Growth and Development of Pediatric Drug Development at the FDA

Lisa Mathis, MD

Associate Director

Pediatric and Maternal Health Team

Office of New Drugs

Center for Drug Evaluation and Research

June 2006

FDA and Pediatric Health

- Series of adverse events resulting from the treatment of children with drugs and biologics in the early 20th century influenced the Food and Drug Administration's ability to regulate medicine

Biologics Control Act of 1902

- Diphtheria antitoxin was made by inoculating horses with increasingly concentrated doses of diphtheria bacteria, then bleeding the animals to obtain their blood serum, which was bottled as antitoxin
- Possibilities for contamination were vast in the production process
- In 1901, thirteen children in St. Louis died after receiving diphtheria antitoxin contaminated with tetanus spores
- This tragedy spurred Congress into passing the Biologics Control Act

1906 Pure Food and Drugs Act

- Medicines from the 19th century contained dangerous substances
- Mrs. Winslow's Soothing Syrup:
- "For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle."
- Contained alcohol and morphine sulfate Causing coma, addiction & death in infants
- Pure Food and Drugs Act prohibited interstate commerce in adulterated or misbranded drugs

1938 Food, Drug and Cosmetic Act

- Elixir of Sulfanilamide introduced in September 1937
- Compounded with an untested solvent, diethylene glycol (chemically related to antifreeze)
- Caused 107 deaths including many children
- President Roosevelt signed the Food, Drug and Cosmetic Act on June 25, 1938
- Firms had to prove to FDA that any new drug was safe before it could be marketed

1962 Kefauver-Harris Amendment

- 1960 a New Drug Application was filed with the FDA for Kevadon (Thalidomide), which had been marketed in Europe since 1956
- FDA felt that the data were incomplete to support the safety
- 1961 the drug was pulled off the market in Germany because of congenital anomalies
- Over 20,000 Americans received thalidomide under the guise of investigational use
- 1962 Kefauver-Harris Amendment that manufacturers had to prove efficacy as well as safety

FDA and Pediatric Health

- These crisis involved children, but resulting laws actually benefited adults
- Information on use of therapeutics in children remained inadequate
- Finally, in the 21st century, laws were passed to specifically address drug use in children

Benchmarks
Pediatric Drug Development

- 1979 Labeling Requirement
- 1994 Pediatric Labeling Rule
- 1997 Food and Drug Administration Modernization Act (FDAMA)
- 1998 Pediatric Rule
- 2002 Best Pharmaceuticals for Children Act
- 2002 Pediatric Rule Enjoined
- 2003 Pediatric Research Equity Act

General Principles*

- Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population
- Product development programs should include pediatric studies when pediatric use is anticipated
- Pediatric development should not delay adult studies nor adult availability
- Shared responsibility among companies, regulatory authorities, health professionals, and society as a whole

*** from ICH E-11**

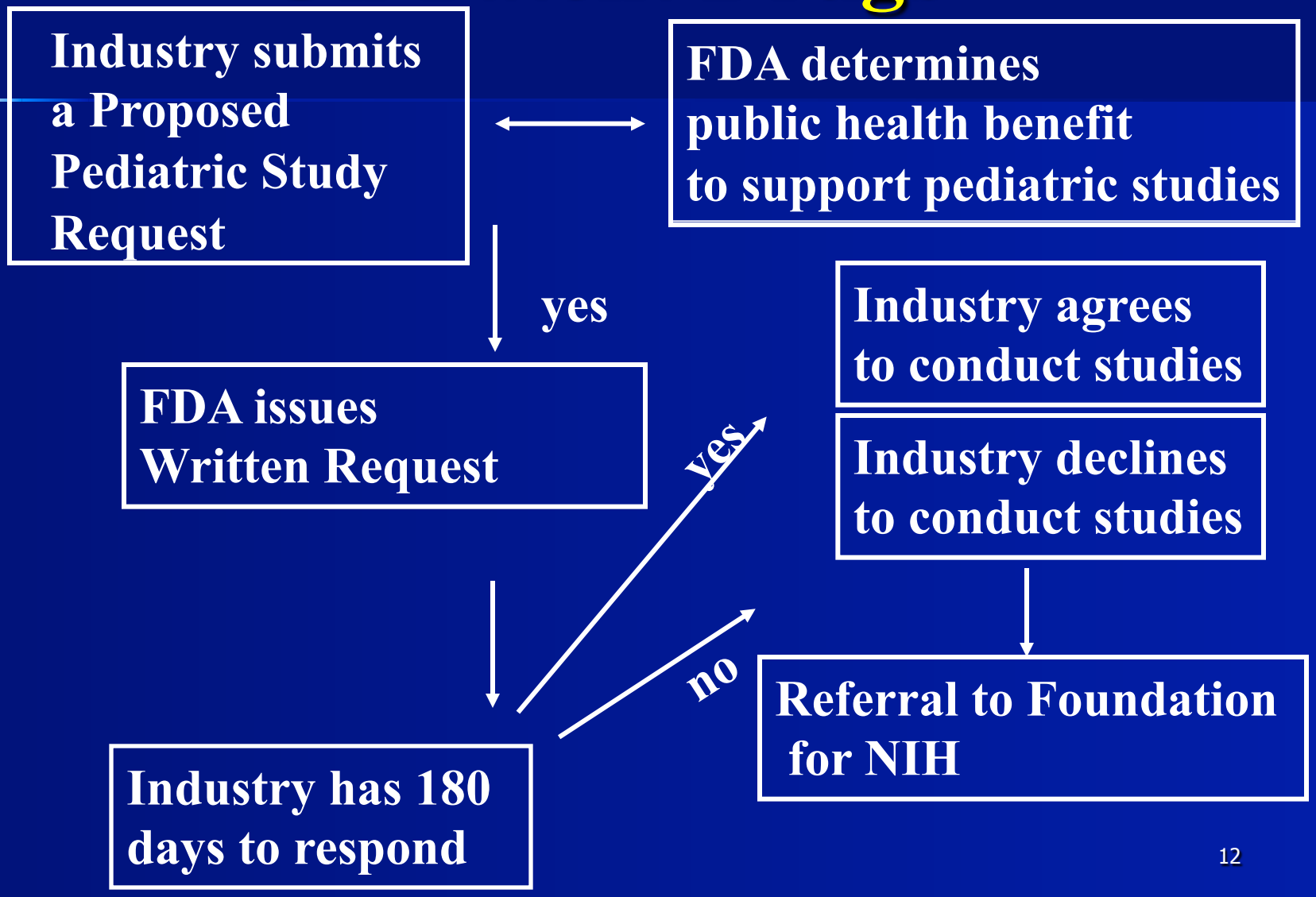
Best Pharmaceuticals for Children Act (BPCA)

- Signed into law January 4, 2002
- Renewed pediatric exclusivity incentive
- Provides additional process for "off-patent" drug development
- Public posting of results
- Reporting of all AE's for 1 year after pediatric exclusivity granted

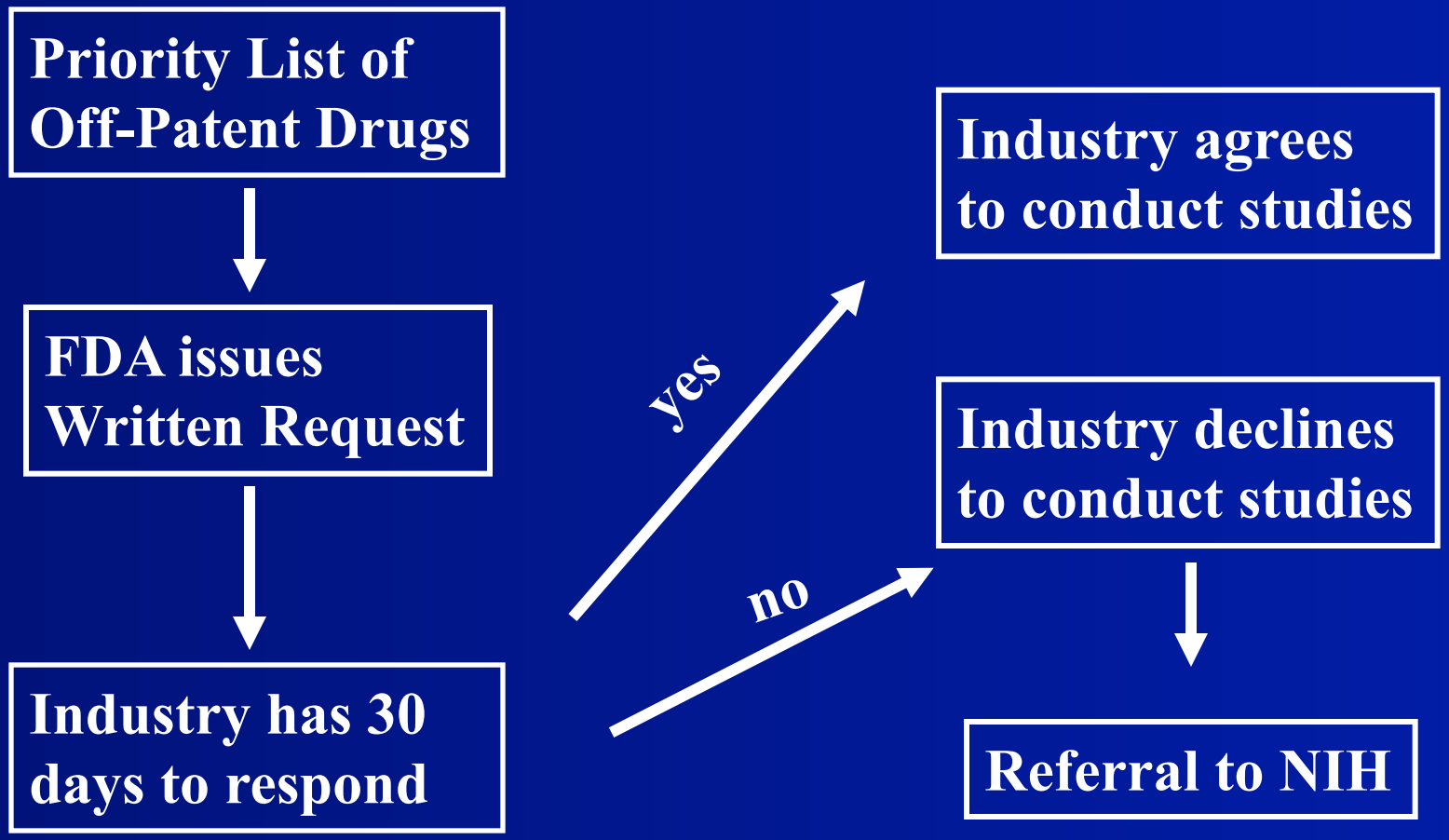
BPCA

- Clinical Investigators may be involved in BPCA through the
  - On-patent process, or
  - Off-patent process

Process for the Study of On-Patent Drugs



Process for the Study of Off-Patent Drugs



Considerations for Issuing a Written request

- **Public Health Benefit?**
  - **Is this a serious, life-threatening condition?**
  - **How frequently does disease/condition occur?**
  - **Are there therapeutic options approved for this indication, and are they labeled for use in pediatrics?**
  - **How often is this drug or others like it used in children (off-label use)?**

Considerations for Issuing a Written request

- What do we know about the drug?
  - Are there any safety signals?
    - Animals?
    - Adult trials?
    - Spontaneous reports?
  - Is there enough safety information to start clinical trials in children?
  - Is there an appropriate risk/benefit?

Considerations for Issuing a Written request

- What information do we need?
  - In what age groups do we need the information?
  - What studies are needed to obtain this information?
    - Extrapolation may prevent children from unneeded exposure to studies, and
    - May result in expedited access for children

Ethics

- Ethical considerations are always important in pediatric trials
- Subpart D (21CFR50)
  - Code of Federal Regulations gives additional protection for children
  - Institutional Review Board may refer a research protocol to a federally mandated ethics panel
  - If involves FDA regulated drug, comes to FDA panel

Pediatric Exclusivity Stats
(April 2006)

- Proposed Pediatric Study Requests 465
- Written Requests issued 317
- Exclusivity granted 118
- Label changes 115
- Number of patients in requested studies 44,763+
- Summaries of Medical/Clinical Pharmacology
  - Summaries on fda.gov/cder/pediatrics 65

www.fda.gov/cder/pediatric/summaryreview.htm

PREA

- Signed December 3, 2003
- Drugs and Biologics affected
- Restored some important aspects from the Pediatric Rule, enjoined in 2002
- Pediatric Assessment required for certain applications unless waived or deferred
- Established the Pediatric Advisory Committee

PREA

- Assessment required for applications:
  - New ingredient
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration
- Guidance Published

Pediatric Assessment

Assessment must contain:

- Data adequate to assess the safety and effectiveness of the drug or biological product, and
- Data to support dosing and administration for each subpopulation

PREA - Waiver

Waiver granted when:

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

PREA - Partial Waiver

Partial Waiver granted (applies to an age subset of the pediatric population) when:

- Same criteria as waivers but with additional requirement
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed

PREA - Deferral

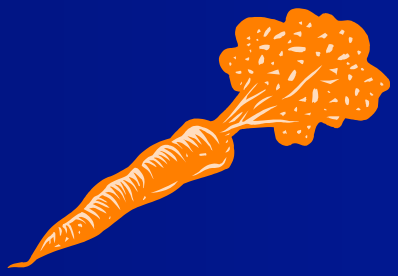
Deferral granted when:

- 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

BPCA vs. PREA

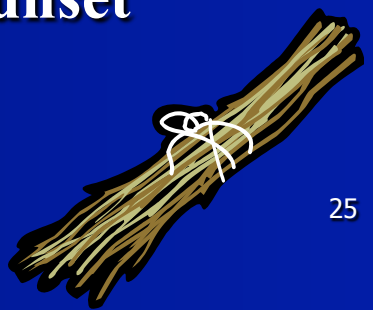
BPCA

- Studies are voluntary
- Includes orphan drugs and orphan drug indications
- Drugs only
- Studies on whole moiety
- 10-1-07 Sunset



PREA

- Studies are required
- Orphan drugs designated exempt
- Biologics and Drugs
- Studies limited to drug/ indication under development
- 10-1-07 Sunset



Back Ups

21CFR50

- Subpart D- Additional Safeguards for Children in Clinical Investigations
  - 50.50 IRB Duties
  - 50.51 Clinical investigations not involving greater than minimal risk
  - 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects
  - 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's condition
  - 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
  - 50.55 Requirements for permission by parents or guardians and for assent by children
  - 50.56 Wards

21 CFR 50.24

- Part 50 – Protection of Human Subjects
  - Subpart D – Informed Consent of Human Subjects
    - 50.24 Exception from informed consent requirements for emergency research.