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Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices: Final Guidance

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Webinar Objectives

• Provide context for and overview of the Guidance

• Describe the key changes from the draft guidance to the final guidance

• Answer clarifying questions about the concepts in the final guidance
Promote Pediatric Medical Device Development

• The FDA is dedicated to promoting timely access to safe and effective medical devices for all patients, and recognizes the unique needs of pediatric patients

• Despite a recognized need, relatively few medical devices have pediatric-specific indications and labeling

• The Final Guidance proposes a framework to leverage appropriate data for minimizing risk to pediatric patients while maximizing access to medical devices indicated for pediatric patients

• The approach may stimulate growth in the number of devices indicated and labeled for pediatric patients
Regulatory Background

• Regulatory authority allowing for extrapolation
  – Title III of the Food and Drug Administration Amendments Act (FDAAA) is the Pediatric Medical Device Safety and Improvement Act (PMDSIA) of 2007
  – PMDSIA specifically authorized the use of adult data to demonstrate pediatric effectiveness
    • CDRH believes extrapolation for safety is also appropriate in some circumstances
What is Extrapolation?

In this guidance, “extrapolation" refers to the leveraging process where an indication in a new pediatric patient population can be supported by existing clinical data from a studied patient population.

• When existing data are relevant to a pediatric indication and determined to be valid scientific evidence, it may be appropriate to extrapolate such data for pediatric use.
Pediatric Definition

Age ranges for pediatric subpopulations:

- **Neonates**: from birth to 1 month of age
- **Infants**: greater than 1 month to 2 years of age
- **Children**: greater than 2 to 12 years of age
- **Adolescents**: greater than 12 through 21 (up to but not including the 22nd birthday)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm
Challenges to support Pediatric Indications

• Small and diffusely scattered potential study populations
  – May confound optimal trial size

• Enrollment and consent procedures
  – May increase trial time

• Increased variation in physiology, pathophysiology, anatomy, and human factors as compared to adults
  – Challenges development of appropriate technologies

Because of these challenges, adult devices are used off-label in pediatrics.
Why Consider Extrapolation?

Leveraging relevant available clinical data when appropriate, may

• Lead to more devices being granted marketing authorization for pediatric indications
• Increase availability of medical devices with appropriate labeling to support safe and effective device use in pediatric patients
• Streamline the process for establishing a pediatric intended use claim
• Enhance and encourage pediatric device development programs
Final Guidance Highlights

• Background
  – Regulatory History
  – The purpose and potential benefits of extrapolation

• Extrapolation Decision Process
  – Figure 1 provides complete decision tree
  – Full vs. partial extrapolation
  – Extrapolation for effectiveness vs. safety

• Examples and Statistical Methodology for Extrapolation
  – Appendix
    • Statistical guidance on potential methods
    • Six hypothetical and one actual example
Objectives of Guidance

- Increase availability of safe and effective pediatric devices by providing a roadmap for leveraging relevant existing clinical data for use in premarket approval applications (PMAs), humanitarian device exemptions (HDEs), and *de novo* requests.
- Explain the circumstances in which the FDA believes it may be appropriate to leverage existing clinical data to support pediatric device indications and labeling.
- Outline the approach FDA uses to determine whether extrapolation is appropriate, and if so, to what extent the data can be leveraged.
- Describe suggested statistical methodology that may be used to leverage the data in a way that increases precision for pediatric inferences.
Guiding Principles

• Fairly and responsibly serve the need of pediatric patients
  – For devices with appropriate labeling to support safe and effective pediatric use

• Guidance does not change
  – threshold for approval
  – need for valid scientific evidence

• Appropriateness of extrapolation is considered
  – case by case, guided by the decision tree
  – separately for effectiveness and safety
Determination of Appropriateness of Extrapolation

Three factors:

1. Similarity
   - Of existing adult response data and/or population characteristics to the intended pediatric sub-population

2. Quality
   - Study design
   - Data collection
   - Measurement

3. Fair and responsible support of
   - Reasonable assurance of safety and effectiveness (or probable benefit for HDEs)
   - Valid scientific evidence
Extrapolation Decision Tree
General Considerations

Relevance of Data
• Does the disease or condition occur in a pediatric (sub)population?
• Endpoint in data set relevant to intended pediatric (sub)population?

Similarity of response to intervention
• Device characteristics
• Disease characteristics
• Population characteristics

Quality of Data
• Is the adult/other population data of sufficient quality to demonstrate safety and effectiveness in pediatric (sub)population?
• If not, is data of sufficient quality for partial extrapolation?
Possible Extrapolation Decisions

- **Full extrapolation:** Existing clinical data are used directly (i.e., as a complete substitute) for prospective pediatric clinical data.

- **Partial extrapolation:** Existing data are combined via a statistical model with pediatric data sources or prospective pediatric clinical data.
  - Partial extrapolation permits utilization of existing clinical data to support demonstration of device safety or effectiveness for use in pediatric patients, with the expectation that some pediatric data are necessary.

- If not appropriate or insufficient to meet the threshold of valid scientific evidence, data will not be extrapolated.
Extrapolation Does not Imply Approval

- A conclusion that extrapolated data may be used does not necessarily mean the data will support an approval decision.
- If extrapolation is deemed appropriate, the data would be considered in conjunction with the totality of evidence to either support or not support a reasonable assurance of safety and effectiveness (or probable benefit)
KEY CHANGES
• Clarifies and explains the following:
  – the guidance applies to PMAs, HDEs and now *de novo* requests where a pediatric indication is sought
    • PMDSIA states that extrapolated data may be used to support a “reasonable assurance of effectiveness (RASE)”
    • Extrapolation for safety may be appropriate in some circumstances
  – PMAs and *de novo* requests both require a demonstration of RASE
  – HDEs require a demonstration of safety and probable benefit
    • Extrapolated data may be particularly useful in HDEs given the rarity of the disease/condition addressed
Changes From Draft Guidance contd.

• Clarifies the concept of “borrowing strength”
  – Quantitative information provided by existing adult/population data may be incorporated in one of two ways:
    • As a substitute for any potential pediatric data
    • As a supplement to “new” pediatric data considered in the context of a statistical model
Changes From Draft Guidance contd.

• Clarifies how to determine “similarity in device effects”
  – Both the direction and magnitude of the device effect should be considered
    • By direction of device effect, we mean that if the device has a benefit for adults, it should also have a benefit for pediatrics
    • The magnitude of benefit should also be similar between populations
Next Steps

Implementation

– CDRH will use pediatric expertise in the evaluation of any application in which extrapolation is considered

– CDRH is developing the PEDs (Pediatric Extrapolation for Devices) Team
  • A centralized group with pediatric expertise
  • Available for consultation regarding extrapolation
  • Enhanced consistency and standardization with respect to extrapolation decisions
Concluding Remarks

- Despite a recognized need, relatively few medical devices have pediatric-specific indications and labeling.
- The guidance proposes a framework for leveraging existing data to augment availability of medical devices indicated and labeled for pediatric patients.
- The guidance provides clarity and predictability for device sponsors and enhances consistency within FDA regarding decisions involving extrapolation.
Thank You
Questions?
Division of Industry and Consumer Education: DICE@fda.hhs.gov

Slide Presentation, Transcript and Webinar Recording will be available at: http://www.fda.gov/training/cdrhlearn
Under the heading-“How To Study and Market Your Device” (subsection- “Cross-Cutting Premarket Policy”)