

FDAAA

Reauthorization of Pediatric Initiatives

Lisa L. Mathis, M.D.
Pediatric and Maternal Health Staff
Office of New Drugs

March 2008



Objectives

- Overview of Pediatric History at FDA
- **Title V: Best Pharmaceuticals for Children Act of 2007 (BPCA)**
 - **Pediatric Advisory Committee Members have been actively involved in this legislation**
- **Title IV: Pediatric Research Equity Act of 2007 (PREA)**
 - **Many new responsibilities for FDA and PAC**
- **Implementation**



Title V: Best Pharmaceuticals for Children Act of 2007 (BPCA)

- “Bestest”



BPCA 2007 Reauthorization

- **Still applies to drugs only**
 - not biologics
- **Reauthorizes pediatric exclusivity incentive**
 - FDA may issue a Written Request (WR) for studies of moiety needed to label drug for pediatric patients
 - 6 months of additional exclusivity for conducting FDA-requested pediatric studies contained in a WR
 - Drug must have existing patent/exclusivity
 - FDA must determine public health need
 - Studies submitted must “fairly respond” to WR
 - Includes timeframe for submission of study reports



BPCA 07- Clarifications for WRs

- **Single WR may include uses that are both approved and unapproved**
 - **A.k.a. labeled and unlabeled**
- **May include preclinical studies**
 - **Not solely preclinical**



BPCA 07- FDA Process Changes Pediatric Review Committee (PeRC)

- **Reviews WRs prior to being issued**
- **May review studies to make recommendation on exclusivity determination**
 - *Previously, only the drug review division makes recommendation to Peds Exclusivity Board*



BPCA 07- Process Changes (cont.)

- **Any application or supplement submitted in response to a WR is subject to a priority review.**
 - *Previously, only supplements were given priority review*
- **Exclusivity determination made within 180 days**
 - **Change from 90 days**
- **Pediatric exclusivity granted only if 9 months left of exclusivity/patent protection at time of exclusivity determination.**
 - *Addresses “de facto” exclusivity*
- **Applicants must submit all available adverse event reports with pediatric study submission**



NDA/Supplemental (sNDA) NDA Review Clock Old BPCA

Standard Reviews of NDA/sNDA



Standard Reviews of NDA/sNDA submitted in response to a WR



Priority Review



Priority Review of sNDA submitted in response to a WR



NDA/Supplemental (sNDA) NDA Review Clock BPCA 2007

Standard Reviews of NDA/sNDA

Day 1 Submission ←————→ **10 Month**
PDUFA Date –
Action Taken

Priority Review

Day 1 Submission ←————→ **6 Month**
PDUFA Date –
Action Taken

Standard Reviews of NDA submitted in response to a WR

Day 1 Submission ←————→ **6 Month** **Day 180**
PDUFA Date – **Exclusivity**
Action Taken **Determined**

Review of sNDA submitted in response to a WR

Day 1 Submission ←————→ **6 Month** **Day 180**
PDUFA Date – **Exclusivity**
Action Taken **Determined**



BPCA 07- Labeling Changes

- **If a study does or does not demonstrate safety or efficacy in pediatric populations (even if inconclusive), the label must include information on the study and a statement of the Secretary's determination**
- **Maintains Dispute Resolution Process**
 - **The process outlines timeframes for decisions, including referral to and recommendation from the Pediatric Advisory Committee.**



BPCA 07- Transparency & Public Notice

- **Notice of exclusivity determination and copy of WR within 30 days**
- **Medical, statistical, and clinical pharmacology reviews of studies, irrespective of regulatory action within 210 days of report submission**
- **Notice of drug for which a pediatric formulation was developed and found safe and effective in exclusivity studies, but was not marketed within 1 year of exclusivity determination – 30 days after 1 year period**



Title IV: Pediatric Research Equity Act of 2007 (PREA)



PREA Basics are Unchanged

“Drugs & Biologics”

- **Pediatric studies required and a pediatric assessment must be submitted for NDA/BLA or supplements with**
 - **New active ingredient**
 - **New indication**
 - **New dosage form**
 - **New dosing regimen or**
 - **New route of administration**
- **Studies may be waived or deferred**



PREA

What is the Pediatric Assessment?

- Contains data from pediatric studies using appropriate formulations for each age group where assessment is required and other data that are adequate to:
 - Assess the safety and effectiveness of a drug or biological product for the claimed indications in all relevant pediatric subpopulations AND
 - Support dosing and administration for each pediatric subpopulation for which the drug or biological product is safe and effective

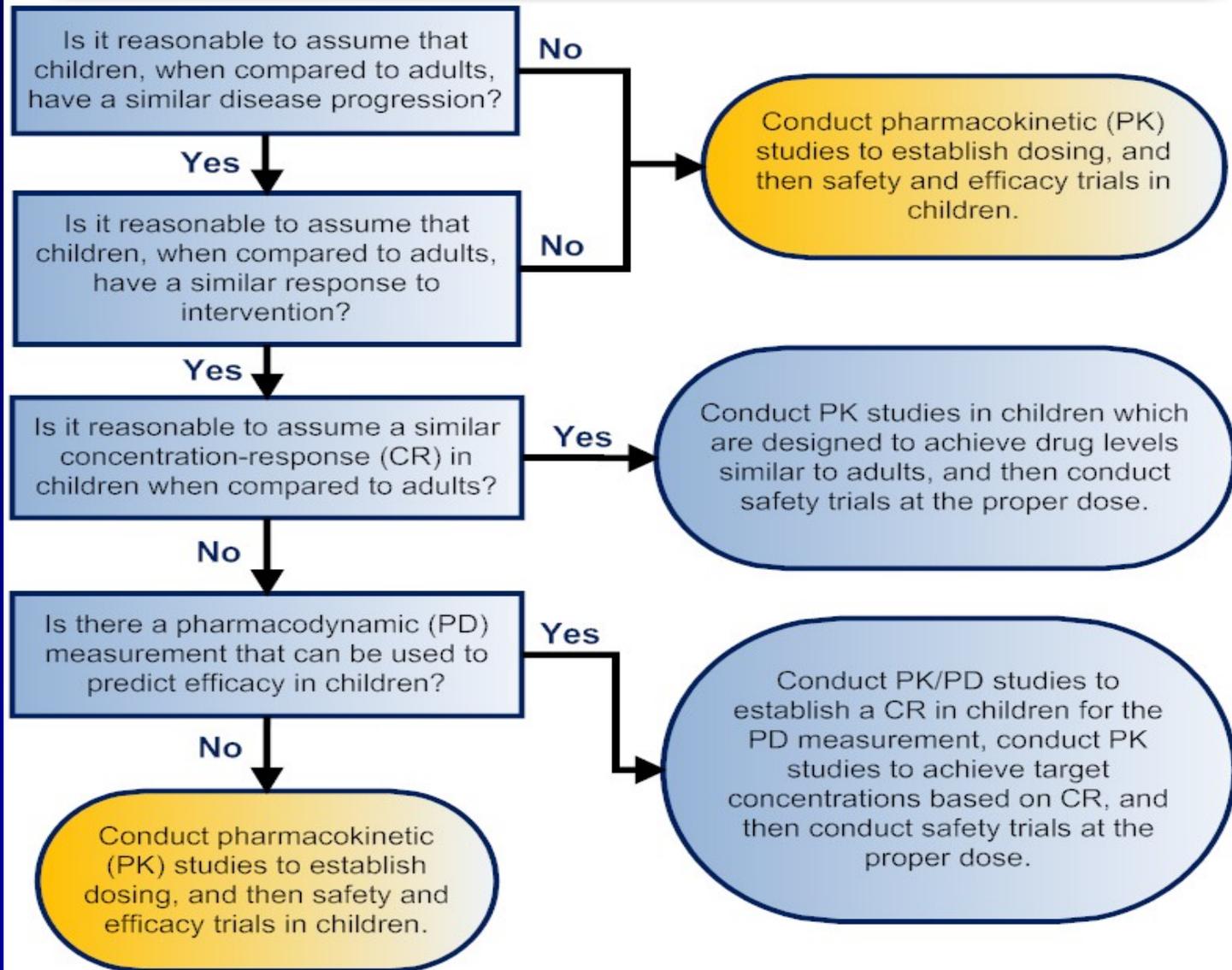


Extrapolation

- **If there is a similar course of disease and effect of treatment [intended or adverse]:**
 - **Can extrapolate effectiveness from adequate and well-controlled studies in adults, when supplemented with other information**
 - **Can extrapolate from one age group to another age group**
- **If extrapolation is used, “pertinent reviews” must contain a brief documentation of the scientific data supporting the extrapolation**



FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under BPCA or PREA)



Deferrals

- **Drug or biologic is ready for approval in adults;**
- **Additional safety and effectiveness data determined to be necessary; or**
- **There is another appropriate reason for deferral**
- **Applicant must submit**
 - **Certification of the grounds for deferral;**
 - **Description of the planned studies (pediatric plan);**
 - **Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.**



Deferral Progress Report

- **FDAAA added:**
 - **If studies are deferred, applicant must submit an annual review detailing progress made in conducting the pediatric studies. Annual reviews must be made public (posted on the Internet).**



Waiver

Criteria for granting FULL WAIVER (birth to 16 yrs):

- Necessary studies impossible or highly impracticable;
- Strong evidence suggests the drug or biologic would be ineffective or unsafe; or
- Drug or biologic does not represent a meaningful therapeutic benefit over existing therapies AND is not likely to be used in a substantial number of pediatric patients



Partial Waiver

Criteria for granting a PARTIAL WAIVER

(subset of the pediatric population):

- Same criteria as full waivers but with additional requirement
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed
 - Supporting data must be submitted and posted



PREA 07

Changes to Waiver and Deferral Processes

- **If studies are deferred:**
 - applicant must submit annual review detailing progress made in conducting the pediatric studies
 - Annual reviews must be made public (posted on the Internet).
- **If a study is waived based on inability to develop a pediatric formulation**
 - the applicant must detail why it cannot be developed and the submission must be promptly posted.



Physician Labeling Rule

Reorganization of Label Sections

Old Format	PLR Format	Section/subsection
Contraindications	Contraindications	4
Warnings	Warnings and Precautions	5
Precautions Pediatric Use	Use in Specific Populations/ Pediatrics	8.4
Adverse Reactions	Adverse Reactions	9
Animal toxicology	Nonclinical Toxicology	13



PREA 07 – Labeling Changes

- **Pediatric study information must be included in product label**
 - **Must occur whether a study does or does not demonstrate safety or efficacy, or is inconclusive**
 - **Pediatric Advisory Committee recommended labeling format**
 - **If indication is granted, information is throughout labeling**
 - **If no indication all information under “PEDIATRICS”**
 - **This allows one to know if there is a pediatric indication or not**



PREA 07 – Labeling Changes (cont.)

- **Dispute Resolution Process**
 - Comparable to that in the BPCA
 - When FDA and sponsor are unable to reach agreement on labeling, the dispute resolution process begins 180 days after submission of the application or supplement *
 - Specific timeframes for decisions, including referral to and recommendation from the Pediatric Advisory Committee

At time of approval, we will have agreed labeling. All peds supplements will not have a 6 month clock



PREA 07

Transparency of pediatric submissions

- **FDA to make available to the public**
 - **Full medical, statistical, and clinical pharmacology reviews**
 - **Previously only summaries of BPCA studies were posted**



BPCA and PREA

Internal Review Committee

- **Pediatric Review Committee “PeRC”**
- **Consultation and Review on mandated activities under BPCA and PREA**
- **Provides quality and consistency**
 - **Interface of BPCA and PREA**
 - **Information requested in pediatric plans, assessments, waivers, and deferrals**
 - **Pediatric Written Requests**



PeRC Activities

- **Consultation to product divisions on all pediatric plans and assessments**
- **Consultation on granting of deferral and waiver requests**
- **Make recommendations on when submissions should receive priority review**
- **Membership participation in activity must be documented**



PeRC Membership – FDA Experts

- **Pediatrics**
- **Clinical pharmacology**
- **Statistics**
- **Chemistry**
- **Legal issues**
- **Pediatric ethics**
- **Expertise related to product under review**
- **Other as deemed helpful**



PeRC “Deliverable”

- **Within 12 months, conduct review of sample of studies submitted, deferrals and waivers granted since PREA 2003**
 - **Quality and consistency of pediatric information**
 - **Appropriateness of waivers and deferrals granted**
- **Intended to provide basis for improvements and new guidance document**



PeRC Responsibilities Include Tracking & Posting

- **FDA to track and post numbers of**
 - **Studies conducted**
 - **Products and the conditions studied under PREA**
 - **Types of studies and descriptors**
 - **Trial design, number of patients studied, and number of centers and countries involved**
 - **Deferrals requested and granted and reasons for granting deferrals, timeline for completion, and number completed and pending**
 - **Waivers requested and granted and reasons for granting waivers**



Tracking & Posting (cont.)

- **Pediatric formulations**
 - Number developed
 - Number not developed and reasons
- **Pediatric labeling changes**
 - Annual summary of labeling changes made as a result of PREA
- **Annual status of deferred studies**
- **PeRC recommendations on priority review status**
 - How often recommended and how often the recommendation was adopted and reasons why it was not adopted



Tracking & Posting (cont.)

Similar to PREA, For BPCA FDA will also post

- Number of studies conducted
- Drugs and drug uses, on and off-label
- Types of studies conducted (e.g., trial design, number of patients, number of centers/countries involved)
- Number of pediatric formulations developed, not developed, including reasons if not developed
- Labeling changes and annual summary of all labeling changes



PREA & BPCA 07

Longer term progress reports

- **FDA to contract with IOM within 3 years to study and report to Congress**
 - **Pediatric WR and studies conducted under PREA and BPCA and resultant labeling changes**
- **GAO to report to Congress**
 - **Effectiveness of BPCA and PREA in ensuring that medicines used by children are tested and properly labeled (due January 1, 2011)**
- **BPCA and PREA sunset October 1, 2012**



PREA & BPCA 07

Annual Safety Review expands to PREA

- **All adverse event reports must be referred to FDA's Office of Pediatric Therapeutics (OPT) for the first year after approved labeling change**
 - **Reports presented to Pediatric Advisory Committee**
 - **Additional reviews beyond the first year as appropriate**



Summary

PREA

- **Drugs and biologics**
- **Studies mandatory**
- **Required studies only on drug/ indication under review**
- **Studies for orphan indications exempt**
- **Standard Review (unless qualifying for priority review)**
- **Peds studies must be labeled**

BPCA

- **Drugs**
- **Studies voluntary**
- **Studies on entire active moiety**
- **WR may be issued for orphan indications**
- **Priority Review**
- **Peds studies must be labeled**



Conclusions

- **New laws renewed many important provisions of BPCA 2002 and PREA 2003**
- **New provisions increase transparency in process**
- **Since laws are intended to work together, new internal review committee will improve consistency**
- **Provides opportunity for the FDA and Industry to work together to advance the public health for children**

