U.S. FOOD & DRUG ADMINISTRATION

# The Landscape of Neonatal Anti-Infective Drug Development

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Facilitating Anti-Infective Drug Development for Neonates and Young Infants
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# Outline

- Regulatory Overview
- Anti-infective drugs with a PREA requirement at the time of initial approval
- Anti-infective drugs commonly used in the NICU
- Summary and thoughts for today

**Disclaimer**: The views expressed are those of the presenter and do not necessarily represent the views of the U.S. Food and Drug Administration.

**Disclosures:** None

# General Principles

- Pediatric patients should have access to drug products that have undergone appropriate evaluation for safety and efficacy.
- Drug development programs should include pediatric studies when pediatric use is anticipated.

# Historical Timeline

- 1990's: Efforts through rule-making (regulation) to encourage/mandate the study of drugs in children. The FDA issued a Rule allowing labeling of drugs for pediatric use based on extrapolation of efficacy in adults in certain circumstances
- 1997: Food and Drug Administration Modernization Act contained economic incentives for pediatric studies
- 2002: Best Pharmaceuticals for Children Act provided mechanisms for studying on and off-patent drugs in children. Established NIH program for pediatric drug development
- 2003: Pediatric Research Equity Act requiring pediatric assessments in certain circumstances. Retroactive for applications submitted on or after April 1, 1999

# Regulatory Overview

- Federal Food, Drug, and Cosmetic Act established requirement for demonstration of "substantial evidence" of effectiveness through adequate and well-controlled investigations (1962 amendment)
- Pediatric Research  Equity Act (2003): for new drugs*, assessments of safety and effectiveness are required for all relevant pediatric subpopulations
  - Adequate and well-controlled studies
  - Extrapolation
    - new active ingredient, new indication, new dosage form, new dosing regimen, new route of administration
- Dosing cannot be extrapolated.
- Safety cannot be extrapolated.

# PREA and BPCA

- **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
- **Best Pharmaceuticals for Children Act (BPCA)**
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - "On-patent drugs": Provides a financial incentive to companies to voluntarily conduct pediatric studies (exclusivity extending beyond the patent expiration)
  - **"Off-patent drugs": 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)**

# PREA and BPCA

**PREA**

- Drugs and biologics
- Required studies usually included in Approval Letter
- Studies may only be required for approved indication(s)
- Products with orphan designation are exempt from requirements
- Pediatric studies must be labeled

**BPCA**

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

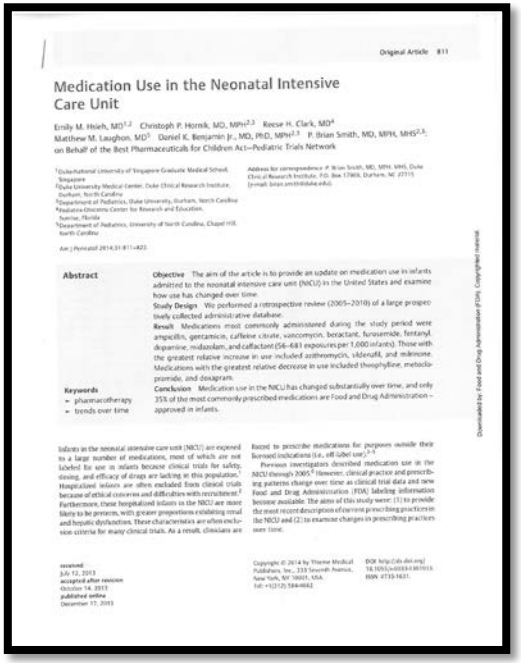
# Antibacterials: PREA Requirement for Initial Approved Indication(s)

| Drug | Approval Year | Pediatric Indication/Dosing | Neonatal Indication /Dosing |
|---|---|---|---|
| Linezolid | 2000 | From birth | Variable [CSF] |
| Ertapenem | 2001 | 3 mo. and older | No data. [CSF] concern |
| Daptomycin | 2003 | Avoid use < 12 mo, neuromuscular effects dogs | |
| Telithromycin | 2004 | Peds trials halted- hepatic adverse rxns adults | |
| Tigecycline | 2005 | Peds trials not conducted – mortality risk adults | |
| Doripenem | 2007 | S/E in pediatric patients not established. | |
| Telavancin | 2009 | S/E in pediatric patients not established. | |
| Ceftaroline | 2010 | 2 mo. and older | |
| Fidaxomicin | 2011 | S/E in pediatric patients not established. | |
| Dalbavancin, Tedizolid, Oritavancin, Ceftolozane/Tazobactam, Avibactam/Ceftazidime | 2014-15 | S/E in pediatric patients not established. | |

# Antifungals: PREA Requirement for Initial Approved Indication(s)

| Drug | Approval Year | Pediatric Indication/Dosing | Neonatal Indication /Dosing |
|---|---|---|---|
| Caspofungin | 2001 | > 3 mo of age | Not studied < 3 mo [CNS] not known |
| Voriconazole | 2002 | > 12 yrs of age | S/E not established. |
| Micafungin | 2005 | > 4 mo of age | S/E not established. |
| Anidulafungin | 2006 | S/E not established < 16 yrs of age. | S/E not established. |
| Posaconazole | 2006 (oral susp)<br>2013 (tab)<br>2014 (iv) | > 13 yrs of age delayed release tabs and oral suspension | S/E not established. |

# Anti-Infectives Most Commonly Used in Neonates



Medication Use in the Neonatal Intensive Care Unit

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Abstract

Objective The aim of the article is to provide an update on medication use in infants admitted to the neonatal intensive care unit (NICU) in the United States and examine how use has changed over time.

Study Design We performed a retrospective review (2005–2010) of a large prospectively collected administrative database.

Result Medications most commonly administered during the study period were ampicillin, gentamicin, caffeine citrate, vancomycin, beractant, furosemide, fentanyl, dopamine, midazolam, and caffeine (56–681 exposures per 1,000 infants). Those with the greatest relative increase in use included azithromycin, sildenafil, and milrinone. Medications with the greatest relative decrease in use included theophylline, metoclopramide, and dexamethasone.

Conclusion Medication use in the NICU has changed substantially over time, and only 35% of the most commonly prescribed medications are Food and Drug Administration–approved in infants.

Keywords
- pharmacotherapy
- trends over time

Pediatrix Medical Group data base:
305 NICUs, 2005-10
Follow up to Clark RH et al.
Pediatrics 2006; 117: 1979-87

Greatest Increase 2005 -10:
Azithromycin, Linezolid, Cefoxitin, Meropenem, Pip/Tazo, Cefepime, Fluconazole, Cefazolin

| Injectable Anti-Infectives included in the Top 50 | Neonatal Label Info |
|---|---|
| Ampicillin (ELBW) | Dosing |
| Gentamicin (ELBW) | Dosing |
| Vancomycin (ELBW) | Dosing |
| Cefotaxime (ELBW) | Dosing |
| Tobramycin | Dosing |
| Fluconazole (ELBW) | Dosing |
| Clindamycin | Dosing |
| Acyclovir | Dose/Trial |
| Ceftazidime | Dosing |
| Oxacillin/ Nafcillin | Dosing |
| Ampho B Products | >1 mo |
| Amikacin | - |

# 2015 BPCA Priority List of Needs in Pediatric Therapeutics

**Criteria for NICHD Updates to the Priority List:**

- Relevance to BPCA mission and goals
- No disqualifying ethical concerns
- Level of evidence available and current gaps
- Consideration of the different populations that may benefit from the research
- Feasibility and availability of the resources needed to conduct the study

**Neonatal Research Priorities: Infections in Neonates**

| Drug | Gap in Knowledge |
|---|---|
| Metronidazole | PK and efficacy in abdominal infections |
| Ampicillin | PK and safety in VLBW |
| Fluconazole | Dosing and safety in VLBW |
| Meropenem | PK, safety in neonates with NEC |

More info: https://bpca.nichd.nih.gov/clinical/Pages/index.aspx

# Pediatric Trials Network
# Ongoing and Completed Studies

| Study Name | Population | Condition | Status |
|---|---|---|---|
| Antibiotic Safety-SCAMP | Premature Infants | Intra-abdominal infections | Enrolling |
| Anti-Staph trio | Premature Infants | Staphylococcal infections | Analysis |
| POPS | Children including neonates | Various Drugs | Enrolling |
| Acyclovir retrospective | Infants | Herpes simplex virus | Closed |
| Ampicillin | Infants | Sepsis/meningitis | Completed |
| Fluconazole safety | Infants | Candidemia | Completed |
| Meropenem | Infants | Intra-abdominal infections | Completed |
| Metronidazole | Premature infants | Serious infections | Completed |

# Neonatal Labeling for Meropenem

- Pediatric studies done in accordance with the Public Health Service act
- PK and safety study in infants < than 91 days of age with complicated intra-abdominal infections (cIAI)
- The study was not statistically powered to establish efficacy as  extrapolation of efficacy to pediatric populations from adult populations was acceptable
- Labeling updated, including dosing recommendations for the use of meropenem in neonates and infants < than 91 days of age with cIAI

(http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050706s035lbl.pdf)
https://www.federalregister.gov/articles/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act

# Summary and Thoughts for Today

- Neonatal labeling for drugs approved since the enactment of PREA is limited, likely due to the clinical trial challenges we are here to discuss. This is particularly concerning as we seek to address unmet need such as infections caused by CRE.
- The anti-infectives administered most frequently to neonates are “off-patent”. Neonatal studies supported through the NIH BPCA program have played an important role obtaining information for those drugs used most frequently in neonates. What are the challenges, successes, and lessons learned?
- There are unanswered questions that impact progress – what are the priorities for a regulatory science research agenda for neonatal anti-infective drug development?


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