Juvenile Animal Studies: Industry Perspective

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Outline

- History
- Regulations
- Nonclinical Guidance
- Usefulness of Juvenile Toxicity Studies
- Considerations
- Challenges
- Future Directions
- Summary

A Bit of History

- 2009: ~ 50% of products had some pediatric use labeling*
  - Studies conducted when pediatric market specifically intended
- Practice → "scale" down from an adult dose
  - Dosing based on weight
  - Age appropriate formulations
- Pediatric clinical trials are difficult
  - Ethical concerns
  - Feasibility to enroll
- Impact of growth and development
  - Development may affect PK/PD
  - Drug may affect development

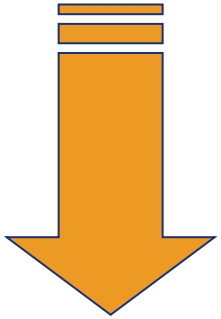
Leading To....

Objective: to improve health of children

↑ high quality and ethical research

↑ availability of medicines

Provide better information on label



Result: promote & require studies through regulations

Pediatric Regulations Over Time

1997 Legislation Renewal Enacted

2003 Legislation Renewal Enacted

Jan 2007 EU Published

2012

Best Pharmaceuticals for Children Act (BPCA)

•Extended to biologics in '10

Pediatric Research Equity Act (PREA)

- Small & Large molecule
- Required as part of every NDA and BLA (unless waiver granted)

European Pediatric Initiative

Reg. EC 1901/2006 "Pediatrics Regulation"

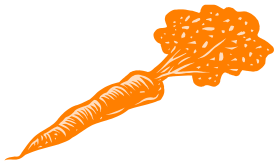
- Approved Pediatric Investigation Plan (PIP) required for every Marketing Authorization Application
  - *Expected at end of Phase 1 (PIP may be modified)*

FDA Safety & Innovation Act (FDASIA)

Pediatric study plans must be submitted within 60 days after end of Phase 2 meeting

PREA

- Drug & Biologics
- Studies - mandatory & apply to indication
- Orphan indications exempt
- Trigger
  - New indication
  - New active ingredient
  - New dosage form
  - New dosing regimen
  - New route



BPCA

- Drugs & Biologics
- Studies - voluntary & apply to active moiety
- Written request may be issued for orphan indications
- Trigger:
  - public health need

Successful completion =
6 months of marketing exclusivity

- **Pediatric Study Plan (PSP)**
  - **Submitted by sponsor within 60 days after EOP2 meeting**
  - Information on disease in pediatric population
  - Request for deferral or waiver and supporting documentation
  - Outline of studies including study objectives and design
    - Including juvenile animal
  - Timeline for submission of studies
  - Age-appropriate formulations
  - Description of supporting studies
  - Agreements with other health authorities
- **Pediatric Review Committee (PeRC)**
  - Processes in place to review and offer comments on plan

- Pediatric Investigation Plan (PIP)
  - **Expected at end of Phase 1**
  - Basis for development & authorization for all pediatric pop. subsets
  - Any new product or indication/route/formulation
  - Includes timing
  - Includes study plan and justification
  - Agreed / amended by Paediatric Committee (PDCO) from EMA
  - Binding to sponsor (compliance check)
    - Modifications possible at sponsor's request
  - Obligation and reward
    - 6 months supplementary protection certificate (SPC) extension
- Nonclinical Working Group
  - Nonclinical experts
  - Make recommendation to PDCO
  - Need for and design of juvenile animal studies

Nonclinical Guidance Comparison

FDA "Nonclinical Safety Evaluation of Pediatric Drug Products" (2006)	EMA "Nonclinical testing in juvenile animals on human pharmaceuticals for paediatric indications" (2008)
Organ systems w/significant postnatal development	Organ systems w/ significant postnatal development - **substantial differences in PK between adults and paediatrics; effects related to delayed or altered development**, which may be evident after treatment termination
One species may be acceptable	**One species will be acceptable**
Cover relevant postnatal period	Cover relevant postnatal period
Before initiation of (long term) pediatric trials	Before initiation of (long term) paediatric trials
Identifiable toxicity at high dose	**"Frank" toxicity should not occur**
"**Less emphasis" on case by case approach** - "Important to include measurement of overall growth, .., assessment of sexual maturation, and neurobehavioral testing"	"**More emphasis" on case by case approach** - Studies may be designed to evaluate effects on growth & development overall OR on selected organ systems
Discussion expected around EOP2	**PIP expected around EOP1b**
	Justification of the potential extrapolation of adult POC data to children *or propose studies to address efficacy in the paediatric population (animal models)*

Usefulness of Nonclinical Juvenile Studies

- May provide additional hazard identification
  - Target organ relevant for developing systems
    - Toxicological or pharmacological
  - Potential effect on growth and development in intended age group
- Address safety concerns that cannot be adequately, ethically, or safely studied in pediatric trials
  - Latent effects
- Potential sensitivity differences
  - Pediatric safety and/or efficacy not always predicted by the adult
- Provide information for clinical trials and labeling
  - Set clinical exposure limits
  - Identification of biomarkers or clinical monitoring
  - Identify age groups in which drug should not be used or where special warnings are needed
    - Preclude pediatric clinical trials
    - Cannot be monitored in clinic
    - Not considered acceptable consequence of treatment

Nonclinical Juvenile Studies

- Need for and design of is case by case
  - Based on the data and pediatric development plan of the specific molecule
- Considerations include:
  - Pediatric population age range
  - Pediatric indication
    - Duration of exposure
  - Clinical plan for adult trials
  - Preclinical program and safety issues identified
    - Organ systems at potential risk (target organs)
  - Potential safety issues in pediatric-human or juvenile-animal
    - May be based on class, mechanism of action, etc
  - Risk/benefits for pediatric population

Designing the Nonclinical Juvenile Study

Objective: meaningful identification of hazard/risk

Design: dependent on hypothesis under investigation

Species selection:

- Target organs: stage & rate of maturation relative to humans
  - Comparison of relevant postnatal development
  - Exposure period
- Endpoints: feasibility, experience/understanding, age appropriate endpoints, timing of testing relative to exposure, interconnection of design elements
  - Dependent on the design
  - May include:
    - clinical pathology, histopathology, reproductive function, developmental landmarks of sexual maturation, neurobehavioral evaluations

Determining Your Design Approach

- Target organ-specific case-by-case study designs
  - Focused or targeted designs
  - Detailed evaluation of specific organ of concern
  - Comparable developmental processes across species is critical
    - Exposure period must be at same stage of development as humans
- Generalized/screening toxicity study designs
  - Similar to repeat-dose toxicity studies
  - Dosing begins at younger age
  - Covers broad periods of organ system development
  - Evaluates same endpoints as standard toxicology studies
  - Other endpoints are added as appropriate
- Combined pre- and postnatal development and juvenile animal study designs

Selecting the Right Species

- Rat often considered the preferred species for nonclinical evaluation for pediatric safety
  - small molecules
- HESI project on cross-species comparative postnatal development
  - Reviews including heart, nervous system, immune system, male and female reproduction systems, lung, kidney, gastrointestinal system and bone

Rodents (Rat and Mouse)

Advantages

- Most frequently used for juvenile testing
- Extensive experience/historical data across labs
- Can test full span of postnatal development
- Ability to procure appropriate numbers of animals, even for early age assessments
- Statistical analysis
- Wide range of tests available
  - Neurobehavioral

Disadvantages

- May not be pharmacologically relevant
- May produce differences in drug metabolism
- Potential immunogenic response
- Small size limits ability to collect multiple biologic specimens
- Route of administration may be limited in very young

Non-Human Primates (NHPs)

Advantages

- Physical size facilitates collection of multiple biologic specimens
- Postnatal development of many organ systems well characterized
- Potentially less immunogenic than other species
- Standardized tests available
  - Neurobehavioral testing (learning & memory)

Disadvantages

- Procurement of appropriately aged animals
- Not practical to test full span of postnatal development
- Limited reference or historical control data for some endpoints
- More expensive (vs rodent)
- Limited appropriate technical experience
- Statistical analysis

Dog

Advantages

- Provides model of prematurity
- Postnatal development of many organ systems well characterized
- Physical size facilitates collection of multiple biologic specimens
- Samples can be collected with minimum restraint and without anesthesia
- Techniques for handling and treating pups well established
- Ability to procure appropriate numbers of animals, even for early age assessments

Disadvantages

- Long time to sexual maturity limits assessment of reproductive development
- Limited reference or historical control data for some endpoints
- Learning and memory tests not well developed
- Potential immunogenic response
- Pharmacological relevance may not have been previously characterized
- Statistical analysis

Minipig

Advantages

- High pregnancy rate and synchronization of mating possible
- Gestation length shorter than NHP
- Similarity of organ system anatomy, size and physiology to humans
- Availability of reference data for juvenile organ development
- Piglets are easily accessible for handling and dosing and allow frequent blood sampling
- Sexual maturation at 4-5 months

Disadvantages

- Limited pharmacological relevance
- Neurobehavioral tests not well developed
- Potential immunogenic response
- Limited labs available with experience

Regulatory Considerations and Challenges

- Pediatric plan required for all drugs
  - Pediatric development experience
  - “Cross functional” approach
- Timing
  - Consideration of pediatric drug development needed earlier in overall drug development plan
    - Might require shift in activities to earlier stages, including nonclinical animal studies
    - Allow time for pilot and follow-up work
    - Include sufficient time for regulatory feedback
  - Differing expectations between regions
    - Simultaneous and consensus for global development
- Proposed strategy must be defined
  - Justification for conduct/design or absence of juvenile animal studies
  - At time of PIP have very little information

Operational Considerations and Challenges

- Logistics
  - Large extremely complex studies often with need for staggered starts, cross fostering, scheduling of tasks, data collection
    - Subsets
      - Primary necropsy, recovery necropsy, neuropathology (primary and recovery), immune function (primary and recovery), reproductive assessment, neurobehavioral testing during dosing, neurobehavioral testing during recovery, TK (terminal and/or serial depending on age)
    - Additional animals?
    - Within litter vs between litter design
    - Litter size
    - Pup identification
    - Time-mated females vs dams with litters
  - Age dependent thus less flexibility in scheduling
  - Exposure differences across development
  - Neuropathology- perfusion
  - GLP vs nonGLP
    - Validated endpoints
  - Selection of species
    - Dogs require additional planning

Operational Considerations and Challenges Continued

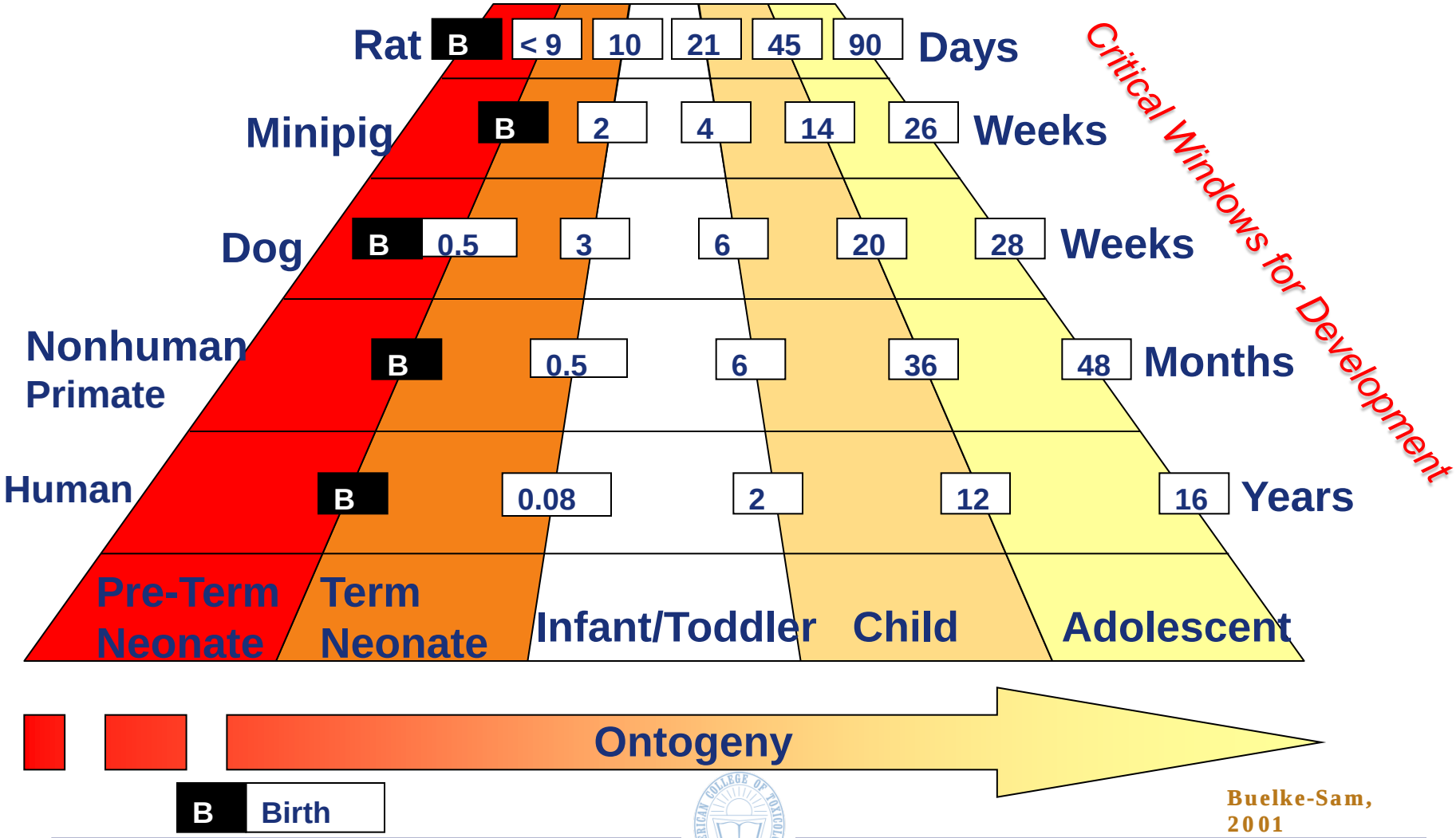
- Feasibility/Technical
  - Limitations in sampling in younger animals
  - Limitations to some routes of administration in younger animals
    - Equipment
  - Age specific responses
    - Experience of staff critical
    - FOB, histological background incidence, clinical pathology reference ranges
  - Strain of species
    - F344 rats and CD-1 nude mice
  - Pregnant NHPs not typically available from breeders
    - Average pregnancy duration in cynomolgus monkeys is 160 days
    - Default litter size is 1
    - Gender distribution of neonates is random

Scientific Considerations and Challenges

- Design studies with “end in mind”
  - Consult with regulatory authorities prior to conduct
    - Important to have desired outcome from a study rather than just conduct a study
  - Study design determines the conclusions which may impact overall clinical development
    - Replacing standard chronic toxicology study with younger aged animals
    - Combination of pre- and postnatal development study with juvenile animal study
  - Data interpretation
    - Relationship to systemic toxicity
    - “Primary” effect or something else
    - Statistics
  - Understanding developmental physiology between humans and animals
    - Maturation of metabolic systems or elimination mechanisms
    - Comparative development of organ systems
    - Age “buckets”
    - Clinical relevance

Caution– when using comparative age categories

Based on reproductive and CNS development



Buelke-Sam, 2001

Future Directions?

- Pharmacology models
  - Oncology
- Pediatric indications
  - Two species
  - Safety pharmacology
    - Cardiovascular assessments, respiratory function
  - Focused areas of concern/issue resolution
    - EEG, abuse liability
- Determining value of juvenile animal studies
  - Development of techniques / knowledge
  - Validity of models / tests
- More “thinking toolbox” and less “box checking”
- Changing business models
  - Outsourcing
  - Development of supporting networks of expertise
  - Collaborative efforts

Key Items to Remember

- Pediatric assessments are required
  - Unless waiver has been granted
- Pediatric drug development requires forethought
  - Significant planning is needed for global development
  - Need/design of juvenile studies is case-by-case
    - In practice, required unless can justify why not
  - Conduct of juvenile animal studies is not straightforward
    - Need to understand models, tools, endpoints
    - Need scientific and technical expertise

The challenge is to develop a scientifically sound, yet technically feasible, strategy

Thank you for your participation in the American College of Toxicology Webinar!

We hope to see you at the 36th Annual Meeting of the American College of Toxicology
Red Rock Resort, Summerlin, Nevada,
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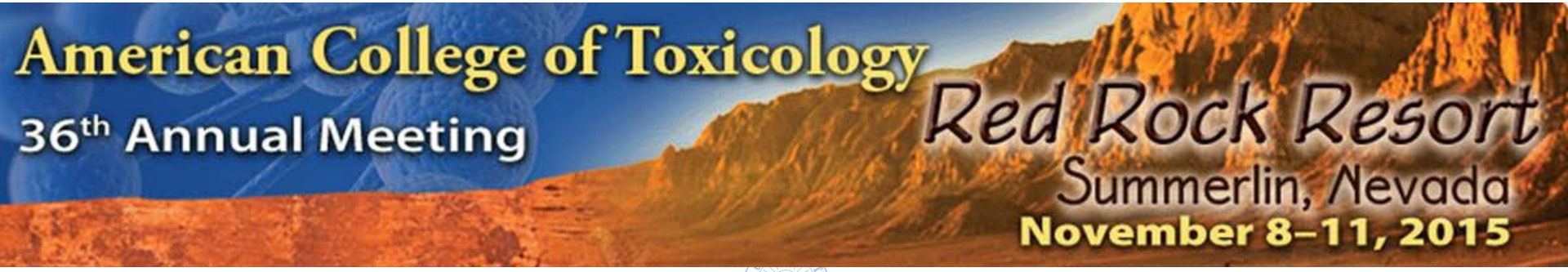

Presenter Bios

- Ikram Elayan, Ph.D.
  - Sr. Reviewer, Division of Psychiatry Products
    US FDA CDER/OND/ODEI/DPP, Silver Spring, MD

Dr. Ikram Elayan received her B.S. degree in Biology and Biochemistry from Bir Zeit University in Palestine, an M.S. degree in Zoology from Brigham Young University, and a Ph.D. in Pharmacology and Toxicology from the University of Utah. In 2001, Dr. Elayan joined the FDA as a pharmacology/toxicology reviewer and is currently a senior reviewer in the Division of Psychiatry Products. In addition to her duties as a reviewer, Dr. Elayan is a member of a variety of committees at the FDA including the Non-clinical Pediatric Working Group and the Neurotoxicity Committee.

Presenter Bios

- LaRonda Morford
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Dr. LaRonda Morford is a graduate of the University of Cincinnati with a Ph.D. in Molecular and Developmental Biology. Following graduation, she spent 12 years at Eli Lilly and Company, where she was a toxicologist responsible for nonclinical safety strategies for drug development teams from lead generation to post-marketing approval (small and large molecules) and the company subject matter expert in nonclinical support of pediatric clinical trials. She then joined Covance, where she was the Associate Director of Lead Optimization Pharmacology-Neuroscience. Her responsibilities included the design and scientific execution of safety and efficacy studies focused on the CNS and consulting on nonclinical juvenile testing and pediatric drug development. In her current role at WIL Research, she is responsible for assisting with the direction of all scientific functions within the disciplines of juvenile toxicology and neuroscience supporting various pharmaceutical, agrochemical and veterinary medical product development programs.