Current FDA Perspective & Future of JAS Testing to Support Pediatric Development Programs

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Disclaimer: Opinions expressed do not necessarily reflect those of the FDA or its policy

Outline

- Introduction-How did we get here?
  - Regulatory background
  - Pediatric Study Plan (PSP) review
- What have we learned?
  - Considerations for Juvenile Animal Studies (JAS)
- Where are we going?
  - International Harmonization-ICHS11 EWG

Pediatric Data Gaps

Historically, drugs given to children w/o the same level of safety/efficacy obtained in adults

In 2001 <30% drugs had pediatric label info

By 2009 46% of US drugs were labeled for pediatric use

[*JAMA 5/19/12 307(19) Sachs et al*]

90% NICU drugs used off label
NICU patients have highest ADE rates

[N Engl J Med 367:1279-81 (2012)]

Why?

- Difficulties in conducting pediatric trials
  - Ethical concerns: adults can consent
  - Limited disease populations
  - Acceptable endpoints & validated pediatric assessment tools
- Children as “little adults”
  - False belief that dosing could be based on weight alone Limited marketing potential compared to adult indications
  - Age appropriate formulations
- Growth & Developmental Issues
  - Organ development may affect drug PK, PD
  - Drug may affect organ development-Safety
- Lack of infrastructure in all arenas
  - Solutions
    - Incentive programs- 6 month market exclusivity
    - Implementation of pediatric regulations/legislation

US Pediatric Drug Legislation

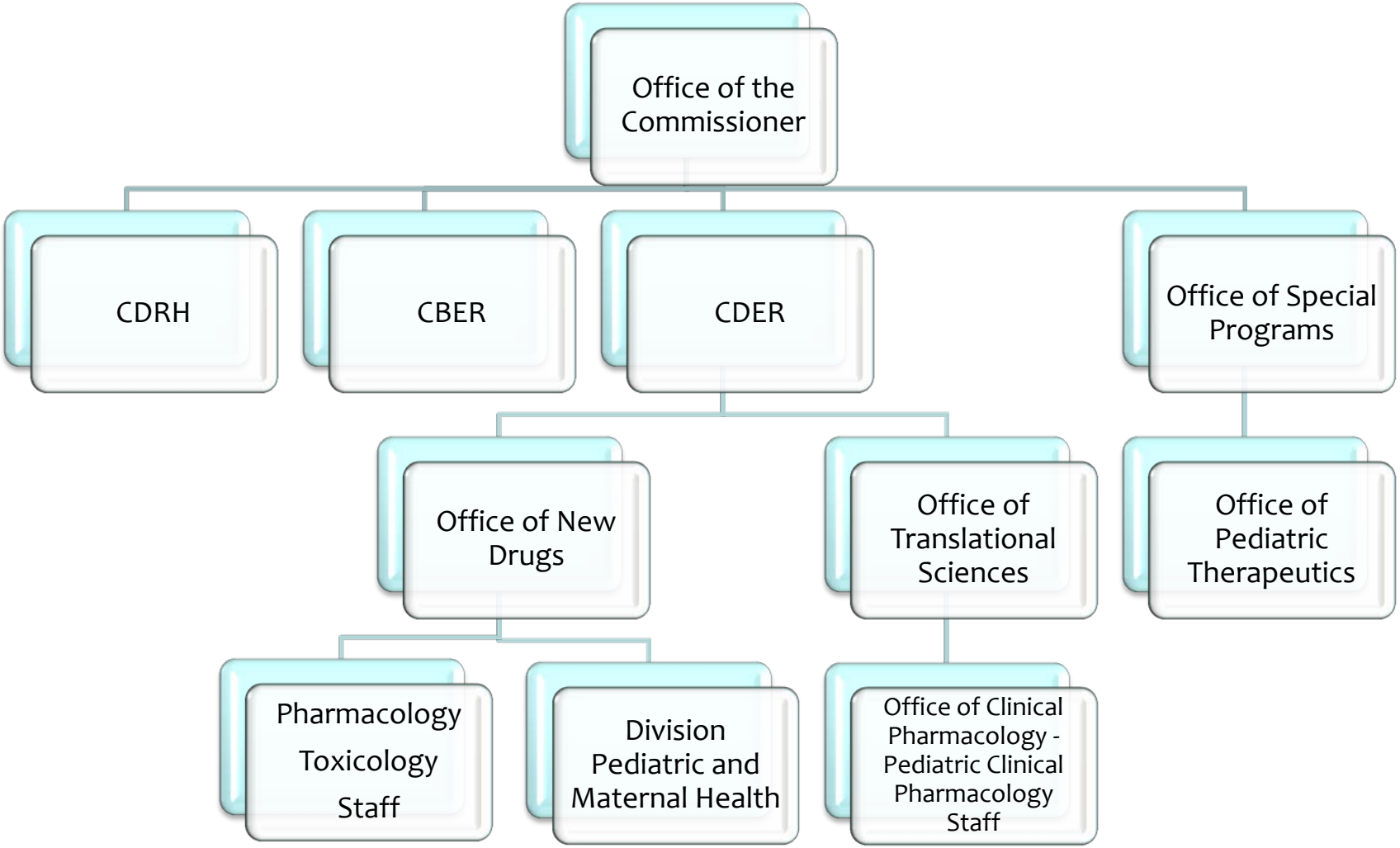
- 1998 Pediatric Rule-
  - Required new & marketed drugs/biologics to be evaluated for safety/efficacy in children if product:
    - Used in substantial number of pediatric patients
    - Provides meaningful therapeutic benefit over existing treatment
    - Not enforceable 2002 US District Court ruling
- 2002 Best Pharmaceuticals Act for Children (BPCA)
  - Pediatric exclusivity reauthorization (on-patent)
  - Referral to study off-patent drugs to NIH
- 2003 Pediatric Research Equity Act (PREA)
  - Replaced the Pediatric Rule
  - Retroactive for all applications from April 1999
  - Est. Pediatric Advisory Committee
- 2007 FDAAA
  - Reauthorization of pediatric initiatives BPCA & PREA
  - Established the Pediatric Review Committee (PeRC)
- 2010 – Biologics Price Competition & Innovation Act (BPCI)
  - Authorized by Patient Protection & Affordable Care Act (PPACA aka “Obamacare”)
  - Biologics now eligible for a written request
- 2012 FDASIA- FDA Safety & Innovations Act

Changes under FDASIA

- Pediatric Study Plans – (PSPs) Sponsors required to submit plans at End of Phase 2

- Must include: Outline of the pediatric study or studies that the applicant plans to conduct *(including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach)*
  - Any request for a deferral, partial waiver or waiver, along with supporting information
  - Includes complete/planned nonclinical data
    - ✓ It is important to provide your rationale for the study in the context of the pediatric trials that you are planning to support and the use of the drug in the pediatric population
- Template is available at FDA website: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf

Pediatrics at FDA



Design Considerations of JAS

- **Important to conduct a well designed, informative study with appropriate endpoints and not just conduct a study**
- Use of available data from adult animals and humans to identif potential targets
  - Potential differences in pharmacological and toxicological profiles between mature & immature systems
  - ADME & dose range finding study is important
- Selection of an appropriate animal model
  - Animals should be treated throughout the stages of development that are comparable to the timing of exposure in the intended pediatric population
  - Special attention to systems that undergo developmental changes during treatment period
  - Attempt to distinguish between acute and permanent effects of the drug by including a recovery group
  - Usually one relevant species, preferably rodent. A non-rodent can be scientifically justified

What have we learned?

Consideration of and inclusion of JAS in pediatric development will increase with the incorporation of pediatric study plans earlier in drug development

- The need for JAS in peds development is based on what you know and what you need to know
  - Prior clinical data in adults or older pediatric age groups
  - What toxicology has been done
  - Known potential hazards

It is important to consult with the Division early on regarding these nonclinical studies in the context of the clinical program

JAS can provide:

Safety assessment

Aid in characterizing the risks

Detect unique toxicity, increased sensitivity

Further analysis of the programs will give insight on when and where these studies have made impact and when and where these studies should be considered

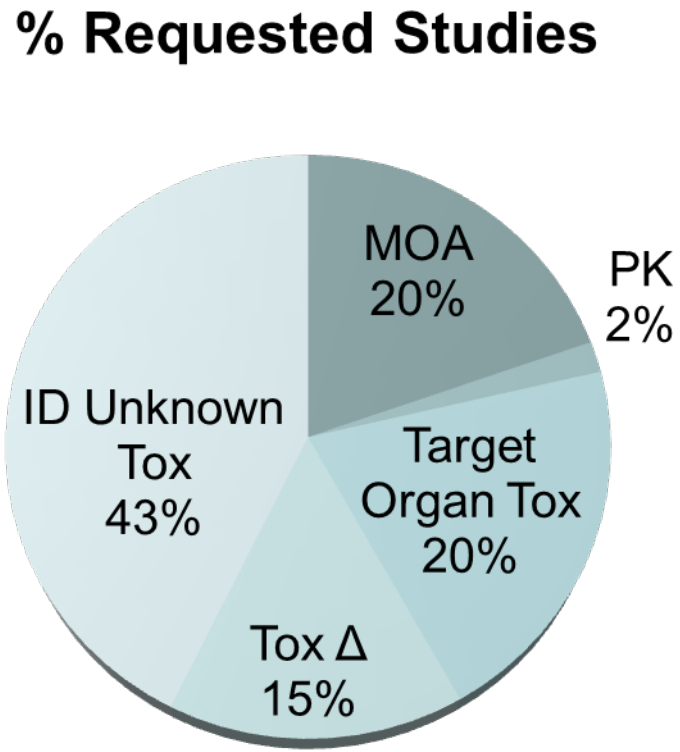
FDA/CDER Data Evaluation 2015

- Prior CDER review: Tassinari et. al. Birth Defects Research (Part B) 92:261-265 (2011)
- FDA/CDER Database for correspondence for all applications with JAS (n=500) 2009-2014
  - Preliminary results from 14 CDER OND Divisions (NDA/BLA/IND)
  - Whether study was recommended by Agency or submitted by the sponsor voluntarily
  - Number of studies and species
  - Outcome of the study data

Rationale for JAS Requests

41% of requested studieswere submitted by 2014

The majority of JAS (55%) submitted with the NDA/BLA



Species Selection

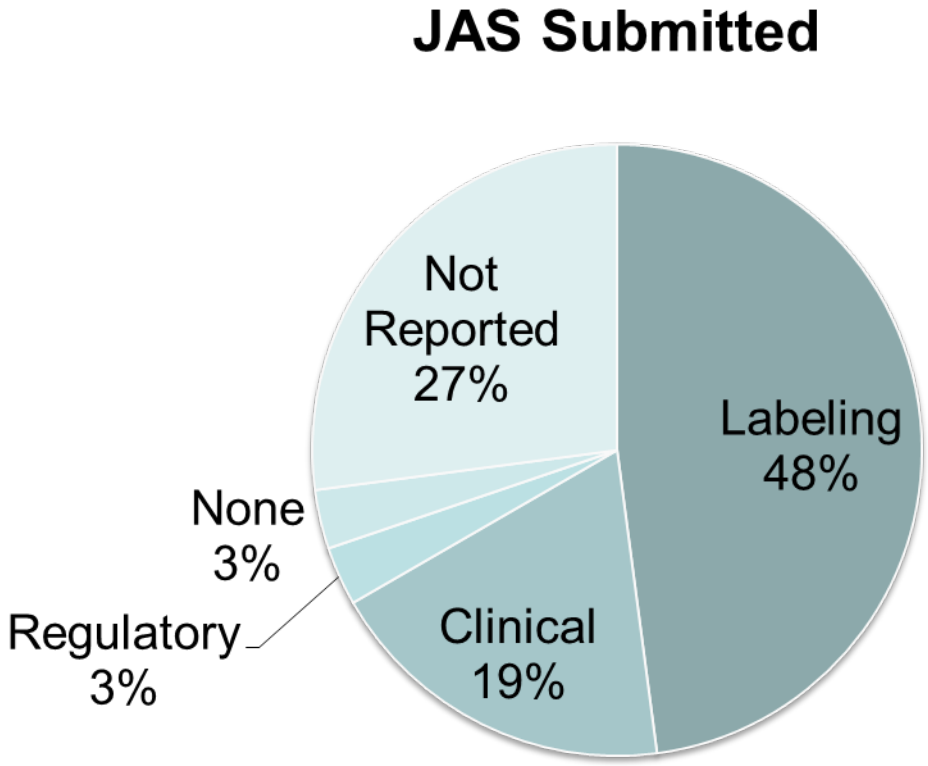
JAS submitted to Agency:

74% Rat> 17% Dog> 5% Monkey> 2% Mouse

29% JAS with > 1 species

- Typically (20%) rat+dog or monkey
- Supported a neurologic or gastroenterology indication (inborn error-peds only indication)

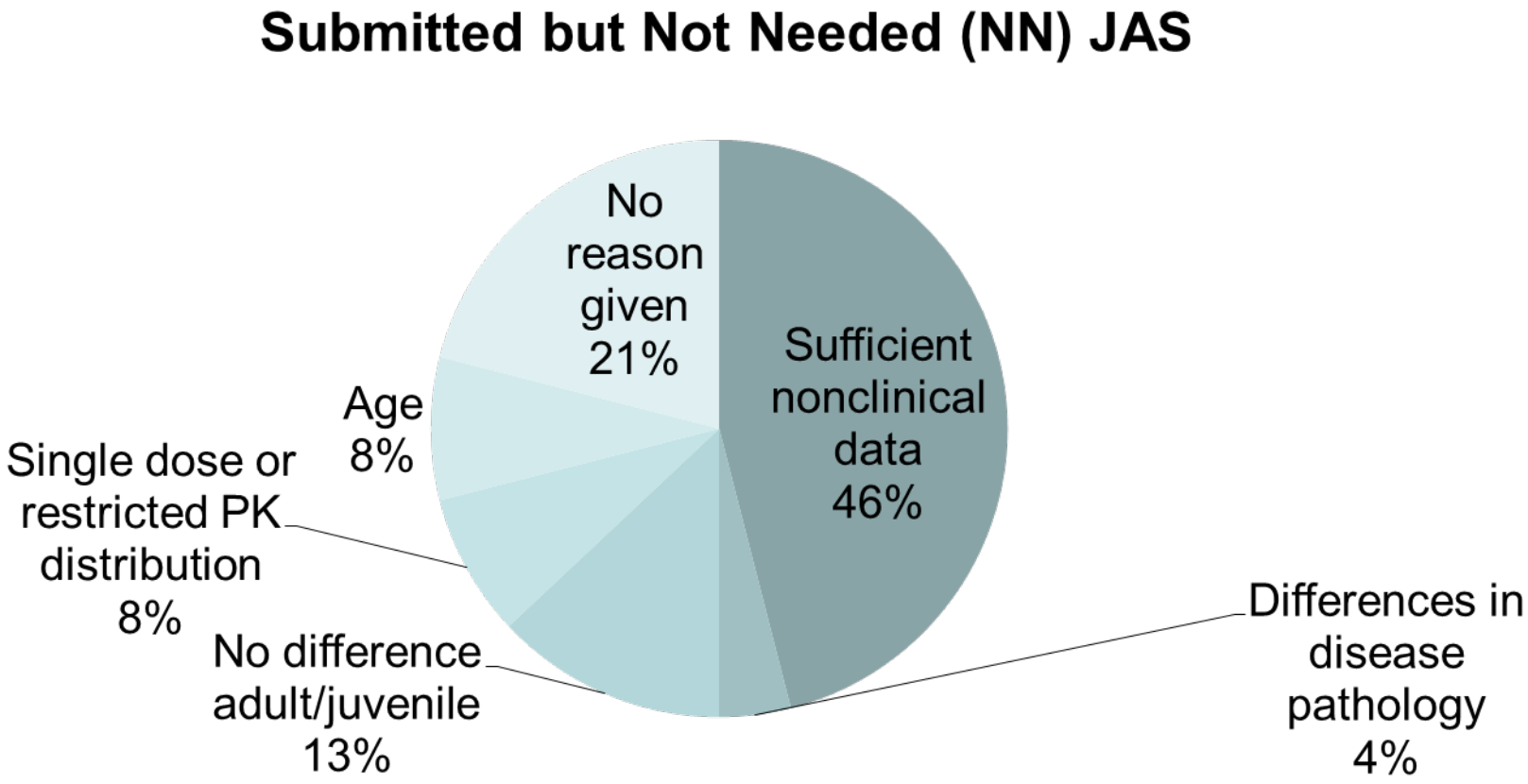
Measuring Outcome of JAS: Regulatory Impact



Outcome of Submitted JAS Studies to CDER

- 21% identified a new toxicity specific to a developing system
- 12% indicated that the toxicity profile of adults and juvenile animal were similar
- 2% show that the juvenile animal was more sensitive to the toxicity than adult

When JAS are Not Needed



Future Considerations

- **ICHS11 EWG (2015) Nonclinical Safety Testing in Support of Development of Pediatric Medicines**
  - On-going global effort to evaluate applications w/ JAS
  - Identify conditions where need or not for JAS
  - What is sufficient existing support for peds trial?
  - Evaluation of what endpoints were included and other study design concepts
  - Identify those associated with consistently meaningful data
  - Identify how the data was used for regulatory decision making and labeling

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