Quantifying BPCA and PREA Submissions – Pediatric Labeling for Antibacterial and Antifungal Drugs

CTTI Expert Workshop April 5, 2016

Improving Pediatric Trials in Antibacterial Drug Development

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Outline

- The goal – pediatric labeling
- Timeline refresher
- Antibacterial drugs with a PREA requirement related to the initial approved indication(s)
- Examples of mechanisms for pediatric labeling for antibacterial drugs
- Antifungal drugs with a PREA requirement related to the initial approved indication(s)

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

The Goal - Pediatric Labeling

- For prescription drugs, the labeling must contain a summary of the essential information needed for the safe and effective use of the drug.
- When data support the use of a drug in a pediatric population for a particular indication, pediatric use information must be placed in relevant sections of labeling.
- When the the evidence is insufficient to support a pediatric indication, this should be communicated in labeling.
- Other information that may need to be included: inactive ingredients that present a safety risk to children, juvenile animal data

Important Sections of the Prescribing Information

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
- ADVERSE REACTIONS
- USE IN SPECIFIC POPULATIONS, *Pediatric Use:*
- CLINICAL PHARMACOLOGY
- CLINICAL STUDIES
- PATIENT COUNSELING INFORMATION

"The safety and effectiveness of DRUG for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from…"

Timeline

- 1994: The FDA issued a Pediatric Rule allowing labeling of drugs for pediatric use based on extrapolation of efficacy in adults in certain circumstances.
- 1997: Congress enacted the Food and Drug Administration Modernization Act that contained economic incentives for pediatric studies.
- 2002: Incentive provisions reauthorized as the Best Pharmaceuticals for Children Act and provided mechanisms for studying on and off-patent drugs in children. Established NIH program for pediatric drug development.
- 2003: Congress enacted the Pediatric Research Equity Act requiring pediatric assessments in certain circumstances. Retroactive for applications submitted on or after April 1, 1999.

A Recent Example of Required Studies Under PREA

1. Conduct an open-label, dose-finding, pharmacokinetics, safety and tolerability study of DRUG in pediatric subjects less than 18 years of age with suspected or confirmed bacterial infections.
2. Conduct a multicenter, evaluator-blind, randomized study to evaluate the safety and tolerability of DRUG versus vancomycin for the treatment of pediatric subjects less than 18 years of age with acute bacterial skin and skin structure infections.

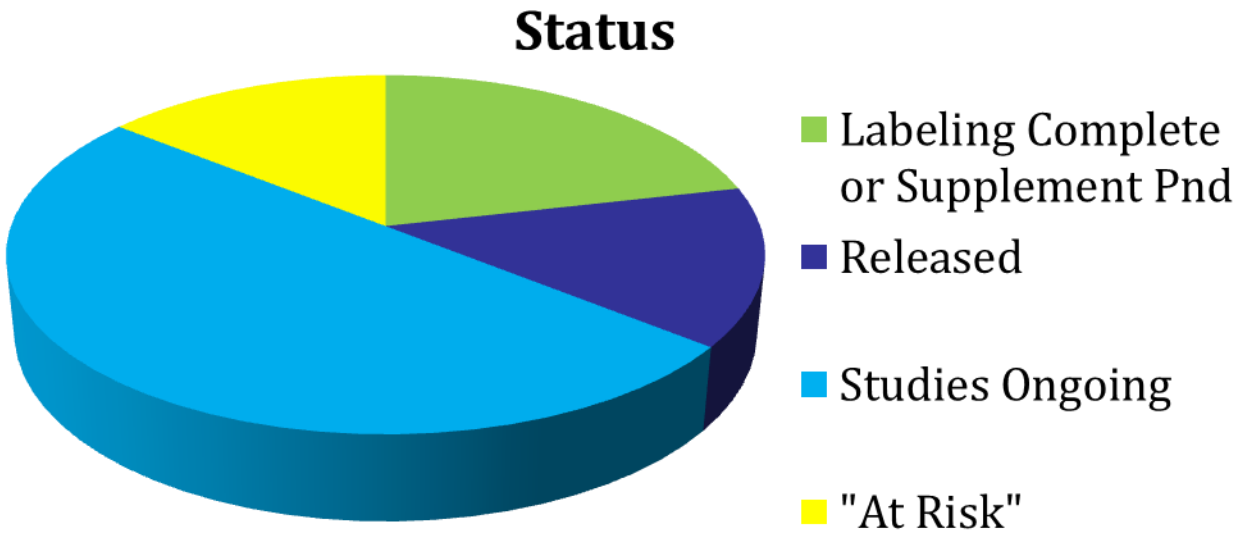
Extrapolation of efficacy in children based on adult evidence of efficacy for anti-infectives is common for some or all pediatric age groups as the disease process and the benefits of the drug are expected to be the same.

Antibacterial Drugs – PREA Requirement 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	S/E in pediatric patients not established.	
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.	

Antibacterial Drugs – PREA Requirement Initial Approved Indication(s)

- All drugs listed their PREA studies in Clinical Trials.gov



- For those drugs with labeling complete or supplement submitted, time from approval in adults to submission of a pediatric labeling supplement has ranged from 2-5 years. The upper range will increase as ongoing studies complete.
- A number of the drugs with studies ongoing have been granted deferral extensions citing slow enrollment.

Antibacterial Drugs – Examples of Mechanisms for Peds Labeling

Drug	Approval / Peds Labeling	Pediatric Indication/Dosing	Neonatal Indication /Dosing
Changes such as a new Indication or Dosage Form may "trigger" PREA.			
Azithromycin Oral Suspension (SR)	1991/ 2008	Children > 6 mo	S/E < 6 mo not established
Voluntary			
Piperacillin/ Tazobactam	1993/ 2006	Children with Appy/ Peritonitis > 2 mo	S/E not established
Cefepime	1996/ 1999	Children > 2 mo	S/E not established
Under BPCA, NICHD conducts studies for a high priority drug, usually off-patent.			
Meropenem	1996/ 2014	Children > 3 mo*	Children < 3 mo based on gestational age

* Conducted under PREA requirement due to a new indication

Antifungal Drugs – PREA Requirement 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) 2013 (tab) 2014 (iv)	> 13 yrs of age delayed release tabs and oral suspension	S/E not established.

Antifungal Drugs – Pediatric Labeling

- For those drugs with labeling complete or supplement submitted, time from approval in adults to submission of a pediatric labeling supplement has ranged from 7-12 ½ years.
- For those drugs with pediatric labeling, there is no neonatal Indication / Dosing information.
- Sponsors have submitted waiver or deferral extension requests, citing slow enrollment challenges. Recruitment of pre-adolescent children seems particularly difficult.
- We were able to find a Clinical Trials.gov listing for the PREA studies for two of the five antifungals.

Summary

- The time lag between approval of an antibacterial or antifungal drug in adults and approval in children is very long for many drugs and needs to be addressed.
- Extrapolation of efficacy in children based on adult evidence of efficacy is common for anti-infectives. Completion of PK and safety trials in children to facilitate pediatric labeling is challenging with slow enrollment commonly cited by sponsors.
- Scientific questions can arise pre or post-marketing that can impact pediatric trial initiation.
- When pediatric use information becomes available in labeling, it rarely includes information for neonates.

- **The Agency appreciates your willingness to share your time and expertise today as we seek to identify ways to increase the quality and efficiency of these important trials.**