediatric use statements” are **required** in the *Pediatric Use* subsection¹
- Include for **all adult and pediatric indications** and **all pediatric age groups**

Examples of “Pediatric Use Statements”



- “The safety and effectiveness of DRUG X (for Indication Y) have been established in pediatric patients aged 6 years and older.” ✓
- “The safety and effectiveness of DRUG X have not been established in pediatric patients (for Indication Y).” ✓
- “DRUG X is contraindicated in pediatric patients ...”¹ ✓
- ~~“DRUG X was studied in 98 pediatric patients 6 years old and older with Disease-A”~~ ✗

¹ For a contraindication in pediatric patients, an alternative recommended pediatric use statement is shown (instead of stating that safety and effectiveness have not been established in pediatric patients) [see 21 CFR 201.57(c)(9)(iv)(G)]

Juvenile Animal Toxicity Data

Juvenile Animal Toxicity Data

Pediatric Use Subsection



- Juvenile animal study data should be summarized in the *Pediatric Use* subsection under the heading Juvenile Animal Toxicity Data when data suggest an adverse signal that has not been previously assessed in a pediatric clinical study
- Generally, should only summarize information that may have clinical relevance

Question 1: Which Statement May Be An Appropriate Pediatric Use Statement



- a) The safety and effectiveness of DRUG-X have not been established in pediatric patients
- b) The safety and effectiveness of DRUG-X for Indication Y have been established in pediatric patients aged 6 months and older.
- c) DRUG-X was studied in 150 pediatric patients aged 1 to 17 years of age for Condition-A
- d) a and b
- e) a, b, and c

Question 2: Include a Pediatric Use Statement for Which Indications in *Pediatric Use*

Subsection - Drug Is Approved for:

- Indication A in adults and pediatric patients
- Indication B in adults only
- Indication C in adolescents only

- a) Indication A
- b) Indication B
- c) Indications A and B
- d) Indications A and C
- e) Indications A, B, and C

Summary

- The Pediatric Labeling Guidance contains important recommendations on how to incorporate pediatric use information in labeling
- Include pediatric use statements for all adult and pediatric indications and all pediatric age groups in *Pediatric Use* subsection

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