



FDA Insight: Pediatric Drug Approval and Supplement Regulation

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October 12, 2018

Disclosure Statement



- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA



- Mrs. Winslow's Soothing Syrup claimed to help babies with teething pain
- The syrup was laced with morphine, a narcotic
- The label did not include morphine as an ingredient
- Many infants died as a result

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Pure Food and Drugs Act

- Passed by Congress in 1906
- Also known as the Wiley Act
- Labeling of drugs must clearly state all ingredients
- Created the U.S. FDA

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- Sulfanilamide is an antibiotic (drug used to treat infections) and saved many lives
- Only available in pill or powder
- Mixed with a sweetened chemical, diethylene glycol, to make it easier to give to children
- Elixir of Sulfanilamide introduced in September 1937
- Diethylene glycol is highly toxic
- Cause 107 deaths in 15 states



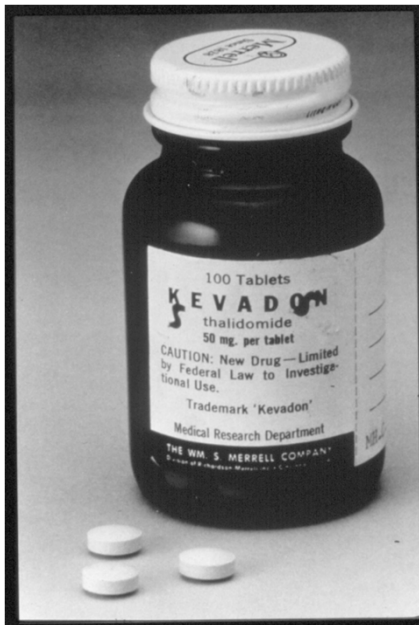
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Food, Drug, and Cosmetic Act

- Passed by Congress on June 25, 1938
- Signed into law by Franklin D. Roosevelt
- A manufacturer of a drug must prove to FDA that their drug is safe before it can be sold



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- Thalidomide, a new sleeping pill, was marketed in Canada and Europe, but not the US
- Found to have caused birth defects in thousands of babies
- Dr. Frances Kelsey, FDA medical officer, helped keep the drug off the U.S. market
- Aroused public support for stronger drug regulation

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Kefauver-Harris Drug Amendments



- Kefauver-Harris Drug Amendments passed in 1962
- Signed into law by President John F. Kennedy
- A manufacturer of a drug must prove to FDA that their drug **is effective** before it can be sold



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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)]

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Adequate and well-controlled study



- Study should “distinguish the effect of a drug from other influences, such as spontaneous change... placebo effect, or biased observation”
- Must incorporate generally accepted scientific principles for clinical trials
- Well-controlled studies of adequate design must show effectiveness, ordinarily a statistically significant effect on a clinically meaningful endpoint, usually replicated, as a basis for approval.

Major Elements of an Adequate and Well-Controlled Study



- Clear statement of purpose
- Permits a valid comparison with a control
 - Concurrent: placebo, no-treatment, active, dose-comparison
 - Historical
- Method of selection of subjects
- Method of assigning patients to treatment/control groups
- Adequate measures to minimize bias
- Methods of assessment of response are well-defined and reliable
- Analysis of the results is adequate to assess the effects of the drugs

21 CFR 314.26: Adequate and well-controlled studies

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FDA Oversight

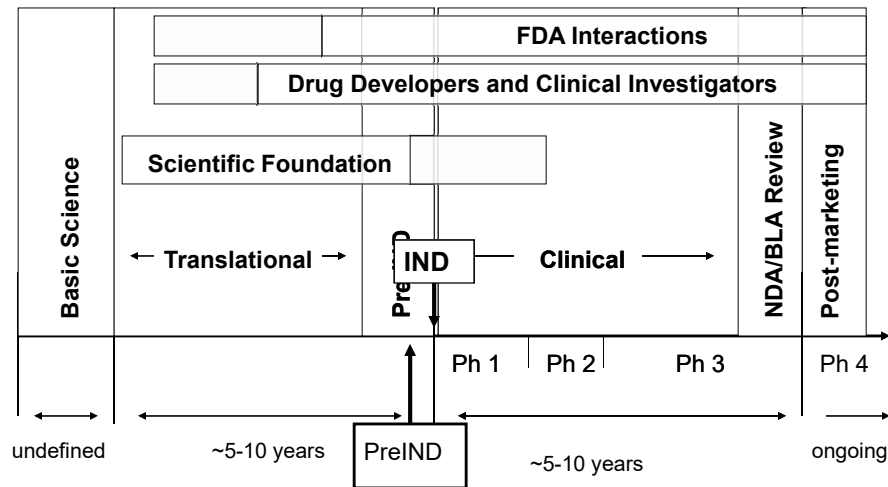


- FDA's primary objectives in overseeing all phases of clinical investigations are:
 - To assure the safety of subjects
 - To assure that quality of scientific evaluation of drugs is adequate to permit an evaluation of the drug's safety and effectiveness
 - To assure that for later phase investigations, the scientific quality of the clinical investigation is adequate to provide data capable of meeting statutory standards for marketing approval

21 CFR 312.22: General principles of the IND submission

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Drug Development Overview



Pediatric Drug Development General Principles



- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated
- Incorporation of regulatory standards into pediatric clinical research strengthens the quality of the research

From FDA guidance to industry titled *E11(R1)- Clinical Investigation of Medicinal Products in the Pediatric Population*, December 2017

Pediatric Drug Development Laws



- **Best Pharmaceuticals for Children Act (BPCA)**
 - Section 505A of the Federal Food, Drug, and Cosmetic Act
 - Provides a financial incentive to companies to voluntarily conduct pediatric studies
 - 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

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PREA vs. BPCA



- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • PREA • Drugs and biologics • Required studies • Studies may only be required for approved indications • Products with orphan designation are exempt from requirements except molecular targets relevant to pediatric cancers • Pediatric studies must be labeled | <ul style="list-style-type: none"> • 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 |
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Special Considerations for Pediatric Product Development

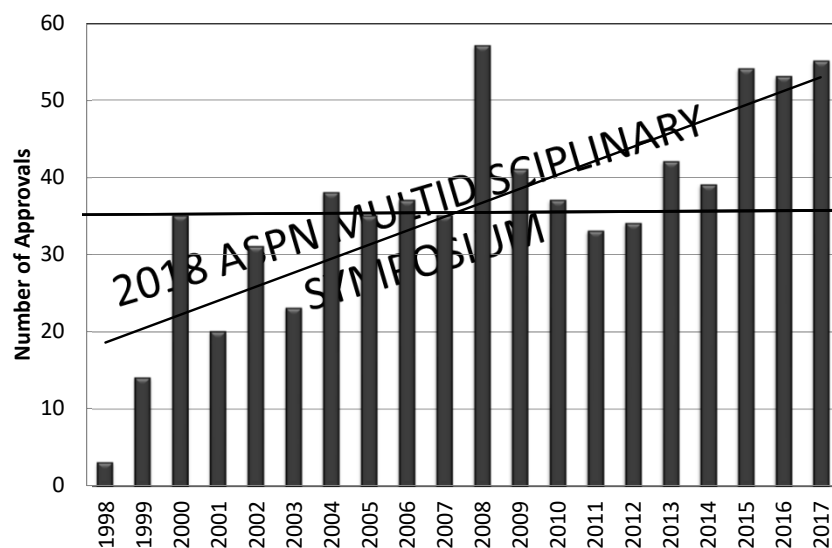


- Ethical considerations
 - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
 - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low”
 - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
- Feasibility considerations
 - The prevalence and/or incidence of a condition is generally much lower compared to adult populations

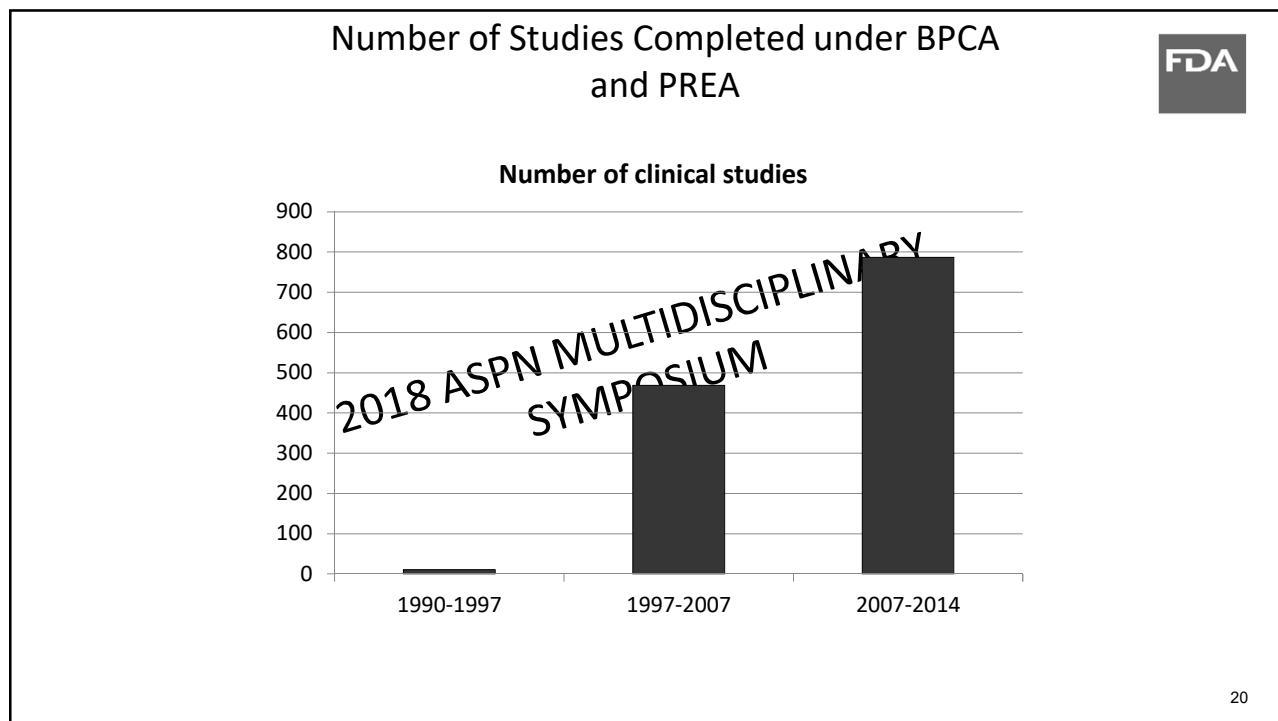
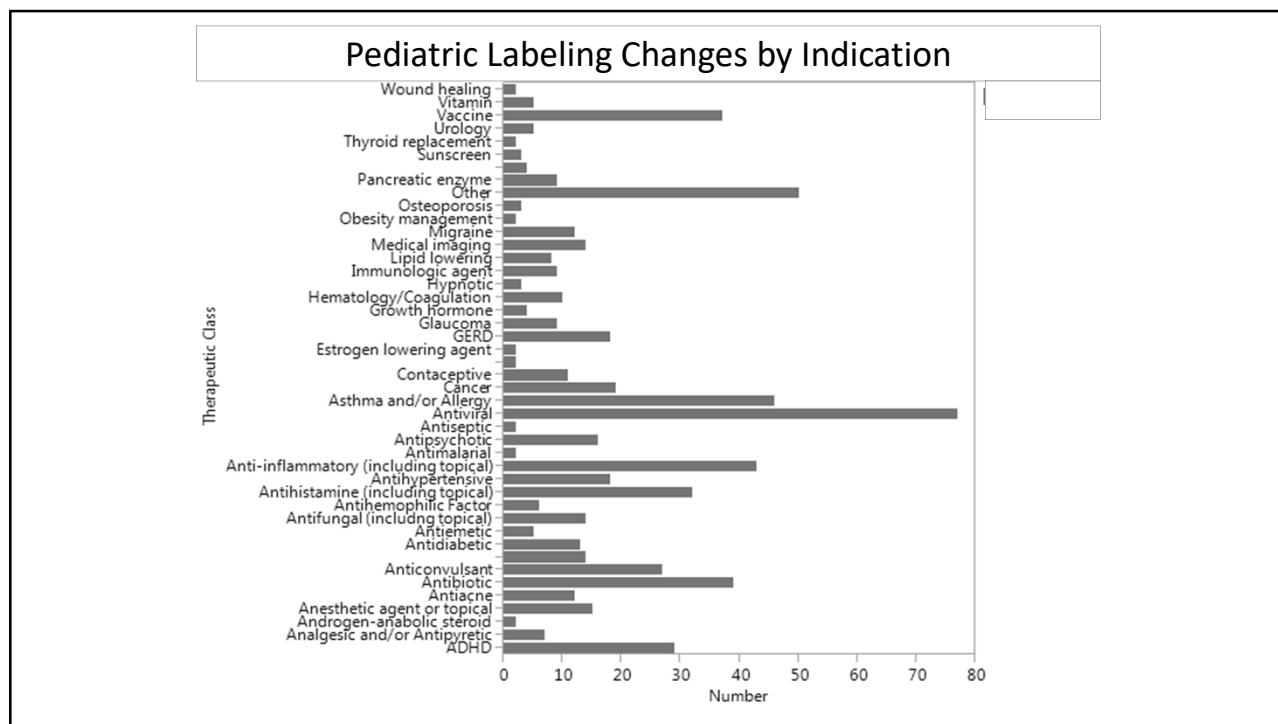
21 CFR Part 50 Subpart D--Additional Safeguards for Children in Clinical Investigations

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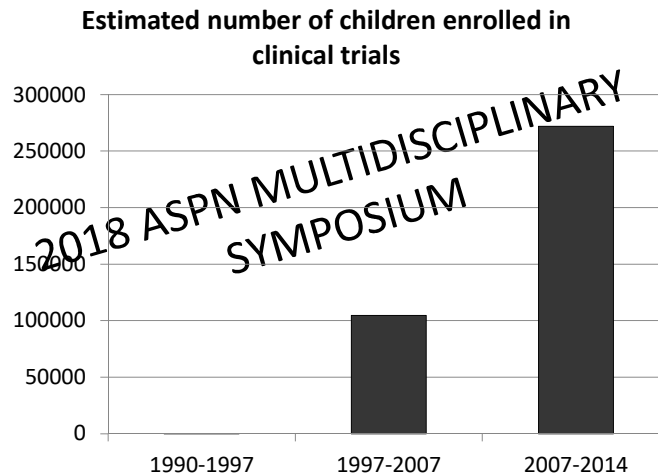
Pediatric Labeling Changes 1998-2017



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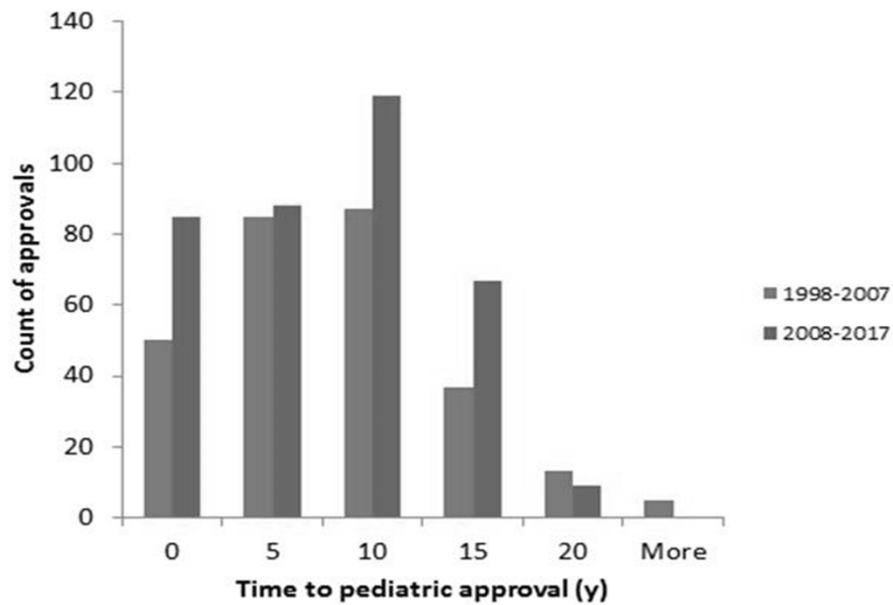


Number of children enrolled in trials under BPCA and PREA



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Time to pediatric approval



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Pediatric Review Committee (PeRC)

- Committee membership
 - Including staff from across FDA
 - Expertise in Pediatrics, Neonatology, Pediatric Ethics, Biopharmacology, Statistics, Chemistry, Law required
 - Appropriate expertise pertaining to the product under review
- Required to review items under PREA
 - All Pediatric Plans, Assessments, Deferrals, and Waivers
- Required to review items under BPCA
 - All Written Requests and Amended Written Requests prior to being issued

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Pediatric Therapeutics Development in the 21st Century

- Increased understanding of overall pediatric drug development
- Increased scientific knowledge
- Increased experience in the use of pediatric extrapolation in drug development
- Time between adult approval and incorporation of pediatric information in labeling is substantial
- Pediatric-specific diseases, including pediatric kidney diseases

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Advancing Pediatric Therapeutics Development



- Pediatric Extrapolation and Innovative Clinical Trial Designs
- Real World Evidence
- Pediatric Oncology and Molecularly Targeted Therapies
- Clinical Trial Networks
- Global Alignment and Collaboration

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Dietary Supplements



- FDA regulates both finished dietary supplement products and dietary ingredients
- Dietary Supplement Health and Education Act of 1994 (DSHEA)
- Manufacturers and distributors are responsible for evaluating the safety and labeling of their products before marketing
- FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market
- **FDA is not authorized to review dietary supplement products for safety and effectiveness before they are marketed**

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Dietary Supplements

- Dietary supplements include vitamins, minerals, herbs, amino acids, and enzymes
- Unlike drugs, **supplements are not permitted to be marketed for the purpose of treating, diagnosing, preventing, or curing diseases**
- FDA can take dietary supplements off the market if they are found to be unsafe or if the claims on the products are false and misleading

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Dietary Supplements

- When searching for supplements on the internet, use noncommercial sites (e.g. NIH, FDA, USDA) rather than depending on information from sellers
- If claims sound too good to be true, they probably are
 - Be mindful of product claims such as “works better than [a prescription drug],” “totally safe,” or has “no side effects”
- **Be aware that the term *natural* doesn't always mean *safe***
- Ask your healthcare provider if the supplement you're considering would be safe and beneficial for you
- FDA website:
<https://www.fda.gov/Food/DietarySupplements/UsingDietarySupplements/ucm109760.htm>

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Summary

- Children are protected through research, not from it
 - Drug development overall and in pediatric kidney diseases and hypertension has improved over the last 20 years
- Dietary supplements are regulated differently than prescription and OTC drugs
- There is still a need to increase the availability of approved products to treat pediatric kidney diseases
- Pediatric medical community must insist on incorporation of evidence based treatment sufficient to support pediatric product labeling
- Seek commitment of the entire pediatric community to address this issue
 - Academic researchers and community practitioners
 - Patients and patient organizations
 - Professional Societies
 - Allied health care providers

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Thank You!