Pediatric Product Development in the U.S.

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Outline of Presentation

- Historical Background
- Developing Products in Pediatrics
  - General Principles
  - Goal
  - Similarities and differences between pediatric and adult development
  - Programs and Processes
  - Lessons Learned
  - References

Historical Background

The Pediatric Knowledge Gap

- **Historically, drugs have been used in children WITHOUT the same level of evidence as has been obtained in adults.**

The Pediatric Knowledge Gap

- **About 80% of listed medication labels disclaimed usage or lacked dosing information for children.**
    - *Physician's Desk Reference* 1973* & 1991 Surveys
- **Only 20-30 % of drugs approved by the FDA were labeled for pediatric use.**
    - 1984-1989* Survey, 1991-2001 Repeat Survey
- **Only 38% of new drugs potentially useful in pediatrics were labeled for children when initially approved.**
    - **1991-1997*, FDA statistics**

WHY The Pediatric Knowledge Gap?

- **The study of drugs in children was discouraged**
  - **Perceived concerns over ethical issues**
  - **Fears of harming children**
  - **Perceived increased liability of testing drugs in children**
- **Belief that dosing could be determined by body weight (little adults”).**

WHY The Pediatric Knowledge Gap?

- **Inherent difficulties in conducting pediatric trials**
  - **Limited populations for certain diseases**
  - **Lack of infrastructure (facilities, equipment, laboratories) and technical expertise.**
- **Lack of pediatric regulation/legislation to incentivize or require drug companies to conduct pediatric trials.**

Impact of The Pediatric Knowledge Gap

- **Children did not receive potentially life-saving or otherwise beneficial therapeutics because they were not approved for use in children.**
- **Children received unapproved therapeutics (off-label use) based on adult studies with no or limited pediatric experience, sometimes with disastrous results.**

American Academy of Pediatrics Committee on Drugs (1977)

- **It is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children.**
- **It is not only ethical, but also imperative that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who need them.**

Closing the Knowledge Gap

- **Over the past 15 years, we have evolved from a view that we must protect children from research to a view that we must protect children through research.**
- **Implementation of Pediatric Regulations/Legislation**
- **International pediatric therapeutics guidance**

History of U.S. Pediatric Regulation/Legislation

- FDAMA Pediatric Exclusivity (incentive) 1997
- Pediatric Rule Regulation (requirement) 1998
  (enjoined 2002 by court-FDA not have authority)
- January 2002: FDAMA Exclusivity Sunsets
- January 2002: (BPCA)
  -Best Pharmaceuticals for Children Act (incentive)
- December 2003: (PREA)
  -Pediatric Research Equity Act (requirement)
- October 2007: Sunset for BPCA & PREA
- September 2007: Food & Drug Administration Amendments Act (FDAAA) –reauthorized BPCA and PREA; includes Devices; sunsets October 1, 2012.

FDAAA 2007 New Initiatives

- **Established Pediatric Review Committee (PeRC).**
- **New labeling mandates**
  - **Requires results of pediatric studies under BPCA or PREA be included in label, regardless of outcome (positive, negative or inconclusive).**
- **Requires pediatric-focused post-marketing safety reporting for all products studied under BPCA or PREA.**

FDAAA 2007 New Initiatives

- **Written Request may include approved and unapproved uses and preclinical studies.**
- **New transparency mandates**
  - **Requires posting complete reviews.**
  - **Posting of annual progress if studies deferred.**
- **Development of age-appropriate formulation required.**
- **New pediatric medical device provisions**
- **Expanded role of NIH**
- **Sunset October 1, 2012.**

ICH Guidance

- **ICH Expert Working Group finalized a guidance for industry in 2000**

E11: Clinical Investigation of Medicinal Products in the Pediatric Population

www.fda.gov/cder/guidance/index.htm

Developing Products in the Pediatric Population

General Principles Guiding Pediatric Product Development

- **As stated in ICH E-11**
  - **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.**
  - **Development of product information in pediatric patients should be timely and, often requires the development of pediatric formulations.**
  - **The rights of pediatric participants should be protected and they should be shielded from undue risk.**
  - **Shared responsibility among companies, regulatory authorities, health professionals and society as a whole.**

Goal of Pediatric Legislation

Conduct of Ethical and Scientifically Valid Pediatric Clinical Trials

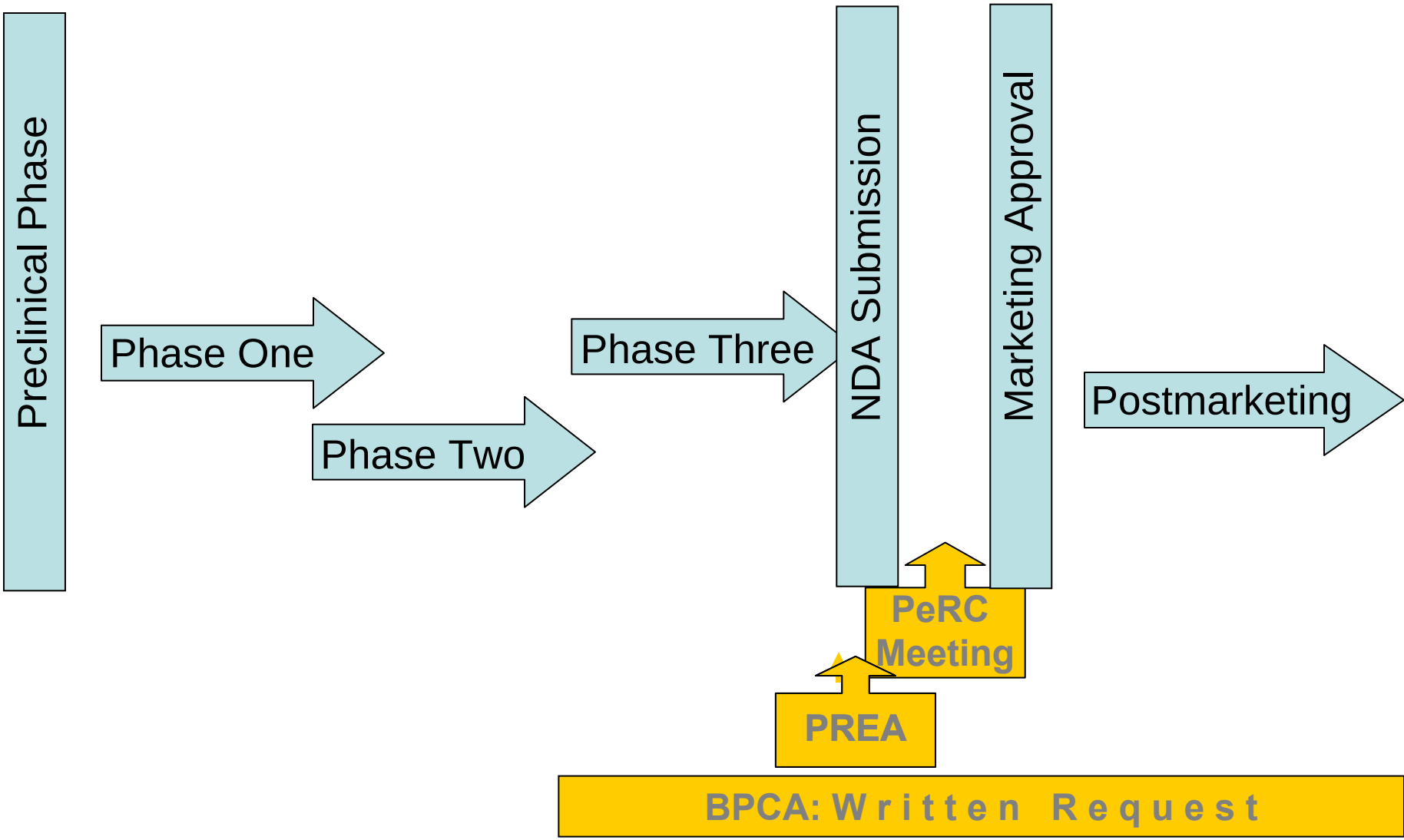
New Pediatric Information in Label

Dissemination

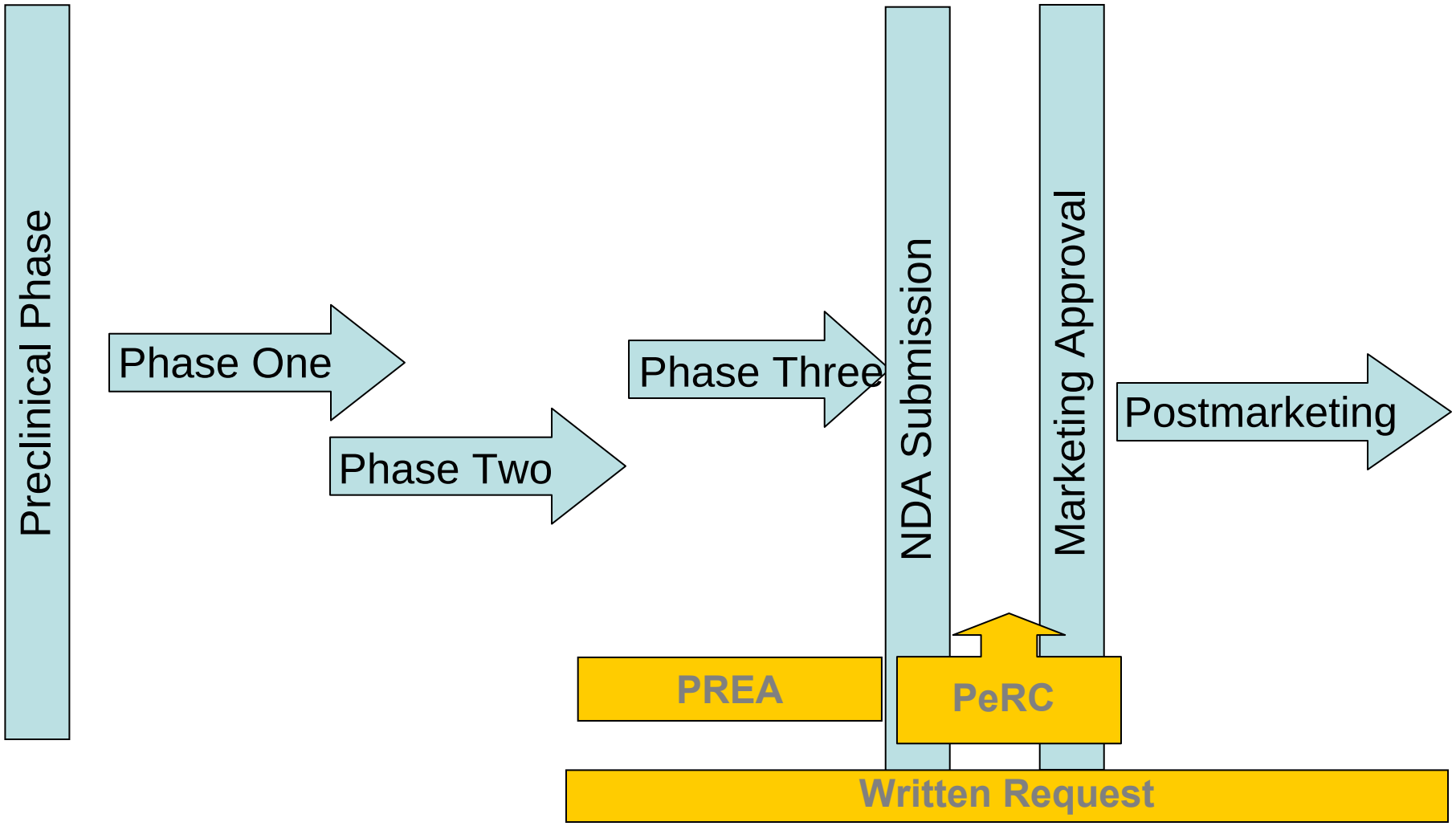
Pediatric Product Development General Principles Regarding Process

- **In general, new products are developed for use in adult and pediatric patients. Pediatric product development should be integrated into the adult development program and not be an add-on or afterthought.**
- **Tools for this integration include those provided by the pediatric legislation: BPCA and PREA.**
- **Pediatric product development must be conducted with the same scientific and ethical rigor as for adults with additional ethical protections for children (Subpart D 21CFR 50.50-50.56).**
- **FDA regulatory requirements must be met for marketing approval.**

Timing in U.S. Pediatric Legislation



New Drug Development:
Usual Implementation Process in U.S.



Similarities Between Pediatric and Adult Product Development

- Scientific development process and review
- Submission requirements
- Labeling process
  - Incorporation of information in labeling must be negotiated with the sponsor and is managed by the technical review division.

Differences Between Pediatric and Adult Product Development

- **Driver**
  - **Adult product development: industry**
  - **Pediatric product development: government legislation**
- **Development of clinical trials**
  - **Centralized (PeRC) for pediatrics since November 2007**
- **Transparency of data**
  - **“negative” pediatric trial results posted and included in labeling**
- **Mandated pediatric focused post-marketing safety reporting to Advisory Committee for the first year after the pediatric labeling change.**

Differences Between Pediatric and Adult Product Development

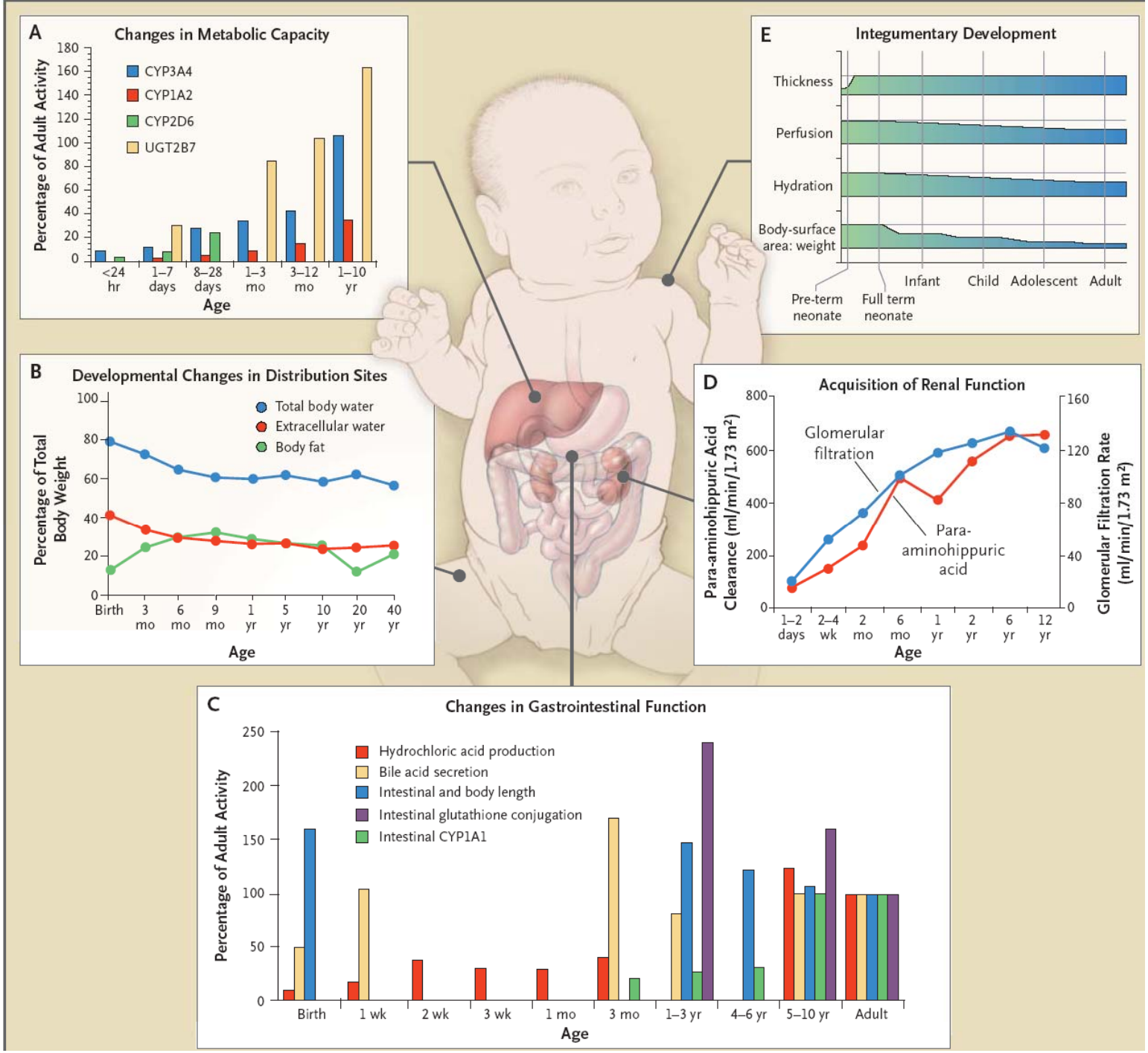
- **More difficult to conduct pediatric trials**
  - **Ethical issues**
    - **Healthy adults can volunteer for a study; children cannot.**
    - **Children cannot consent- both parental permission and the child's assent often are needed.**
  - **Special facilities, equipment, nurses, laboratories and expertise are needed.**

Differences Between Pediatric and Adult Product Development

- **More difficult to conduct pediatric trials (continued)**
  - **Limited patient population to study**
    - **Children tend to be healthy**
    - **Children's illnesses tend to be acute so limited chronic patient population to study**
    - **Small populations → multicenter and often international studies to enroll an adequate number of patients.**
  - **Not only the child but the entire family is involved.**

Differences Between Pediatric and Adult Product Development

- **Many age subsets require studies, not just one study covers all of pediatrics.**
  - **Birth through adolescence spans a wide range of organ developmental maturation (e.g. CNS, liver, kidney, lung, skeletal, reproductive and immune systems), which may affect drug pharmacokinetics, efficacy and safety.**



Kearns et al.,
NEJM 349: 1160

Differences Between Pediatric and Adult Product Development

- **Sequential approach by pediatric age (i.e. adolescents before younger age groups) may be taken during pediatric product development.**
- **Timing: pediatric drug development**
  - **Serious or life-threatening disease**
    - **May initiate pediatric studies after preliminary PK and safety information is obtained in adults**
  - **Not serious or life-threatening disease**
    - **May initiate pediatric studies after adult Phase 3 studies have been completed to provide assessment of risk/benefit.**

Differences Between Pediatric and Adult Product Development

- **Juvenile animal studies may be needed prior to conduct of pediatric studies.**
- **Age-appropriate pediatric formulations may be needed to assure accurate dosing. Different drug concentrations of these formulations may also be needed. Safety of excipients must be considered.**
- **Age-appropriate and validated pediatric endpoints and assessment tools may be lacking or limited.**
- **PK: sparse sampling and application of modeling/simulation to pediatric trials.**
- **Chronic effects of therapy on growth and cognitive and sexual development of pediatric patients is needed.**

Differences Between Pediatric and Adult Product Development

- **Extrapolation: UNIQUE TO PEDIATRICS**
  - **If the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients, FDA may conclude that pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.**
  - **A study may not be needed in each pediatric age group if efficacy data from one age group can be extrapolated to another age group.**

Pediatric Product Development: Programs and Processes

- **BPCA: voluntary program driven by public health need**
  - **Written Request (WR): legal document that outlines studies requested by FDA**
    - **On-patent (incentive: 6-month patent extension)**
    - **Off-patent or generic process (List and contracting process coordinated by NICHD**
    - **WRs declined by sponsor can be sent to NIH**
- **PREA: requirement program triggered by NDA submission for adult indication**
- **Orphans Program**
- **New Drug Development process**
  - **Disease or condition occurs only in pediatrics**
  - **Progression and requirements similar to adults: pre-IND, IND, NDA & post-marketing. Possible additional considerations include need for juvenile animal studies; age-appropriate formulation and toxicity of excipients; need for long-term safety studies to assess effects of therapy on growth and development.**

BPCA and PREA Programs

BPCA Written Request Process

- **Initial questions FDA asks before issuing a WR requesting pediatric studies:**
  - **Is there a public health benefit?**
  - **Is the risk/benefit appropriate?**

BPCA Written Request Process

- **Is there a public health benefit?**
  - **Serious life-threatening condition?**
  - **How frequently does disease/condition occur?**
  - **How often is this drug or others like it used in children?**
  - **Offer a meaningful therapeutic benefit?**
    - **Significant improvement in the treatment, diagnosis, or prevention of disease compared to already approved drugs?**

BPCA Written Request Process

- **Is the risk/benefit appropriate?**
  - **Risk: Is there adequate safety data to move into pediatrics?**
    - **Animal data, including juvenile animal data, if needed?**
    - **Adult data?**
  - **Benefit: meaningful therapeutic benefit over existing therapies.**
    - **Are there validated pediatric efficacy endpoints?**
  - **Ethical considerations: Subpart D (Code of Federal Regulations, 21CFR50.54, that gives additional protections for children involved in clinical trials).**

PREA Process

- **Trigger: NDA or BLA adult submission or supplements with new indication, active ingredient, dosage form, dosing regimen or route of administration.**
- **Questions FDA asks before requiring pediatric studies**
  - **Is the product ready for approval in adults? If "yes", pediatric studies will be deferred.**
  - **Are additional safety and efficacy data needed in adults before studying pediatric patients? If "yes", pediatric studies will be deferred.**

PREA Process

- **Questions FDA asks before requiring pediatric studies (continued)**
  - **Are necessary studies impossible or highly impractical? If "yes", pediatric studies will be waived.**
  - **Is there strong evidence that the product would be ineffective or unsafe? If "yes", pediatric studies will be waived.**
  - **Does the product represent a meaningful therapeutic benefit over existing therapies AND is it likely to be used in a substantial number of pediatric patients? If "no", pediatric studies will be waived.**
  - **Note that waivers may be full waivers (i.e. apply to entire pediatric age range: birth to 16 years) or partial (i.e. apply to an age subset of the pediatric population- e.g. neonates).**

PREA Process

- **Questions FDA asks before requiring pediatric studies (continued)**
  - **Has FDA granted orphan designation to the product and indication under development? If "yes", PREA does not apply.**
  - **Have reasonable attempts to produce a pediatric formulation necessary for that age group failed? If "yes", a partial waiver will be granted.**

Pediatric Product Development Under BPCA and PREA

- **BPCA**
  - **Public health benefit--- yes**
  - **Risk/benefit appropriate--- yes**
- **PREA**
  - **Full pediatric waiver--- no**
  - **Orphan designation granted--- no**

Then we ask …

- **What information do we need?**
- **In what age groups do we need the information?**
- **What studies are needed to obtain this information?**

BPCA and PREA Programs

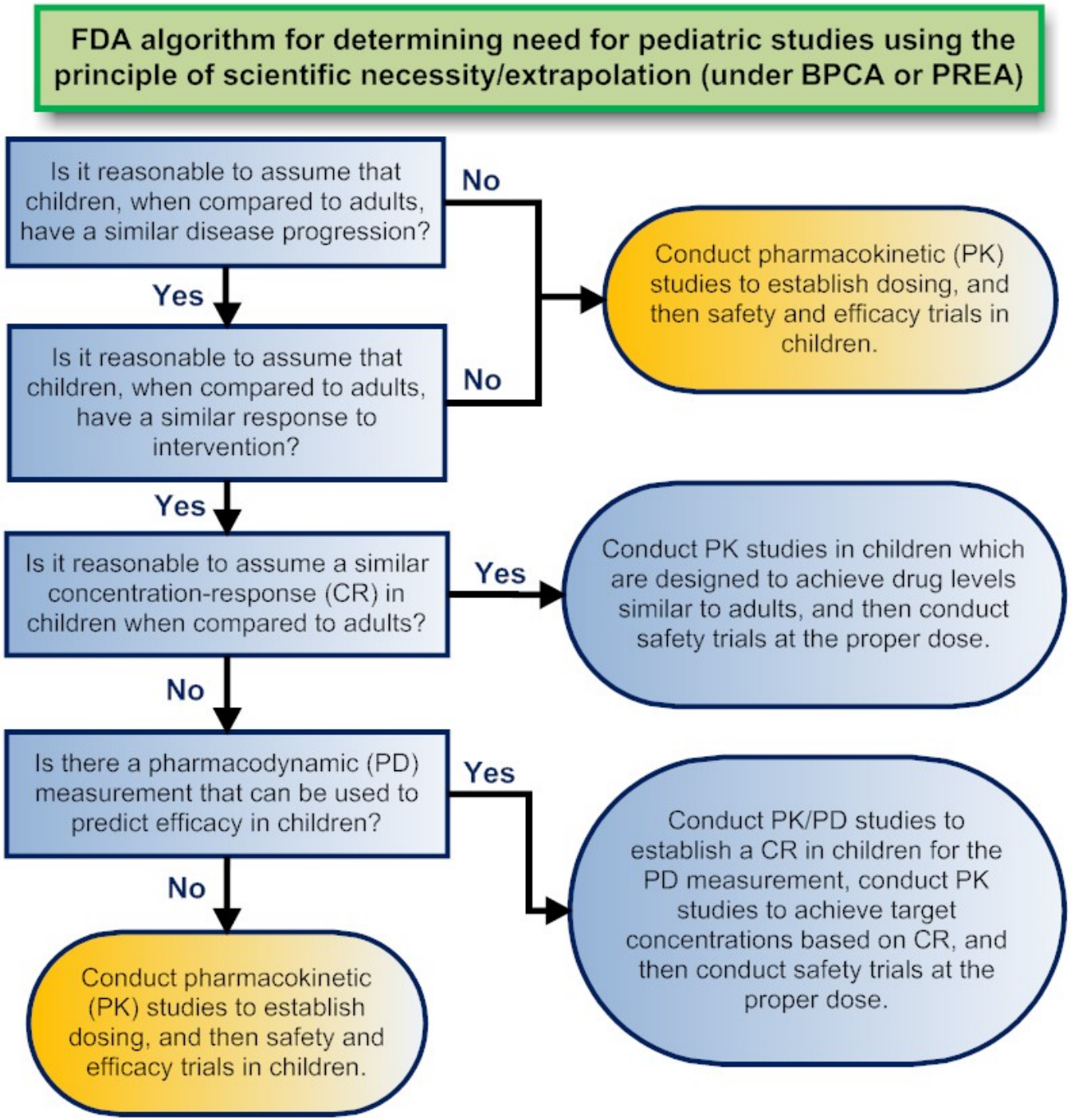
- **What information do we need?**
  - **BPCA**
    - **Driven by public health need. Consider all indications (in addition to if there is a PREA requirement) where there is potential public health benefit to study the active moiety.**
  - **PREA**
    - **Limited to drug under review and indication proposed in adults**
  - **BPCA and PREA**
    - **Information requested must be adequate to support dosing, safety and efficacy.**

BPCA and PREA Programs

- **In what age groups do we need the information?**
  - **BPCA and PREA**
    - **Address all pediatric age groups where there is potential public health benefit. Neonates: most understudied, greatest need.**
    - **Need for age-appropriate pediatric formulations**

BPCA Written Request Process

- **What studies are needed to obtain this information?**
  - **BPCA and PREA**
    - **Can we extrapolate efficacy from adults to pediatrics or from older pediatric patients to younger? If "yes", sponsor must provide data to support extrapolation. Extrapolation reduces the number of pediatric patients exposed to clinical trials. If extrapolation is not applicable, adequately powered and well-controlled pediatric studies are generally needed.**
    - **Study design must be adequate to support dosing, safety and efficacy.**


FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under BPCA or PREA)
Is it reasonable to assume that children, when compared to adults, have a similar disease progression?
No
Yes
Is it reasonable to assume that children, when compared to adults, have a similar response to intervention?
No
Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.
Yes
Is it reasonable to assume a similar concentration-response (CR) in children when compared to adults?
Yes
Conduct PK studies in children which are designed to achieve drug levels similar to adults, and then conduct safety trials at the proper dose.
No
Is there a pharmacodynamic (PD) measurement that can be used to predict efficacy in children?
Yes
Conduct PK/PD studies to establish a CR in children for the PD measurement, conduct PK studies to achieve target concentrations based on CR, and then conduct safety trials at the proper dose.
No
Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.

BPCA and PREA: Accomplishments

- **Pediatric legislation is meeting the goals of ICH E-11, which is to properly evaluate therapeutics intended for use in children. Almost 400 products have been studied in pediatric patients AND the information has been incorporated into labeling.**

Accomplishments: Pediatric Legislation (BPCA, PREA, Rule) 1998-Sept. 2010

- **Pediatric Labeling Changes N=398**
  - Expanded age 303
  - New or enhanced safety information 74
  - Safety & efficacy not established 72
  - Specific dosing change/adjustment 33
  - Pediatric formulation 27
  - Boxed Warning with pediatric info 18
  - New molecular entity 17
  - Extemporaneous formulation 10
  - PK differences (pediatrics vs. adults) 7

Orphan Program

Office of Orphan Products Development

The U.S. Orphan Drug Act Signed in 1983

- **Established the public policy that the Federal Government could/would assist in the development of products for the diagnosis, prevention or treatment of rare diseases or conditions.**

Definition of Orphan Product

- **A product intended to treat a rare disease or condition affecting fewer than 200,000 persons in the United States**

or

- **A product which will not be profitable within 7 years following approval by the U.S. Food & Drug Administration.**

OOPD and Pediatrics

- **OOPD supports the development of products in the pediatric population through**
  - **Orphan designations**
    - **OOPD conducts scientific and regulatory review of orphan product designation requests.**
  - **Grants**
    - **OOPD awards and administers grants to defray orphan product clinical study costs.**
  - **Humanitarian Use Device Program**
    - **OOPD conducts scientific and regulatory review of humanitarian use device designation requests.**

OOPD and Orphans

- **Incentives for sponsors to receive orphan drug designation includes 7-year marketing exclusivity to the first sponsor obtaining FDA approval of a designated orphan drug for a specific indication.**
- **To obtain orphan designation**
  - **Sponsor submits designation request to FDA/OOPD**
  - **OOPD Staff reviews requests**
  - **Criteria**
    - **Is population <200,000 in the U.S. (prevalence)?**
    - **Is there a valid scientific rationale for the use of the drug in the proposed indication/ disease/ condition?**

OOPD and Grants

- **Goal of Grants Program**
  - **Encourage clinical development of products, including drugs, biologics, medical devices, or medical foods, for use in rare diseases or conditions affecting < 200,000 individuals in the United States.**
- **Also, a practical program for advancing marketing approvals and relevant publications that impact on rare diseases.**
- **Supports academic and industry sponsored clinical trials research.**
  - **IND/IDE must be in effect at time of the grant application submission (IND must be active and include the protocol for which funding is requested.**
- **Domestic or foreign, public or private, for-profit or nonprofit entities.**
- **Submit grant application to OOPD.**

IDE= Investigational Device Exemption

OOPD and Pediatric Devices

- **OOPD manages the Humanitarian Use Device (HUD) Designation Program**
- **HUD designation is first step in obtaining a Humanitarian Device Exemption (HDE)**
- **Recent FDAAA legislation has lifted the HDE ban on making a profit for pediatric devices**

FDA and Pediatric Devices

- **Why HDE?**
  - **Premarket approval applications for new medical devices *ordinarily* must show that products are safe and effective.**
  - **For very rare diseases, FDA will approve such devices if manufacturers demonstrate the safety and probable benefit to patients.**

Lessons Learned from Pediatric Studies

Lessons Learned From Pediatric Studies

- **PK and, thus, dosing may differ between pediatrics and adults and even within pediatric age groups.**
  - **Benazipril: higher oral clearance in hypertensive children (6-12 years old) and adolescents compared to adults. Terminal elimination half-life in pediatric patients was one-third that observed in adults.**
  - **Gabapentin: higher oral clearance in pediatric patients 1 month to <5 years of age compared to older children with higher doses required in children <5 years of age.**
  - **Lamivudine: substantially reduced oral clearance in patients <3 months old and particularly in 1 week old neonates.**
  - **Methylphenidate: apparently 40% reduced oral clearance in children (6-12 years old) compared to adolescents.**

Lessons Learned From Pediatric Studies

- **Since PK and, thus, dosing may differ between pediatric and adult patients and even within pediatric age groups, it is important to conduct PK studies prior to conduct of clinical efficacy trials to determine an appropriate dose(s) to be given in the clinical trials.**

Lessons Learned From Pediatric Studies

- **Efficacy not established in pediatrics or data were insufficient to recommend pediatric use**
  - **Examples**
    - **Many antidepressants for treatment of major depressive disorder**
    - **Most triptans for treatment of acute migraine**
      - **Failed triptan trials informed design of almotriptan adolescent migraine study and efficacy was demonstrated for this product.**

Lessons Learned From Pediatric Studies

- **Safety profile different between pediatric and adult patients**
  - **Examples**
    - **Hostility/aggression: gabapentin, tolterodine LA and ADHD drugs**
    - **Apparent increase in pediatrics for CNS adverse events for many types of products.**
    - **Suppression of linear growth: fluoxetine and systemic corticosteroids.**

Lessons Learned From Pediatric Studies

- **Age-appropriate and validated endpoints are needed to permit assessment of efficacy.**
- **Age-appropriate formulations are needed to permit accurate and safe dosing.**
- **Ethical considerations are always paramount in pediatric trials.**

Lessons Learned From Pediatric Studies

- **There are still large knowledge gaps**
  - **Long-term safety and effects on growth, sexual development, cognition/ learning and behavior continue to be understudied.**
  - **Neonates remain mostly unstudied as to the safety and efficacy of the therapies being used to treat them.**

The Future: Neonates
Most Vulnerable but Greatest Need

Lessons Learned
Small populations require the world as a village for clinical trials

Lessons Learned
To Move Pediatric Therapeutics Forward, We Must Work Together

References
FDA Guidances for Industry

- Guidance for Industry (Draft): How to Comply with the Pediatric Research Equity Act.
- Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act.
- Pediatric Oncology Studies in Response to a Written Request
- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products.
- Content and Format of Pediatric Use Supplements.
- Nonclinical Safety Evaluation of Pediatric Drug Products.
- Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients.

References
Non-FDA Guidances

- **ICH- E11 Clinical Investigation of Medicinal Products in the Pediatric Population.**
- **American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations" (February 1995).**
- **European Pediatric Guidance, "Clinical Investigation of Medicinal Products in Children" (August 1997).**

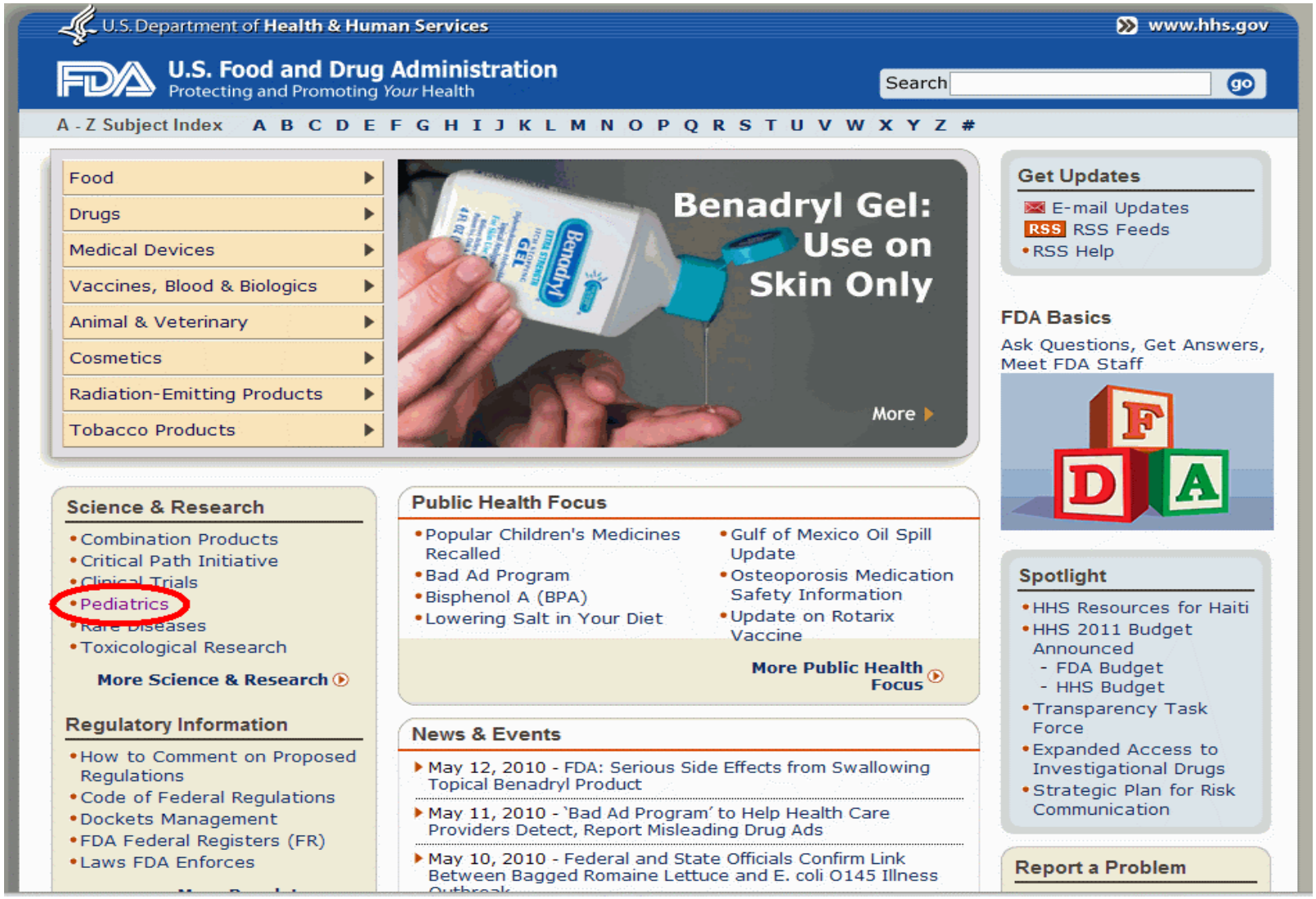
References
FDA Regulations and Related Laws

- **Pediatric Research Equity Act of 2003 [PDF] (Public Law No: 108-155)**
- **Guidance for Industry (Draft): How to Comply with the Pediatric Research Equity Act**
- **Best Pharmaceuticals for Children Act, January 4, 2002 (Public Law No. 107-109). [PDF]**
- **21 CFR 201.57 Specific Requirements on Content and Format of Labeling for Human Prescription Drugs.**
- **FDA Modernization Act: Section 111 (FDAMA).**

Useful Links

- **Link to FDA's website**
  - **http://www.fda.gov**
- **Link to FDA's OPT website**
  - **http://www.fda.gov/oc/opt/default.htm**
- **Link to FDA's Pediatric and Maternal Health website**
  - **http://inside.fda.gov/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/default.htm**
- **Link to FDA's Office of Orphan Products Development website**
  - http://www.fda.gov/orphan

FDA Homepage



FDA's OPT Homepage

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