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FDA/CDRH Webinar

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- Describe the key changes from the draft guidance to the final guidance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

CONTEXT AND OVERVIEW

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

Changes From Draft Guidance

- 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?

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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”)