Regulatory Perspectives on Priorities and Methods for TB Trials in Children and Pregnant Women

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- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

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Objectives

- Review laws and regulations pertaining to pediatric therapeutics development
- Review laws and regulations pertaining to drug development considerations for pregnant and lactating women
- Provide overview of regulatory context for TB drug development in children, pregnant, and lactating women

Pediatric Drug Development General Principles

- Children first described as the therapeutic orphan in 1963 by Harry Shirkey, M.D.
- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

U.S. Evidentiary Standard for Approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

U.S. Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Section 505A of the Federal Food, Drug, and Cosmetic Act
  - Provides an incentive in the form of marketing exclusivity to companies to voluntarily conduct pediatric studies for therapies with potential public health benefit in children
  - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)
- Pediatric Research Equity Act (PREA)
  - Section 505B of the Federal Food, Drug, and Cosmetic Act
  - Requires companies to assess safety and effectiveness of certain products in pediatric patients
  - PREA does not apply to any drug for an indication for which orphan designation has been granted
- **Goal of both programs is to increase the number of approved therapies for children**

PREA vs. BPCA

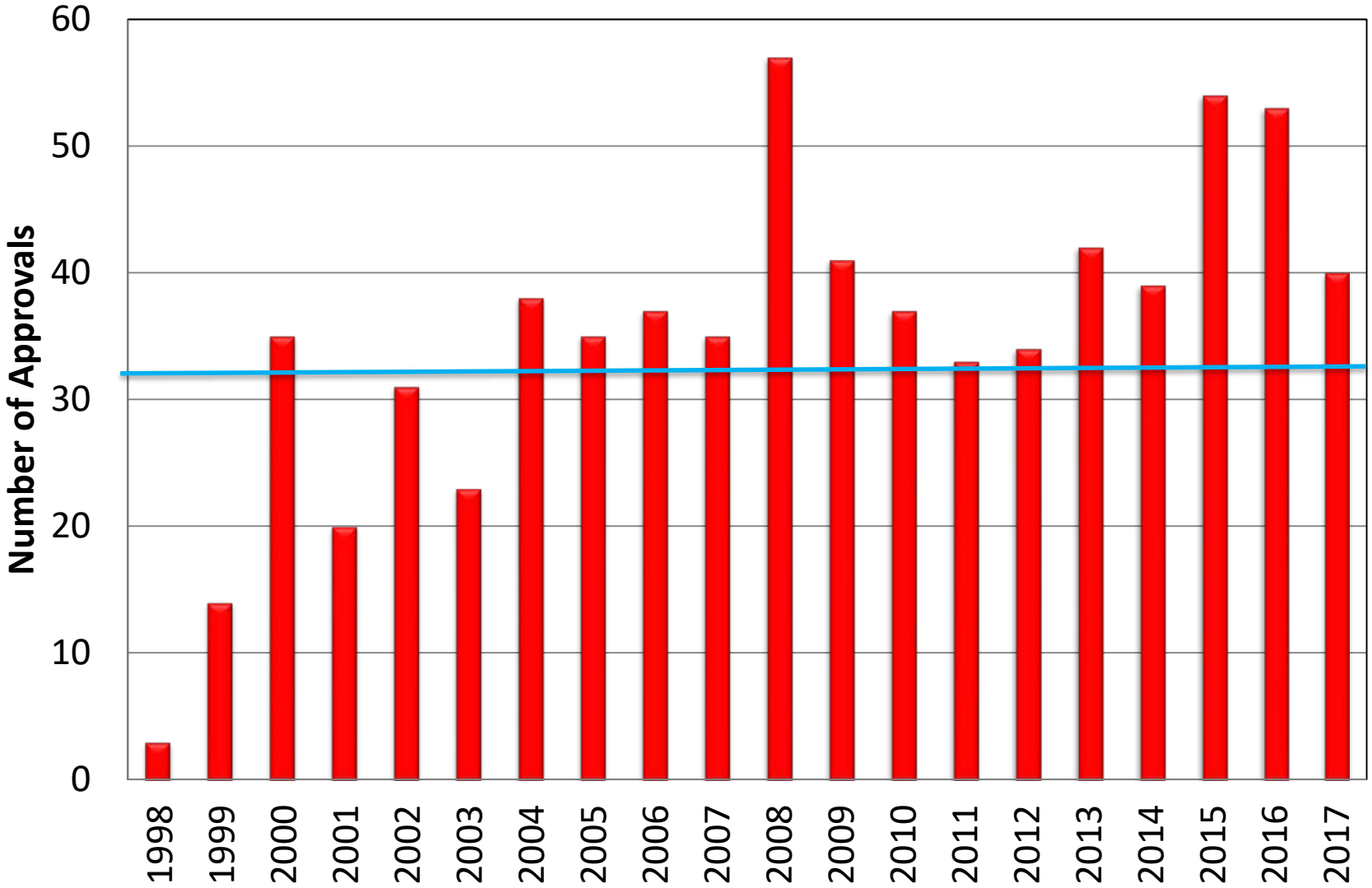
PREA

- Drugs and biologics
- **Required** studies
- Studies may only be required **for approved indication(s)**
- **Orphan drug exemption** (with exception of molecular targets for cancer)
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for products with orphan designation
- Pediatric studies must be labeled

Pediatric Labeling Changes 1998-Current*



* Through September, 2017

Pediatric Extrapolation

- "Pediatric extrapolation" is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

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Pregnancy and Lactation

45 CFR Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

- Originally promulgated on August 8, 1975 and revised several times
- Pertains to research involving fetuses, pregnant women, and human *in vitro* fertilization. Pregnant women or fetuses may be involved in research if all of the following conditions are met:
  - (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
  - (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
  - (c) Any risk is the least possible for achieving the objectives of the research;
  - (d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

45 CFR Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

- (e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- (f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- (g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- (i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Ethical Considerations for Including Women as Research Participants

- American College of Obstetricians and Gynecologists Ethics Committee Opinion published November 2015
- Recommendations
  - Potential for pregnancy should not automatically women for participation in clinical studies
  - Address obstacles to participation (e.g., lack of adequate child care)
  - Representation of all potentially affect individuals, including diverse and underserved populations
  - Pregnant women should be defined as “scientifically complex” rather than “vulnerable”
  - Contraception requirements should be tailored the actual risks of pregnancy in an individual study for an individual study participant
  - Requiring participation consent from a woman’s intimate partner is neither warranted nor ethically justified
  - Consideration of enrolling pregnant women in research requires balance of risk of fetal harm with potential for benefit and the importance of information to be gained on the health of women and fetuses

Recent Changes to 45 CFR 46

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

- Changed January 19, 2017 and takes effect July 19, 2018
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Draft Guidance for Industry "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials"

- Published April 9, 2018
- There is need for data to inform safe and effective treatment during pregnancy, such that clinicians and patients do not have to undertake a risk-benefit analysis for the use of drugs and biological products in pregnant women with limited human safety information
- In certain situations, it is ethically and scientifically appropriate to collect data in pregnant women in clinical trials conducted during drug development
- Ethical Considerations
  - FDA regulations do not contain a section similar to 45 CFR part 46, subpart B; however, FDA recommends that these requirements be satisfied for FDA-regulated clinical research.
  - Mirror the same 10 requirements under 45 CFR 46 Subpart B

Other Guidance Highlights

- General guidelines for research conducted premarketing setting:
  - Adequate nonclinical studies (including studies on pregnant animals) have been completed and the clinical trial holds out the prospect of direct benefit to the pregnant woman
  - And/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)
- General guidelines for research conducted Postmarketing setting:
  - Adequate nonclinical studies (including studies on pregnant animals) have been completed
  - And there is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women
  - And one of the following:
  - Efficacy cannot be extrapolated and/or Safety cannot be assessed by other study methods
- Women who become pregnant during a clinical trial
  - Unblinding should occur so that additional counseling can be given
  - Additional considerations are discussed

Other Clinical Trial Considerations

- Minimizing Risk to the Pregnant Woman
  - Obtain adequate reproductive and developmental toxicology data in relevant nonclinical models
  - Identify the trial population that will derive the most benefit while trying to minimize risk
  - Considering the gestational timing of exposure to the investigational drug in relation to 323 fetal development
  - Choosing appropriate control populations
- Disease Type and Availability of Therapeutic Options in the Pregnant Population
- Timing of Enrollment
- Pharmacokinetic Data
- Safety Data Collection and Monitoring
- Stopping a Clinical Trial That Enrolls Pregnant Women

Differences in Regulatory Approval Paths

- Pediatric patients are considered a distinct population from adults
  - Historically viewed as “little adults”
  - Differences in metabolism, development, ontogeny of organ systems
  - Efficacy can be different
  - Dosing and safety must be established
- Pregnant patients are still considered to be adults
  - Efficacy established in non-pregnant patients supports efficacy in pregnancy
  - Dosing and safety may be different
- **Approval pathway for drugs in pediatric and pregnant patients is different**

Regulatory considerations related to TB drug development in children and pregnant women

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TB Drug Development: Pediatrics

- FDA Guidance*
- Pulmonary TB therapeutics development
  - Pediatric extrapolation is generally accepted
  - PK information to establish appropriate dosing in all relevant pediatric age groups is needed
  - Adequate pediatric safety database is needed
- Extrapulmonary TB therapeutics development
  - Pediatric extrapolation may not be feasible (e.g., patients < 5 years of age)
  - Dose and duration of therapy may be different compared to pulmonary TB therapy
- Timing of pediatric clinical trials
  - Generally after antimycobacterial activity and safety data are obtained in adult patients
  - Adult dosing has been characterized

*FDA Draft Guidance: Pulmonary Tuberculosis: Developing Drugs for Treatment

TB Drug Development: Pediatrics

- TB considered an orphan disease
  - Affects less than 200,000 people in the U.S.
- Orphan drug designation may be possible
  - Products that receive orphan designation for treatment of TB are exempt from requirements under PREA
  - Still possible to seek advice from pediatric experts within FDA
- Timing of pediatric studies should be discussed with FDA early in overall drug development
  - Pediatric trials may not need to be delayed until after adult approval
- Coordination with other global regulatory authorities is possible

TB Drug Development: Pregnant Women

- FDA Guidance*
- Programs should address pregnant women
- Considerations for enrollment of pregnant women in clinical trials:
  - Fetal risk considerations based on results from nonclinical and reproductive toxicology studies as well as an any available clinical data
  - Available data about correct dosing in pregnant patients
  - Whether safety and efficacy have been demonstrated in nonpregnant populations
  - Therapeutic options for treatment of pregnant patients with TB
  - Ethical considerations based on maternal/fetal risk and benefit
- When safe and effective therapies are available, safety and effectiveness in nonpregnant population should be established first

*FDA Draft Guidance: Pulmonary Tuberculosis: Developing Drugs for Treatment

TB Drug Development: Pregnant Women

- Data collection in pregnant women enrolled in clinical trials should include the following at a minimum:
  - Steady-state PK assessments
  - Gestational age at enrollment
  - Gestational timing and duration of drug exposure
  - Pregnancy outcomes including adverse maternal, fetal, and neonatal events
  - Infants born to mothers who received the investigational drug(s) should be followed by investigators until at least 12 months of age
- Women who become pregnant during a clinical trial may be reconsented and continued in the clinical trial
- If the potential benefits of continued treatment outweigh
  - The risks of ongoing fetal exposure to the investigational drug
  - The risks of discontinuing maternal therapy
  - and/or The risks of exposing the fetus to additional drugs if the woman is placed on an alternative therapy

Summary

- U.S. laws and regulations are intended to provide protections necessary to conduct appropriate research in children and pregnant patients
- U.S. laws and regulations are also intended to support collection of data needed on the safe and effective use of medications in pediatric and pregnant patients
- FDA is committed to working with all stakeholders to collect such data in the most efficient and timely process

Thank you