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-ICH S11 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
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

Pediatrics at FDA

Office of the Commissioner

- CDRH
- CBER
- CDER

Office of New Drugs
- Pharmacology
- Toxicology
- Staff

Office of Translational Sciences
- Division Pediatric and Maternal Health

Office of Special Programs
- Office of Pediatric Therapeutics

Office of Clinical Pharmacology - Pediatric Clinical Pharmacology Staff
Pediatric Review Committee (PeRC)

- Internal Review Committee
  - Membership drawn from experts across FDA including CDER, PMHS, CBER, OPT
- Expertise includes
  - Pediatrics (including Neonatology), Clinical Pharmacology, Chemistry, Safety, Statistics, Toxicology, Legal, Ethics
- Provides consultation and review to help improve quality and consistency of pediatric information in pediatric plans and assessments across the Agency
- Reviews
  - PREA – Pediatric Study Plans
  - PREA - waiver and deferral requests
  - PREA - pediatric plans and pediatric assessments
  - BPCA - pediatric written requests
Pediatric Drug Development is Global

• FDA/EMA Pediatric Interactions
  – Regular exchange of nonclinical & clinical scientific information
    • Monthly Tcon to discuss product specific pediatric development
    • PIPs, WR, PREA requirements, pending regulatory actions & safety issues
  – Avoid exposing children to unnecessary or inadequate trials
  – Sharing safety data to reduce risk
  – Sharing trial data to inform future studies
Global Planning in Pediatric Drug Development

**US**

- Preclinical testing
- Phase 1
- Phase 2
- Phase 3
- Written Request issued (BPCA)
- Pediatric study plans (PSP)
- Agreed PREA requirements
- EOP2
- Submission & Review
- Marketing Approval
- PMR

**EU**

- Adult PK
- PIP process begins
- PIP modifications
- Approved PIP required for MAA submission
- Post Marketing Requirements

**PIP**

- Approved PIP
- Required for MAA submission

Marketing Application Authorization [MAA]
**Guidelines: Peds Nonclinical Safety**

**Regional**
- EMA “Nonclinical testing in juvenile animals on human pharmaceuticals for paediatric indications” (2008)
- JMHLW Guideline on the nonclinical safety testing for paediatric medicines with juvenile animals (2012)

**International**
- Statements in ICH M3R2/Q&A, ICHS6, ICHS9, ICHS5 Note 17
- ICHS11 EWG (2015)
Juvenile Toxicity Studies (JAS)

- Nonclinical studies are conducted to support FIH dosing
- Same regulatory expectations
  - Inclusion in WR as appropriate
  - Expectation based on case - no disease or class exclusions
  - Consider safety of excipients, and salt forms also if part of active moiety
- Earlier review & discussion of the Pediatric Study Plan
  - Coordination with EMA
  - Engagement with PeRC
- Attention to the youngest patients- focus on neonates
- JAS are tool used to provide supportive data for pediatric development when adult human/animal data is considered insufficient
  - Guidance for Industry Nonclinical Safety Evaluation of Pediatric Drug Products

Why juvenile animal studies?

• Address pediatric safety concerns not addressed by clinical or standard tox due to developmental differences compared to adults
  – Assess safety concerns that cannot be studied in peds trials
    • Adequately/Safely/Ethically-irreversible AE
      – Provide info for adequate clinical monitoring
      – JAS are considered on a case-by-case basis
    – A scientific justification should support the need/no need for these studies
JAS: Bridging the Data Gap

Direct Dosing
Juvenile animal studies

Repro Seg III

Repeat dose studies

Birth

Weaning
PND 21

Indirect exposure

Adult
~PND60
A Need or No Need for JAS?

- A scientific justification should support the need/no need for these studies: Consider:
  - Indication
  - Age of pediatric population
  - Extent and timing of exposure to the drug
  - PK/PD differences between adults and juveniles
    - Pharmacology of drug (both primary and secondary)
    - Receptor(binding)/site distribution
    - Distribution of the drug in the body
  - Maturity/immaturity of system/s affected by drug distribution
  - What toxicities are identified from adult animals
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 identify 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


• 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 studies were submitted by 2014.
The majority of JAS (55%) submitted with the NDA/BLA.

% Requested Studies

- ID Unknown Tox 43%
- MOA 20%
- Target Organ Tox 20%
- Tox Δ 15%
- PK 2%
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

JAS Submitted

- Labeling: 48%
- Clinical: 19%
- Not Reported: 27%
- None: 3%
- Regulatory: 3%

None: 3%
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

Submitted but Not Needed (NN) JAS

- No reason given: 21%
- Sufficient nonclinical data: 46%
- Differences in disease pathology: 4%
- Age: 8%
- No difference adult/juvenile: 13%
- Single dose or restricted PK distribution: 8%
Future Considerations

  - On-going global effort to evaluate applications w/ JAS
  - Identify conditions where need or not for JAS
  - What is sufficient existing support for pediatric 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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