Berkeley School of Public Health

EASL European Association for the Study of the Liver

Forum for Collaborative HIV Research

Session IV:
Pediatric Working Group Updates

Berkeley School of Public Health

EASL European Association for the Study of the Liver

Forum for Collaborative HIV Research

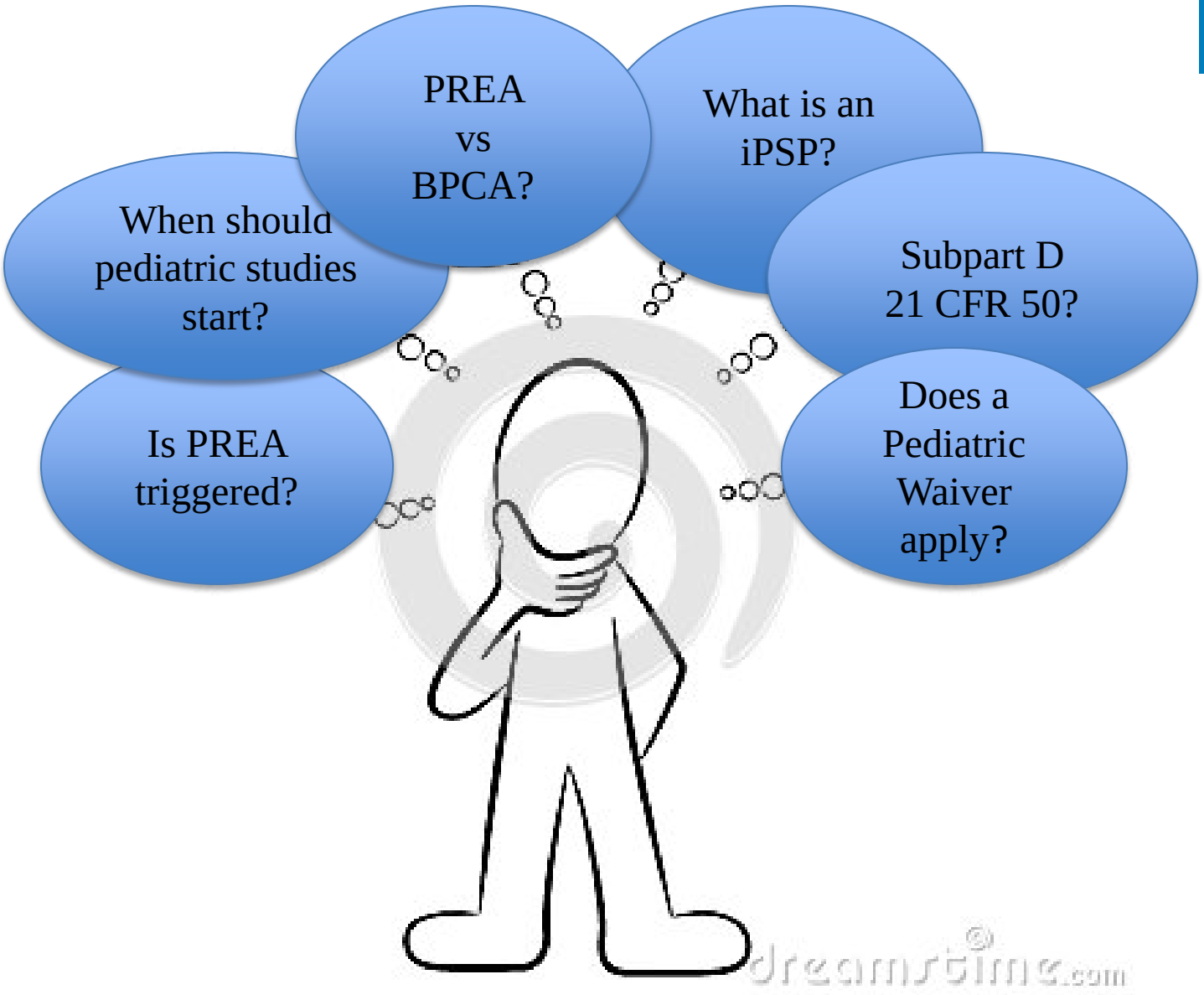
Regulatory Updates

Law and Regulations for Trials in Pediatric Patients

Ruby Mehta, MD
Division of Gastroenterology and Inborn Errors Products (DGIEP)
Office of New Drugs, CDER, FDA
November 10, 2016
Liver Forum

Disclosures

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies



Source: Generated by presenter utilizing cartoon sketch from www.dreamstime.com

Outline

- Pediatric Legislation Landmarks
  - Best Pharmaceuticals for Children Act (BPCA),2002
  - Pediatric Research Equity Act (PREA),2003
- Pediatric Study Plan
- Extrapolation
- Subpart D (21 CFR 50)
- Special Considerations for Pediatric Clinical Trials (Role of DPMH and PeRC)

Two Definitions of Pediatric Patients

- 0 to 16 years old
  - Labeling regulations for prescription drugs: [21 CFR 201.57(c)(9)(iv)]
- *Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted [21 CFR 50.3(o)]

Pediatric Drug Development

- BPCA and PREA introduced to foster drug development in children
  - Ultimate goal to encourage appropriate use of medications in this population
  - Help inform labeling (Prescribing Information)
  - Before these laws, only 22% drug labeling had pediatric information[1]
    - In 2009, 46% had pediatric information in PI[2]

[1]Sachs et al. Pediatric Information in Drug Product Labeling, *JAMA*, 2012:1914-5.

[2] New Pediatric Labeling Information Database, http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

BPCA and PREA

- **Best Pharmaceuticals for Children Act (BPCA)**
  - **Provides a financial incentive** to companies to voluntarily conduct pediatric studies
  - FDA and the **National Institutes of Health** partner to obtain studies in pediatric patients

- **Pediatric Research Equity Act (PREA)**
  - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients (Pediatric Assessment)

Proposed Pediatric Study Request

- A sponsor may request that the FDA issue a WR by submitting a Proposed Pediatric Study Request (PPSR)
- PPSRs can come from traditional sponsors (on patent) or from the NIH (usually off patent)
- PPSR should contain:
  - Rationale for studies and design
  - Detailed study design
  - Appropriate formulations for each age group

BPCA vs. PREA

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
  - **e.g., Breast CA drug (estrogen receptor antagonist) studied in pediatric condition with excess estrogen production (McCune Albright syndrome)**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled (information should be available in PI)

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from PREA
- Pediatric studies must be labeled

Pediatric Research Equity Act (PREA)

- Is triggered in following circumstances:
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration
  - New active ingredient

PREA: Pediatric Assessment

- **Data** from pediatric studies using appropriate formulations for each age group and other data
  - **To assess the safety and effectiveness** of a drug/biologic for the claimed indications in all relevant pediatric subpopulations
  - **To support dosing and administration** for each pediatric subpopulation for which the drug or biological product is safe and effective

PREA: Deferral Requirements

The sponsor must submit all of the following:

1. Certification of the grounds for deferring the assessments

2. A Pediatric Study Plan

3. Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time

4. A timeline for the completion of such studies

PREA: Pediatric Waiver

- Necessary studies are impossible or highly impracticable
- Evidence strongly suggests the drug/biologic would be ineffective or unsafe
- Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used by a substantial number of pediatric patients
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed (partial waiver only)

Pediatric Review Committee (PeRC)

- Established by legislation to carry out the activities described under BPCA and PREA
- Intended to increase the consistency of implementation of provisions of BPCA and PREA across FDA
- Committee Membership:
  - Expertise in Pediatrics, Neonatology, Pediatric Ethics, Biopharmacology, Statistics, Chemistry, Law required
  - Appropriate expertise pertaining to the product under review

Pediatric Study Plan (PSP)

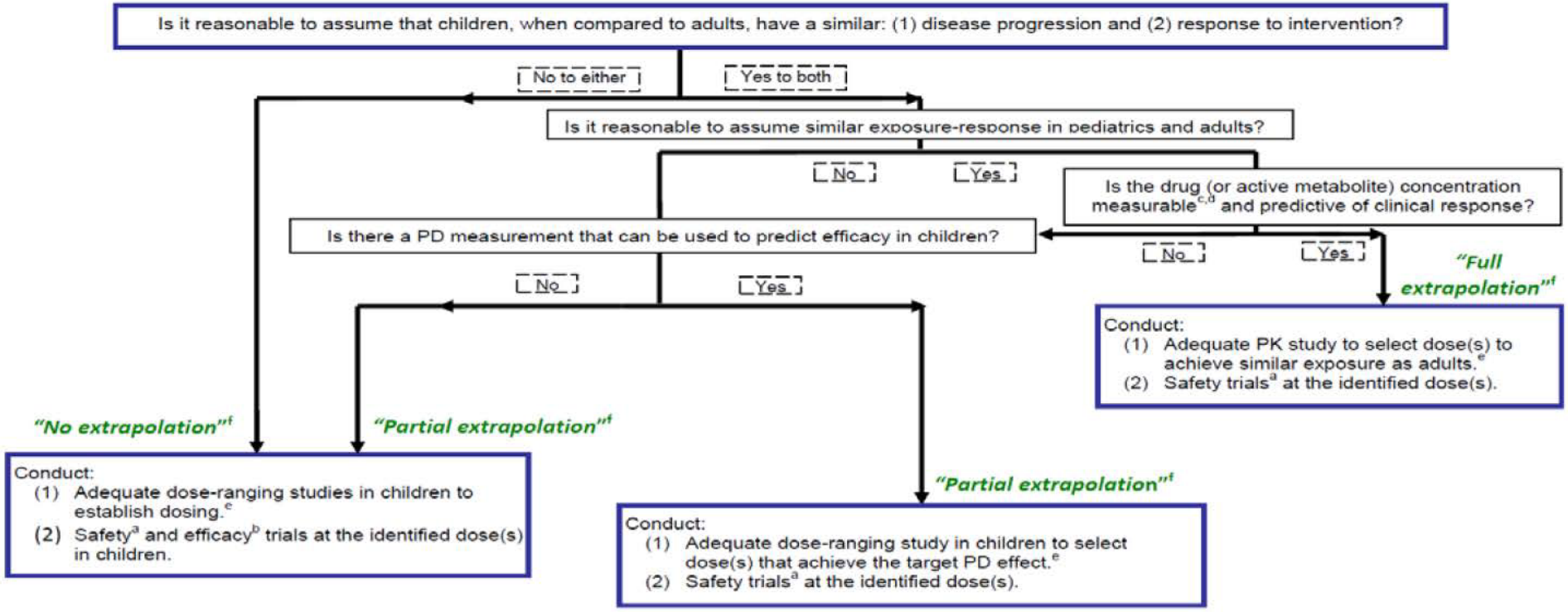
- Outline of the pediatric study(ies) the sponsor plans to conduct
- The intent of the PSP:
  - Encourage sponsors to design pediatric studies as early as possible in product development
  - When appropriate, to conduct those studies prior to submitting the NDA/BLA
- PSP has replaced “Pediatric Plan” requirements
- Strict timelines
- Must be reviewed and agreed upon by FDA

Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, …pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as PK studies"

Pediatric Research Equity Act of 2007 (Title IV FDA Amendments Act 2007)

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

Dunne J et.al, ***Extrapolation of adult data and other data in pediatric drug-development programs.*** *Pediatrics. 2011*

Origins of 21 CFR 50 subpart D

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (referred to as The National Commission) issued their Report and Recommendations on Research Involving Children in January 1978
- The ethical framework proposed by The National Commission was adopted as “subpart D” by HHS in 1983 (45 CFR 46) and FDA in 2001 (21 CFR 50)
- A review of their deliberations provides important background as we discuss and debate the ethics of the development of pediatric medical countermeasures

43 Fed. Reg. 2083 (1978)

Research Involving Children

- Children are vulnerable and require additional safeguards:
  - "The National Commission recognizes, however, that the vulnerability of children, which arises out of their dependence and immaturity, raises questions about the ethical acceptability of involving them in research. Such ethical problems can be offset, the Commission believes, by establishing conditions that research must satisfy to be appropriate for the involvement of children."

Early Agreement
Ethical Justification

- Two types of pediatric research were agreed upon early in The National Commission's deliberations.
  - Research that does not present greater than minimal risk (this became §CFR 50.51)
  - Research where an intervention presents greater than minimal risk, but where the risk is justified by the anticipated direct benefit to the enrolled children and the relation of the anticipated benefit to such risk is at least as favorable as that presented by available alternative approaches (this became §CFR 50.52)

No Prospect of Direct Benefit

- If a procedure presents greater than minimal risk AND offers NO prospect of direct benefit, then in compliance with 21 CFR 50 subpart D:
  - The key protocol issue (procedure/intervention) goes to the federal panel for review under 21 CFR 50.54
- This must be requested by an IRB, not the FDA

Implementation of 21 CFR 50.54

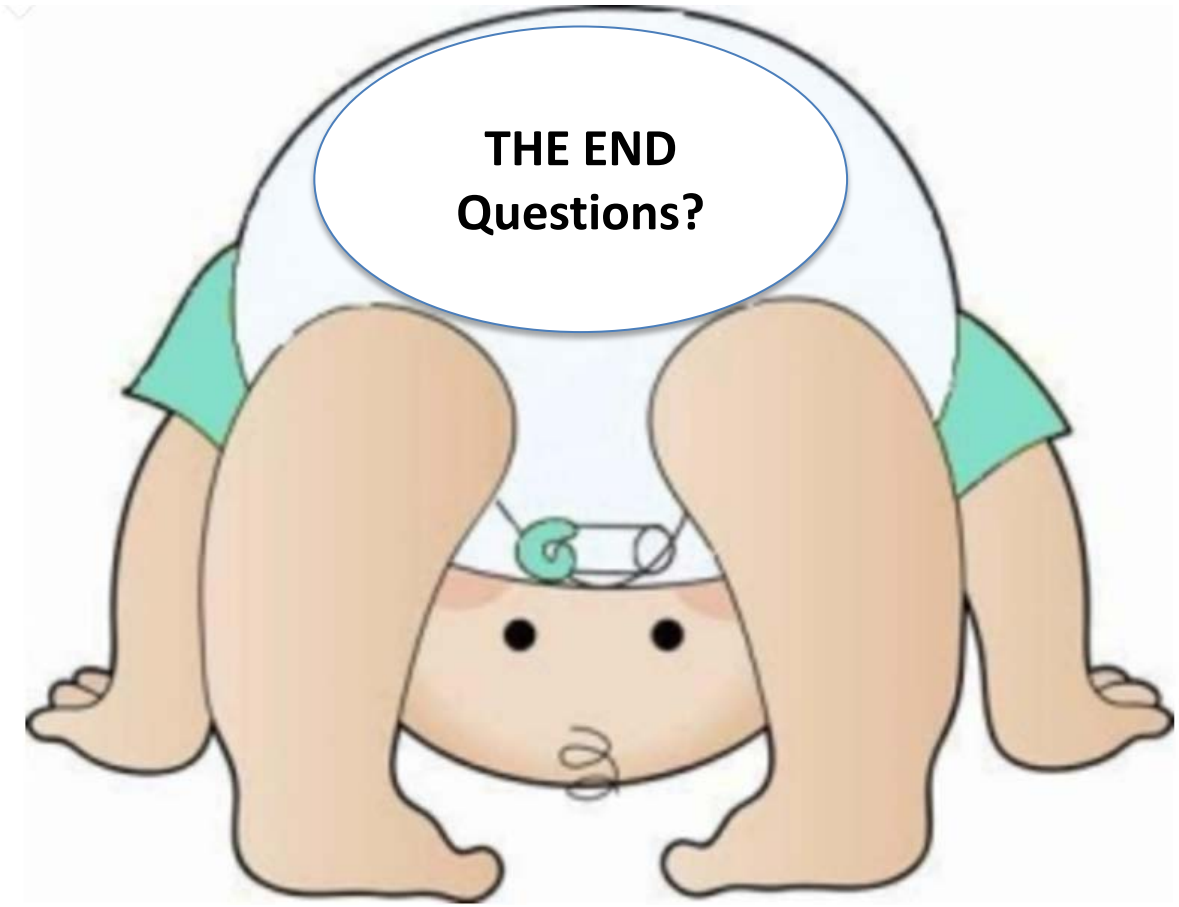
- The criteria for approval of a clinical investigation include:
  - Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a *serious problem* affecting the health or welfare of children; and,
  - Consultation with a *panel of experts* in pertinent disciplines; and,
  - Opportunity for *public review and comment*; and,
  - Will be conducted in accordance with *sound ethical principles*; and
  - Adequate provisions are made for soliciting the *assent* of children and the *permission* of their parents or guardians
  - Administration of an intervention that presented a minor increase over minimal risk to children lacking a disorder or condition

21 CFR Subpart D §50.53

- National Commission developed a fourth category of research out of concern that frequent referral to a National Advisory Board would prove burdensome
- Concerned that this category could be abused based on an assessment that the research is important:
  - The restriction that the risks of interventions that do not offer any prospect of direct benefit must be no more than "a minor increase over minimal risk" was added
    - Examples: PK data collection with administration of single dose

Ethical Principles of Liver Biopsy

- Prospect of Benefit
  - Scientific and clinical necessity should be well articulated in the protocol as well as a reasonable frequency of the procedure
- Risk (minor increase or not)
  - Discussion of the risk of the procedure and how risk can be minimized
- If cannot meet one of these criteria consider a scientific justification


THE END
Questions?

Resources

- Draft Guidance for Industry Pediatric Study Plans, July 2013: http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/UCM360933.pdf
- Pediatric Drug Development
  - Guidance for Industry: E11, Clinical Investigation of Medicinal Products in the Pediatric Population
- Pediatric Ethics
  - 21 CFR 50 Subpart D

Resources

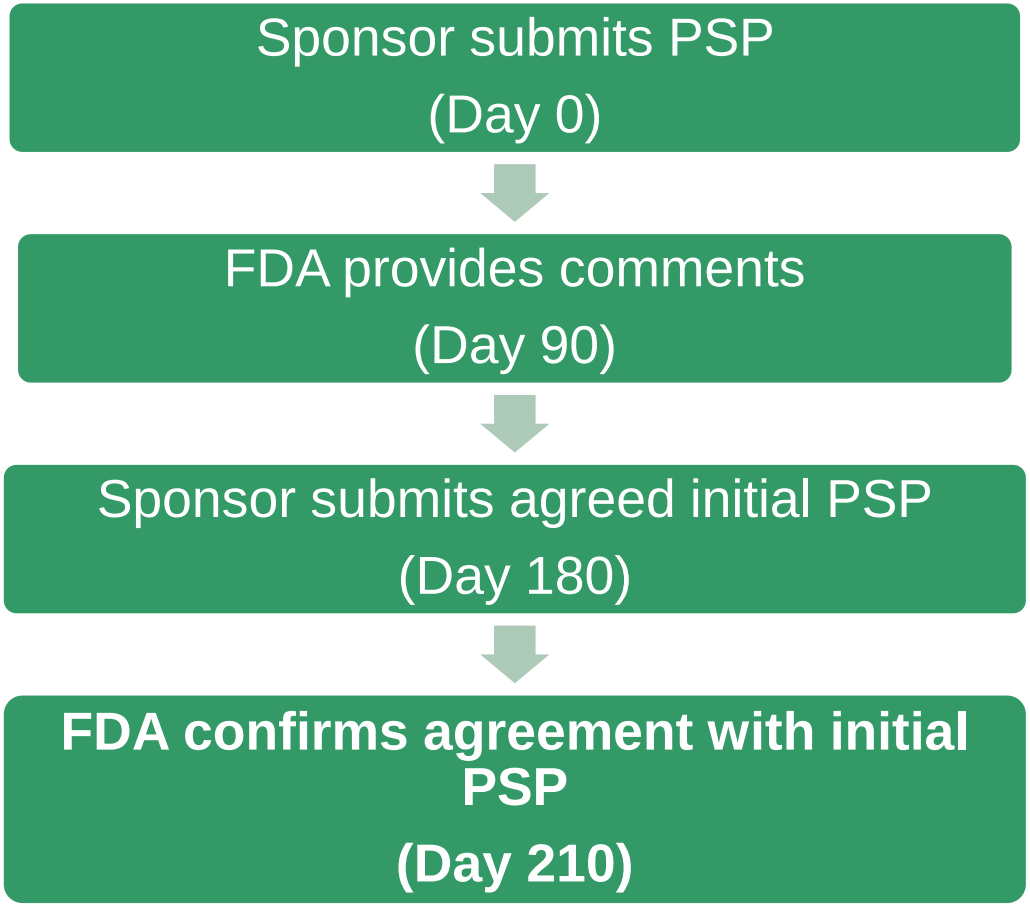
- Pediatrics - including information on FDASIA, PREA and BPCA, and related statistics
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

- Maternal Health
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm174098.htm

Resources

- DPMH
  - http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/default.htm
- Issued Pediatric Written Requests and Inadequate Written Request Letters
  - http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm022224.htm
- Pediatric Review Committee (PeRC)
  - http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

What Happens After a PSP is Submitted?



iPSP Contents

1) Overview - Disease Condition
2) Overview - Drug/Biologic Product
3) Plan for Extrapolation
4) Plan to Request Waiver(s)
5) Summary of Planned Nonclinical and Clinical Studies
6) Pediatric Formulation Development

iPSP Contents

7) Nonclinical Studies
8) Clinical Data to Support Design and/or Initiation of Studies
9) Planned Pediatric Clinical Studies
10) Timeline of the Pediatric Development Plan
11) Plan to Request Deferral
12) Agreements with Other Regulatory Authorities

Subpart D

- § 50.51
  - Not involving greater than minimal risk to children or minor increase over minimal risk
- § 50.52
  - Greater than minimal risk but presenting the prospect of direct benefit to individual subjects

Prospect of Direct Benefit- Component Analysis

- A protocol may (and usually does) contain multiple interventions or procedures, some that offer a prospect of direct (clinical) benefit and others that do not.
- The interventions and procedures must be analyzed and justified separately (i.e., as "components" of the protocol).
- Thus, a protocol may include components that must be evaluated under §50.52/§46.405 (PDB) and others that must be evaluated under §50.53/§46.406 (no PDB).

Prospect of Direct Benefit (PDB)

- A “direct benefit” of an experimental intervention or procedure should improve the health or well-being of the individual child.
- Whether intervention offers a “prospect of direct benefit” must be evidence-based (e.g., adult humans or animal disease models).
  - Do these data make us reasonably comfortable that children might benefit from this intervention/product? Is the dose and duration of treatment with the investigational drug sufficient to offer the intended benefit? Appropriateness of the proposed timing for a repeat liver biopsy assessing histology for discerning the differences from placebo arm, whether the justification is adequate?

Prospect of Direct Benefit (PDB)

- Whether intervention offers PDB separate from whether PDB of sufficient probability, magnitude and type to justify the anticipated risks of the intervention, given the overall clinical context.
  - Risk/benefit evaluation is a complex judgment, similar to clinical practice.
  - Justification of appropriate balance of risk and potential benefit may include importance of “direct benefit” to child; possibility of avoiding greater harm from disease; degree of “tolerable” uncertainty; disease severity (e.g., degree of disability, life-threatening); and the availability of alternative treatments.


FDA
U.S. FOOD & DRUG
ADMINISTRATION