



# American Course on Drug Development and Regulatory Sciences

Pediatric Drug Development Workshop

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# Toxicology for Pediatric Drug Development

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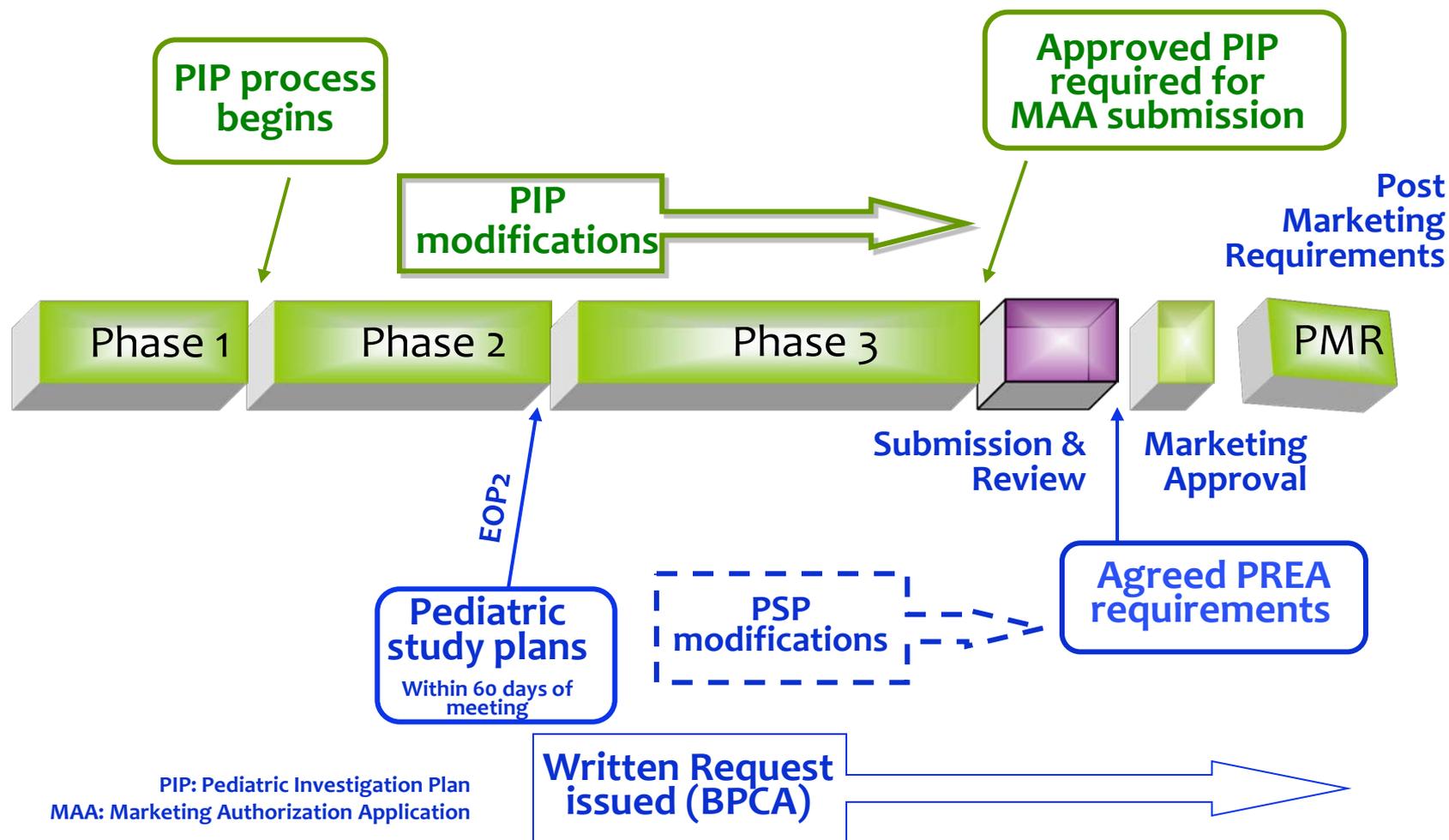
FDA/CDER/OND

# Outline

- Pediatric Drug Regulations
- Nonclinical Pediatric Drug Development
  - Juvenile Animal Studies (JAS)
  - CDER Experience

*Disclaimer: This presentation does not necessarily represent the opinions and policies of the FDA. No conflicts of interest to disclose.*

# Pediatric Planning in the Drug Development Process - Timing





# US Pediatric Regulations

- **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 (ObamaCare)
  - Biologics now eligible for a written request
  - 2012 FDASIA- Safety & Innovation Act
- **2012 FDA Safety & Innovation Act (FDASIA)**
  - No major changes to BPCA, neonates included
  - Changes to PREA- Requirement for Pediatric Study Plans (PSP) & extension for deferred studies

# Non-clinical Studies for Safety Assessment

- Safety pharmacology & pharmacodynamics (POC)
- Pharmacokinetics/Toxicokinetics
  - ADME: (absorption, distribution, metabolism, elimination)
- General toxicology
- Genotoxicity
- Carcinogenicity
- Reproductive toxicology
- Local tolerance
- Special studies
  - Juvenile animal studies (case-by-case basis)
  - Animal models of human disease?

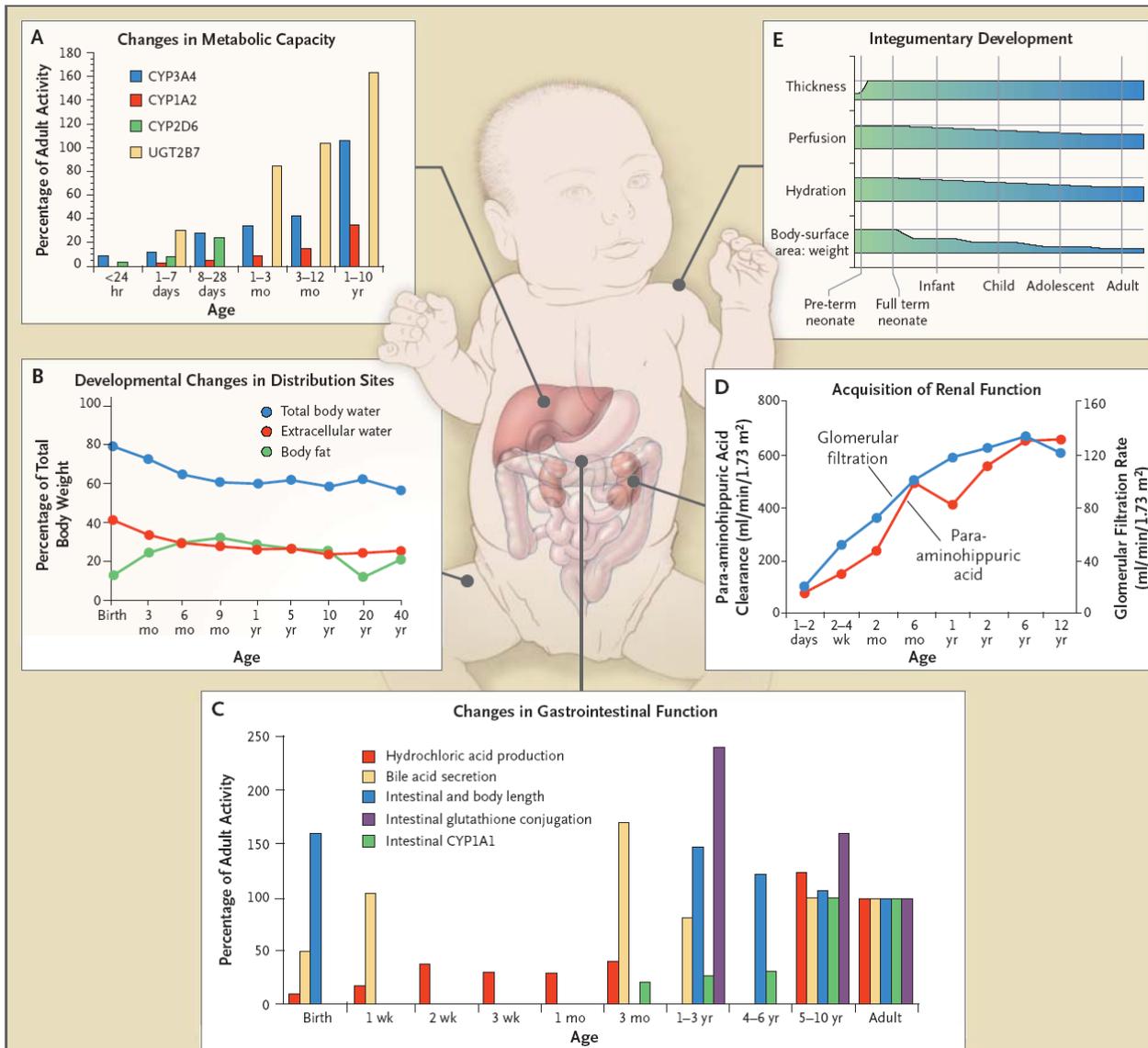


# Adequate Nonclinical Studies Provide

- Understanding of MOA
- Establish exposure (dose) response relationship
- Relationship to duration & extent of systemic exposure
- Identification of target organs & characterization of toxic effects
- Assess potential reversibility of toxic effects
- Extrapolate to potential human risk
- Estimate safe starting dose/regimen, route for clinical trials including FIH [21 CFR 312.23(a)(8)]
- Identify parameters for clinical safety monitoring & guide patient eligibility
- Assist in management of risk

# Differences Between Juveniles and Adults

- Systems are continuously developing
- PK/PD differences between adults and juveniles
  - This can affect the drug/biologic efficacy
  - Conversely the drug/biologic can affect development
  - Different sensitivities between adults and juveniles
- Data from adult animals/humans not always relevant
  - General toxicity studies (direct dose adult animals)
  - Pre-Postnatal studies (indirect exposure)
  - Extrapolation of efficacy but not safety from humans
  - JAS are a tool to fill in the gap



# Neonates/Premies=Pediatric Orphans

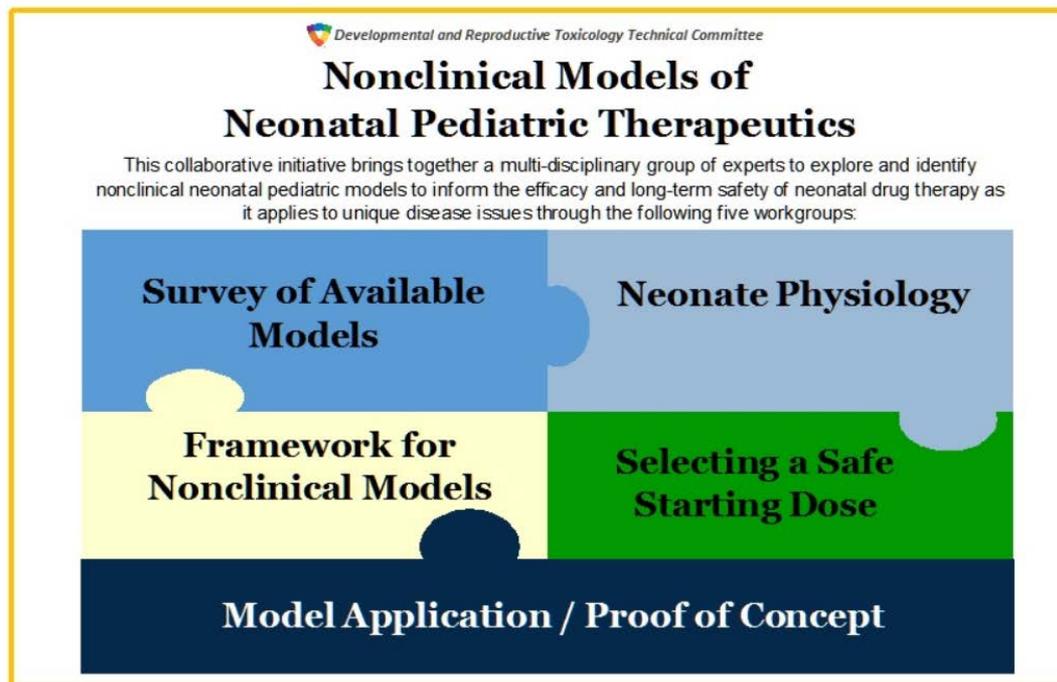
- 90% NICU drugs used off label
- ADE 3X more likely
- NICU patients have the highest medical errors and ADE rates
- Unique disease conditions: NEC, ROP, NAS, BPD, PHN brain injury-IVH, WMI, NDI, infection, preterm labor/delivery
- Significant physiological differences in organ system development & responses:
  - Glucose, thermoregulation
  - Neurologic, cardiopulmonary, immunologic

**Can't extrapolate from adult/pediatric disease**

# Neonatal Clinical & Nonclinical Initiatives



- Innovative trial designs
- Trials that allow for extrapolation
- Criteria for initiating trials in neonates
- PBPK & PKPD modeling
- Clinical outcome measures
- Biomarkers



- What questions are we asking the animal model to address?
- Consider the relevance of animal models of neonatal disease/condition

# Nonclinical Pediatric Safety

## Introduction

- Nonclinical studies are usually conducted to support first in human dosing and marketing of drugs [ICHM3(R2); ICHS6; ICHS9]
- Pediatrics are a unique patient population
- Juvenile Animal Studies are conducted when existing data from adult animals and humans are insufficient to support the proposed clinical trials in children [CDER Nonclin.Safety Eval. Ped Drugs]
- Harmonization between the different regions regarding the need for these studies is under discussion (ICHS11 EWG)

## **Need for Harmonization-ICH S11 Goal**

- When are JAS needed to support clinical trials and when are they not needed?
- When are previous animal data and human safety data considered insufficient to support pediatric studies?
- What is the design of this study?
- What studies are needed for pediatric-only indication when data from adult animals or humans are not available?

# Regulatory Background

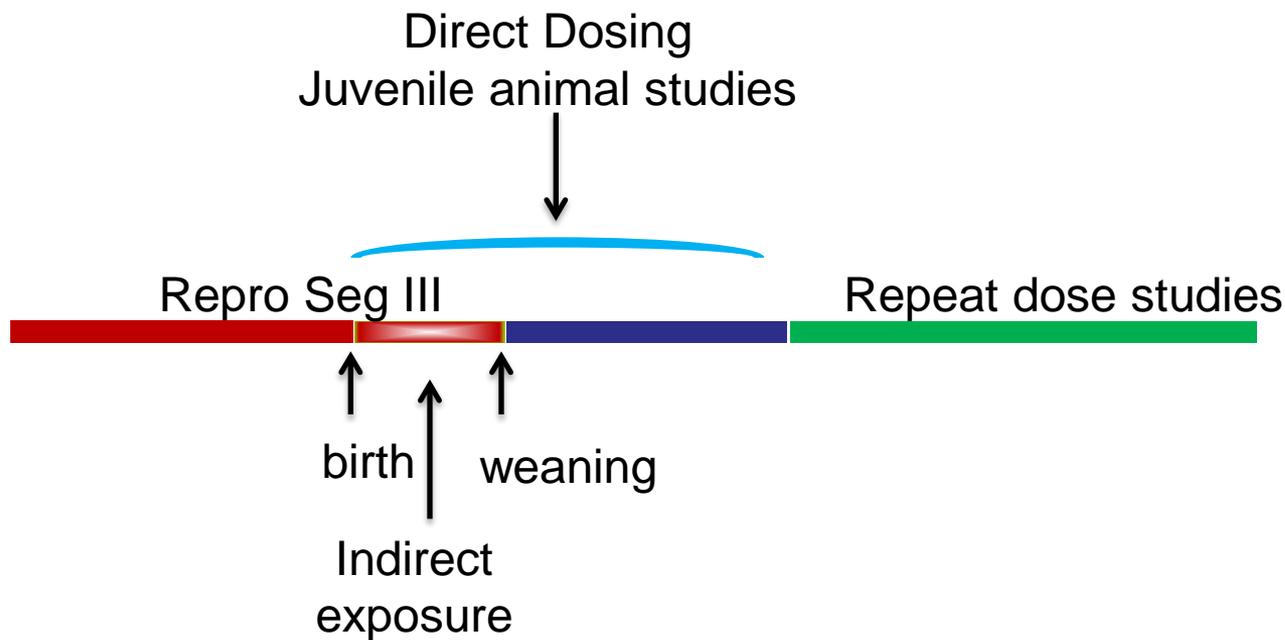
- ▶ JAS are considered on a case-by-case basis
  - FDA Guidance for Industry- Nonclinical Safety Evaluation of Pediatric Drug Products, 2006
    - Statements in ICH M3R2/Q&A
    - ICH S5 Note 17
  - EMA “Nonclinical testing in juvenile animals on human pharmaceuticals for paediatric indications” (2008)
  - JMHLW Guideline on the nonclinical safety testing for paediatric medicines with juvenile animals
  
- ICHS11 EWG
  
- ▶ A scientific justification should support the need/no need for these studies

# When do you need a JAS?

- When you have residual uncertainty about the human risk assessment
  - ❖ Is there a developmental concern based on prior data or pharmacology?
  - ❖ Can you manage the clinical risk?
  - ❖ Can you monitor for the concern?
  - ❖ Can you adjust the clinical dose/duration/age?
  - ❖ Can you determine a safe pediatric start dose?
- Use available data from adult animals and humans to identify potential targets
- JAS is a tool used to address information missing from the existing development program to enable pediatric trials to proceed safely & to assess endpoints that can not be assessed in pediatrics

# JAS as a Tool

- Juvenile Animal Studies are conducted when existing data from animals and humans are insufficient to support the proposed clinical trials in children



# Considerations for the Need of JAS

- ▶ Scientific Justification:
  - Indication
  - Age of pediatric population
  - The extent and timing of exposure to the drug
  - Pharmacology of drug (both 1<sup>o</sup> & 2<sup>o</sup>)
  - Distribution of the drug in the body
  - Receptor/binding site distribution
  - PK/PD differences between adults and juveniles
  - Maturity/immaturity of system/s exposed to drug
  - Toxicities identified from adult animals and how they relate to juveniles

# General Design of JAS

- Relevant studies conducted in young animals of an age range developmentally comparable to that during which exposure would occur in humans
- Animals should be treated throughout the stages of development that are comparable to the timing of exposure in the intended pediatric population
- Temporal developmental differences between animals and humans (use of the appropriate model)
- Design emphasizes assessment of effects on growth and development, with other standard toxicologic endpoints included as appropriate for risk characterization
- Attempt to distinguish between acute and permanent effects of the drug by including a recovery group at the end of treatment period

## Case Study: Linaclotide (Linzess)

- MOA: 14aa guanylate cyclase-C agonist, acts locally on the luminal surface of the intestinal epithelium.
- Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP).
- Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit.
- NME for IBS-C 290 mcg orally once daily (5 mcg/kg/day)
- & for CIC 145 mcg orally once daily (2.4 mcg/kg/day)

# CASE Study- Linaclootide

Toxicity	Species	NOAEL (mg/kg) M/F	Multiples of maximum recommended clinical dose
<b>13-week oral</b>	Rat	M: 50; F: 100	10,400; 20,800
	Mouse	Not determined	-
	Monkey	Not determined	-
<b>26-week oral</b>	Mouse	M & F: 20	4,170
<b>39-week oral</b>	Monkey	M & F: 5	1,040
<b>9-week oral juvenile</b>	Mouse (7-day old)	M & F: 0.003 (< 9 days)	0.6
		M & F: 0.010 (≥ 9 days)	2
<b>5-day Oral Juvenile</b>	Rabbit (14-day old)	M & F: 40 (tolerated dose)	8,330

- Limited oral bioavailability (< 0.20% in all species tested)



# CASE Study- Linaclootide

## Drug-Related Deaths in a Dose-Ranging Study in Neonatal/Juvenile Mice

Dose (mcg/kg/day)	Age at Start of Dosing		
	Age 7 Days	Age 14 Days	Age 21 Days
0.1	0/16	0/16	0/16
10	0/16	0/16	0/16
50	16/16	0/16	NT
100	16/16	11/16	0/16
600	NT	NT	16/16

NT: not tested

All deaths occurred within 24 hr after the first dose.

Surviving animals received 5 daily doses.

# CASE Study- Linaclootide

## Drug-Related Deaths in a 9-Week Study in Mice Commencing on Postpartum Day 7

Dose (mcg/kg/day)	Deaths	Time of Death
Control	0/40	
1	0/40	
3	0/40	
10	5/40	1 - 2 days
30	16/16*	8 - 24 hr

\* Toxicokinetic group (no main study group)

# CASE Study- Linaclootide

*Value: Data from both range finding and definitive studies were utilized in the labeling to limit use in pediatric patients.*

- A PMR was requested to evaluate the cause of death in neonatal and juvenile mice*
- Label was currently updated based on the findings from the PMR*

# Updated Linzess Labeling

## 8.4 Pediatric Use

LINZESS is contraindicated in children under 6 years of age. The safety and effectiveness of LINZESS in pediatric patients under 18 years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop diarrhea and its potentially serious consequences.

Avoid use of LINZESS in pediatric patients 6 through 17 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in pediatric patients 6 through 17 years of age [see *Contraindications (4), Warnings and Precautions (5.1, 5.2) and Nonclinical Toxicology (13.2)*].



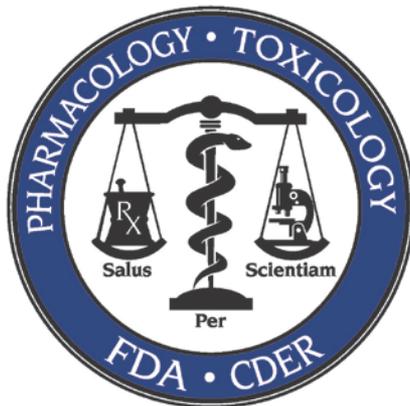
# Updated Linzess Labeling

## 13.2 Animal Toxicology and/or Pharmacology

In toxicology studies in neonatal mice, linaclotide caused deaths at 10 mcg/kg/day after oral administration of 1 or 2 daily doses on post-natal day 7. These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in neonatal mice. Supplemental subcutaneous fluid administration prevented death after linaclotide administration in neonatal mice [*see Contraindications (4) and Warnings and Precautions (5.1)*].

In studies conducted without supplemental fluid administration, tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice, linaclotide was well tolerated at a dose of 50 mcg/kg/day, but deaths occurred after a single oral dose of 100 mcg/kg. In 3-week-old mice, linaclotide was well tolerated at 100 mcg/kg/day, but deaths occurred after a single oral dose of 600 mcg/kg. Linaclotide was well tolerated and did not cause death in 4-week-old juvenile mice at a dose of 1,000 mcg/kg/day for 7 days and in 6-week-old juvenile mice at a dose of 20,000 mcg/kg/day for 28 days

Linaclotide did not cause death in adult mice, rats, rabbits and monkeys at dose levels up to 5,000 mcg/kg/day. The maximum recommended dose in adults is approximately 5 mcg/kg/day, based on a 60kg body weight. Animal and human doses of linaclotide should not be compared directly for evaluating relative exposure [*see Nonclinical Toxicology (13.1)*]



# OVERVIEW OF CDER NONCLINICAL PEDIATRIC SAFETY DATA

# Data Collection

- Prior CDER review:
  - Tassinari et. al. Birth Defects Research (Part B) 92:261-265 (2011)
- FDA/CDER Database
  - Juvenile animal studies (JAS) 2009-2014
  - Reviews from 15 CDER OND Divisions
  - Correspondence & reviews
- All applications with juvenile animal studies (JAS n=359)
- Submitted for review 2009-2014
  - Whether study was recommended by Agency (n=277; 77%) or not recommended (n=82; 23% )
  - Of the required studies n=103 JAS (37%) were submitted and reviewed
  - Required based on signal from prior data n=46; 45%
  - Based on uncertainty n=55; 53% required

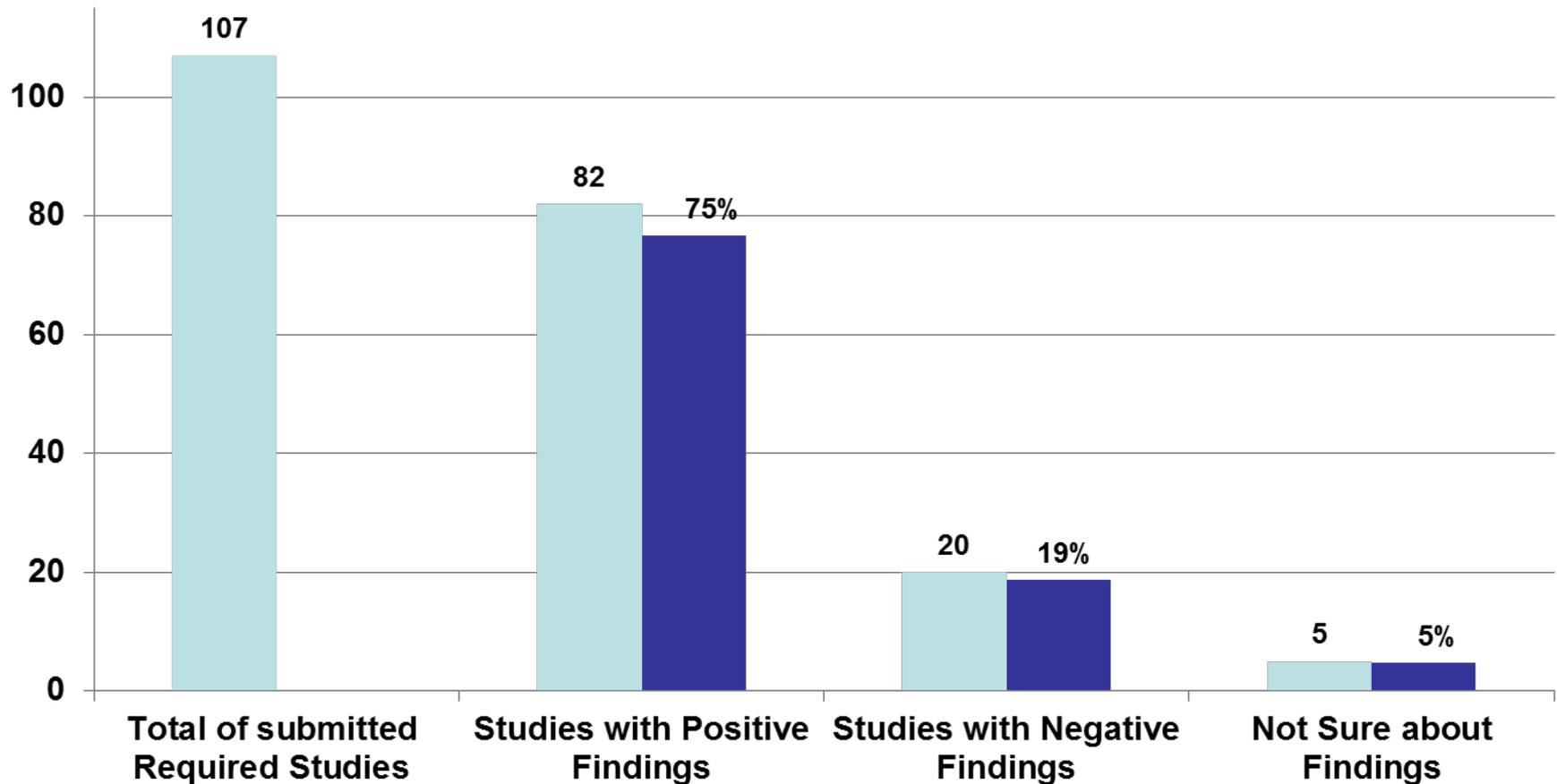
# Rationale for Requested Study

- Prior data & uncertainty were major reasons for requesting a JAS by Agency
  - Prior data= nonclinical data & pharmacology
  - Uncertainty= unknown drug risk & target present in a developmentally sensitive system
- Rationale for not requesting a study was primarily based on prior data
- Majority of studies requested were for CNS, GI, CV & endocrine indications
- Sponsor initiated studies were conducted based on uncertainty across indications

# JAS Study Species

- For most studies a juvenile rat was chosen  
n=73
  - PND <10 36/73=49%=>unique tox 65%
  - PND 21 25/73=34%=>unique tox 84%
- Dog 10/62=16%, Monkey 5/62=8% show a new toxicity compared to adult
- 9% JAS with > 1 species
  - Typically dog or monkey
  - Supported a neurologic or GI indication

# Drug Related Findings Identified in Requested Juvenile Animal Studies



- A fairly large percentage of requested studies have positive findings.
- Positive findings =drug related adverse finding

# What does the database tell us about the study design?

- Most JAS perform standard battery of histopathology
- No standard study design
- Added developmental endpoints not in adult toxicity studies include: growth, bone, developmental landmarks
- Positive JAS outcome from the database correlated to these endpoints: histopathology, bone, neurologic (behavior/learning), reproductive, immuno, endocrine

# 42 Data Elements Collected

## Administrative Data

- Application & document number
- Date
- Drug
- Drug class
- Sponsor
- Division
- Indication
- Reviewer

## Study Data

- Correspondence & review content
- Safety/Regulatory action
- Reason for JAS request
- Species
- Age
- Duration
- Endpoints & rationale,
- Recovery

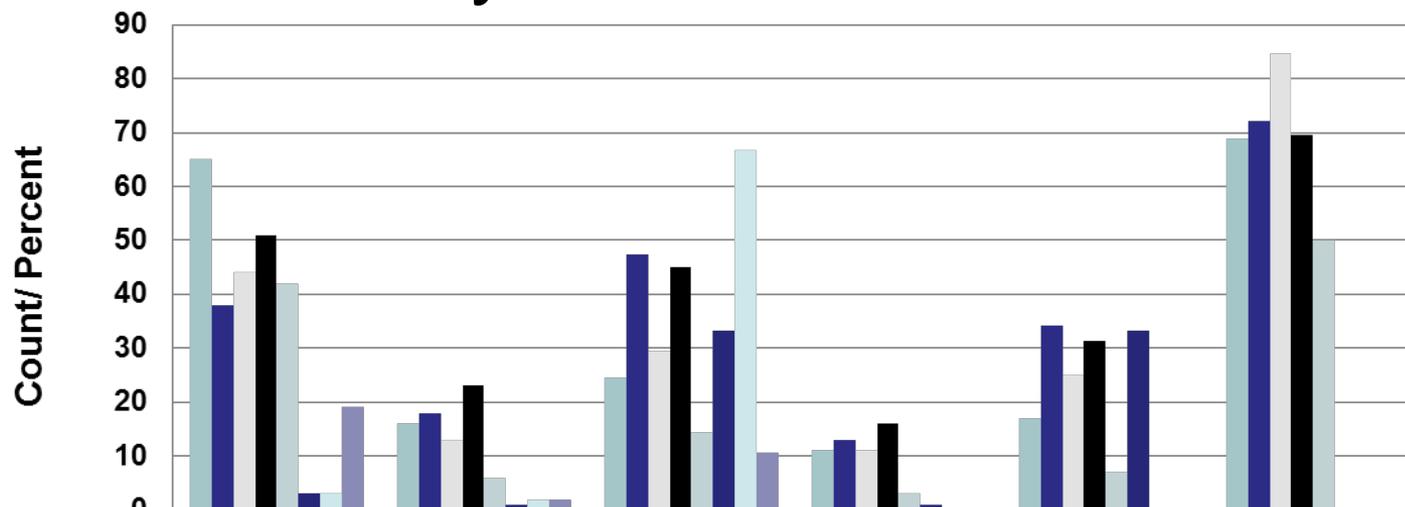
# Prior Data & Uncertainty Affect Endpoint Selection

Prior data	48
Uncertainty	46
NA	4

Prior data	Pharmacology	20
	Adult Toxicity	24
	Segment III Animal Data	1
	Juvenile Animals	8
	Human Clinical Data	3
Uncertainty	Target in developmentally sensitive system	15
	Unknown risk	41



# Correlation of Endpoints to Drug Related Toxicity in JAS



	End Points Sought	# of Application with +ve Data Obtained for the Specific EP	% of EP Sought	# of Applications with a Regulatory Role with the EP	% of EP Sought	% of +ve Data with the Eps
General toxicity/ General histopathology	65	16	25	11	17	69
Developmental landmarks	38	18	47	13	34	72
Bone development	44	13	30	11	25	85
Neurobehavior /Neurological outcome	51	23	45	16	31	70
Reproductive development	42	6	14	3	7	50
Immunotoxicity	3	1	33	1	33	0
Endocrine	3	2	67	0	0	0
Other systems	19	2	11	0	0	0

In 60% Studies: Neuro, Gen Tox-histopath, Dev Landmarks, Bone endpoints correlate to drug related toxicity in same organ system

# Endpoint Selection Summary

- Majority of studies requested endpoints for:
  - General tox (i.e. histopath), developmental landmarks, neuro, bone, repro
  - Not many studies requested immuno or endocrine endpoints
- Drug related toxicity with regulatory impact was observed in studies with:
  - Bone, developmental landmarks, neuro, general tox (histopath), repro endpoints
  - Specific endpoints requested based on prior data had a greater association with positive study outcome compared to when an endpoint was requested based on uncertainty



# % JAS Results Compared to Adult

JAS Findings vs. Adult	Endpoints (% of Total n=86)							
	General	Dev.	Bone	Neuro	Repro	Immu	Endo	Total
Same target toxicity	52		7	21	5	0	3	67
Same target ↑sensitivity	15		2	6	0	0	0	22
Same target new toxicity	23		3	7	5	1	0	33
Different target toxicity (not tested adult)	0		13	20	0	1	0	28
Adult N/A								10
Target not tested in adult	0	37	13	20	0	1	0	47
New dev toxicity		37						37
Not similar tox to adult	36	37	17	30	5	2	0	72
Not similar tox & not ↑sensitivity	23	37	15	27	5	2	0	63
Same target different tox	36		6	13	5	1	0	49
Total # studies	71	37	22	42	9	2	3	100

# Safety/Regulatory Outcome

- 72% Studies have that identified unique toxicity/↑sensitivity correlate to a regulatory outcome in NDAs
- 38% correlate to a safety outcomes in INDs

Outcome	% Safety	% Regulatory
Safe to proceed	27	0
Inadequate data	13	4
Clinical hold	13	0
Monitoring	47	4
Additional studies	0	0
Limit age of peds	0	4
Label	33	93

Safety issue: an issue related to the outcome of a JAS when the drug was in the investigational stages (e.g, deciding if a clinical trial was safe to proceed, whether additional monitoring was needed in the clinical trial, etc.)

Regulatory issue: issues associated with approved products – reflected in labeling

# Possible Predictors of Outcomes

- 83% (86/103) JAS with findings
- Prior adult toxicity data correlated with the JAS toxicity  $43/86=50\%$
- Pharmacology data correlated with JAS toxicity  $52/86=60\%$
- Both pharmacology & prior data correlate with JAS toxicity identification  $30/85=35\%$ 
  - In  $11/86=13\%$  JAS, neither correlate

# JAS Negative Outcome

- 11% JAS (11/103) do not have any findings
- Most of these studies were requested because of uncertainty
- Endpoints evaluated were similar to those with positive outcome
  - Histopathology of standard tissues
  - Additional developmental endpoint e.g. growth, bone, developmental landmarks

# Summary

- A JAS was requested primarily because of prior data or uncertainty of risk due to a developing system
  - Majority of studies were requested for neuro, GI, CV, endocrine indications
- The absence of findings in JAS are of value for safety and regulatory outcome
- Prior toxicity signals in adult animals, human clinical data and pharmacology may associate with a positive drug related toxicity response in a JAS
- JAS often identified a drug-related toxicity not identified in prior adult toxicity studies
  - Neurologic, GI, Developmental landmarks and bone are endpoints that correlate with identification of new toxicities &/or increased sensitivities in juvenile compared to adult animals
- New toxicities led to safety and/or regulatory outcomes

# Drug Exposure & Identification of Unique Toxicity/Increased Sensitivity

Studies	Unique Toxicity/ ↑sensitivity	↑ Exposure J vs A	No ↑ Exposure J vs A	Unknown Exposure J vs A
#	54	4	29	21
% Total	100	7	54	39

Identification of a unique toxicity or increased sensitivity in immature (J) compared to adult (A) animals is not associated with increased drug exposure

# JAS Added Value

- Often JAS identified a drug-related unique toxicity or increased sensitivity compared to adult animal toxicity profile
- Identification of a unique toxicity or increased sensitivity in immature compared to adult animals is not associated with increased drug exposure in the immature compared to the adult animal

# Summary

- A JAS was requested primarily because of prior data or uncertainty of risk due to a developing system
  - Majority of studies were requested for neuro, GI, CV, endocrine indications
- JAS often identified a drug-related toxicity not identified in prior adult toxicity studies
- Positive JAS data reflects primarily new toxicity rather than an increased sensitivity of immature animals
- Increased sensitivity is seen, but it doesn't reflect increased exposure in juvenile versus adult animals. Likewise increased exposure doesn't explain the unique toxicity observed in JAS

# Summary Continued

- Neurologic, GI, Developmental landmarks and bone are endpoints that correlate with identification of new toxicities &/or increased sensitivities in juvenile compared to adult animals
- New toxicities led to safety and/or regulatory outcomes
- Prior toxicity signals in adult animals, human clinical data and pharmacology may associate with a positive drug related toxicity response in a JAS
- The absence of findings in JAS are of value for safety and regulatory outcome

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