EXCIPIENTS USED IN PEDIATRIC DRUG PRODUCTS:
Are Juvenile Toxicology Studies Needed?

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EXCIPIENTS USED IN PEDIATRIC DRUG PRODUCTS

- Objectives:
  - Define Pharmaceutical Excipients
  - Types and Use
  - Selection of Excipients for Pediatric Formulations
  - "Good Intentions Gone Bad"
  - When Should Juvenile Animal Studies Be Conducted?
  - Points to Consider When Designing a Nonclinical Juvenile Animal Study

EXCIPIENTS

Pediatric Drug Products
EXCIPIENTS

• New Excipients (FDA, 2005)
  – "Any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration."

EXCIPIENTS

EXCIPIENTS

EXAMPLES

• Fillers
• Extenders
• Diluents
• Wetting Agents
• Solvents
• Emulsifiers
• Preservatives
• Flavor
• Absorption Enhancers
• Sustained-Release Matrix
• Coloring Agents

EXCIPIENTS IN FORMULATIONS

• Points To Consider (EMA, 2013 - draft)
  1. The choice of a suitable excipient in a pediatric formulation is one of the key elements of the pharmaceutical development
  2. The basic considerations regarding use of excipients are similar for medicines developed for all age groups
  3. Inclusion of any excipient in a pediatric formulation requires additional safety considerations
  4. Use of novel excipients must be weighed against the use of other excipients with an established safety profile, other dosage forms or routes of administration
LESSONS LEARNED

"Everyone will extract different lessons from these tales." (Robertson, 2003)

EXCIPIENT-RELATED TOXICITY

• Not all excipients are inert substances; some have been shown to be potential toxicants.
• The Federal Food, Drug, and Cosmetic Act of 1938 (the Act) was enacted after the tragedy of the Elixir of Sulfanilamide in 1937 in which an untested excipient was responsible for the deaths of many children who consumed the pharmaceutical.
• The Act required manufacturers to perform safety testing of pharmaceuticals and submit new drug applications (NDAs) demonstrating safety before marketing.
• Since that time, the agency has become aware that certain other excipients used in commerce can cause serious injuries in consumers of prescription and over-the-counter drug products in the US and other countries.

Source: FDA, 2005

EXCIPIENT-RELATED TOXICITY

Benzyl Alcohol – “Gasping Syndrome”

• In 1981, Gershanki et al. reported cases of “gasping syndrome”
  - Premature infants exhibited severe metabolic acidosis, hepatic/renal failure, signs of neurological deterioration and gasping respiration
  - Unmetabolized benzyl alcohol (benzoic acid) was in the urine
  - Conjugation of benzoic acid to hippuric acid is deficient in premature infants
• Observed in infants of low BW who had central venous catheters (umbilical artery/vein) that were flushed frequently using bacteriostatic normal saline containing 0.9% benzyl alcohol.
• FDA recommended the exclusion of benzyl alcohol from flush solutions and diluents used in newborns.

Prior to FDA recommendations to cease use in such infants, ~70% of hospitals were using benzyl alcohol diluents in the care of sick newborn infants.
EXCIPIENT-RELATED TOXICITY

**E-Ferol (Vitamin E Toxicity)**

- Classified as "one of the most deadly pharmaceutical errors in American history."
- E-Ferol = Vitamin E plus Polysorbate 80
- Used to treat infants with retrolental fibroplasia (RLF)
- Since very small infants were not fed orally in the 1st week of life, and since IM injections were considered traumatic, an IV form of vitamin E was introduced in 1983
- The new product was widely accepted by neonatologists who were encouraged about the potential to prevent or ameliorate RLF
- Premature babies exposed to E-Ferol began to exhibit hepatomegaly, thrombocytopenia, cholestatic jaundice, ascites and anemia
- There were no infant deaths associated with E-Ferol, cause of illness was not established
- Suspected elevated levels of polysorbate
- This product was not approved by the FDA

**Propylene Glycol Toxicity**

- Propylene glycol (PG) used widely as a solvent, extractant and preservative in various pharmaceutical formulations; generally regarded as nontoxic
- Metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway
- Not fully functional until 12 to 30 months of age
- Large volumes associated with CNS issues in neonates and children
  - Other adverse events: toxicity, cardiovascular effects, allergies, immotility and acute renal failure
- Intravenous parenterals containing PG must be infused slowly
- PG also has a laxative action at high oral doses through high osmotic pressure effects

**Ethanol Toxicity**

- Widely used as a co-solvent to aid solubility
- In US, maximum permitted quantities in OTC products:
  - <0.5% for children under 6 yrs
  - <5% for children 6 to 12 yrs
  - <10% for children over 12 yrs
- Acute (overdose) or chronic (long-term use) toxicity is possible
- May cause adverse symptoms of intoxication, lethargy, stupor, coma, respiratory depression and cardiovascular collapse
- Source: Mills, 2010

**FACTOID**

- In 1859, PG was first described by C. Wurtz
- In 1932, Seidenfeld and Hanzlik found PG to be less toxic than ethylene glycol; accepted as a pharmaceutical solvent
- In 1983, serum hyperosmolality (>300 mosm) reported in infants
- Source was a parenteral multivitamin preparation (MVI-12) containing PG; not recommended for use in patients <11 years of age
- Change in multivitamin preparation led to a 10-fold increase in PG dose
- 49 infants received excess PG; each weighed under 1500 g

Source: Robertson, 2003
EXCIPIENT-RELATED TOXICITY

Peanut Oil Toxicity

• Peanut oil is used as a food additive and as a solvent in intramuscular injections
• It has been suggested that the use of peanut oil in childhood (infant formula and topical preparations) can lead to later episodes of hypersensitivity, and therefore, should be discontinued

Source: Mills, 2010

EXCIPIENT-RELATED TOXICITY

Lactose Toxicity (Immature Metabolism)

• Lactose occurs widely in dairy products and is used in infant feed formula.
• In pharmaceutical preparations, it is widely used as a diluent in tablets and capsules, as a sweetener in liquid formulations and as a carrier in dry powder inhalation products.
• Lactose intolerance occurs when there is a deficiency in the intestinal enzyme lactase, leading to GIT build-up of lactose. There is then the risk of abdominal bloating and cramps.
• Lactase is normally present at high levels at birth, declining rapidly in early childhood (4 to 8 yrs). Hypolactasia (malabsorption of lactose) can thus occur at an early age and, furthermore, this varies among different ethnic groups.
• Significant lactose intolerance can also occur in adults but this is rare.

WHEN SHOULD STUDIES IN JUVENILE ANIMALS BE CONSIDERED?
The following information sources (listed in hierarchy) should be consulted in order to assess the safety profile of each excipient in a pediatric formulation, resulting in an overall conclusion as to whether or not additional data are needed.

- Are there Commission/CHMP/ICH guidelines available related to this excipient?
- Is there a CHMP opinion available relating to this excipient?
- Is this excipient approved in current pediatric medicines?
- Is the excipient included in the EU food legislation?
- Are there any other sources of information (incl. toxicological, preclinical or clinical data) available supporting the use of this excipient?

Points for consideration in the evaluation of the safety profile of excipients in pediatric formulations for a specific target age group.

Source: EMA, 2013 - draft
The ability to predict from the existing nonclinical and clinical data as to whether studies in juvenile animals are necessary increases with age. Therefore, the likelihood of conducting a nonclinical study in older juvenile animals decreases. In addition, the duration of treatment and the type of therapy are also factors that determine whether a nonclinical study in juvenile animals is warranted.

Modified from Lewis et al., 2013

REGULATORY STATUS

- **United States: Food and Drug Administration (FDA)**

- **Europe: European Medicines Agency (EMA)**
  - Guideline on the need for Nonclinical Testing in Juvenile Animals on Human Pharmaceuticals for Pediatric Indications (2008)
  - Pediatric Investigation Plans (PIP)

- **Japan: Ministry of Health, Labour and Welfare (MOHW)**
  - Japanese Pharmaceutical Manufacturers Association has a guidance
  - Japanese guidance is not much different that that of US
POINTS TO CONSIDER

1. Need for testing?
2. One or two species?
3. Is the drug for pediatric use only (chronic studies starting at juvenile ages)?
4. Design juvenile toxicology studies as part of the full drug development program and allow time for any follow-up/ investigative studies
5. Parameters (biomarkers) to be evaluated in clinical trial
6. Assessment of organ development not in short-term clinical trial(s)
7. Discuss plans with regulatory agencies (EMA for PIPs)
8. Harmonize plans with multi-agency comments

WHEN TO DOSE

Age Definitions

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Human (Postnatal Days)</th>
<th>Rat (Postnatal Days)</th>
<th>Dog (Postnatal Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>less than term</td>
<td>1 to 4</td>
<td>1 to 4/10</td>
</tr>
<tr>
<td>Neonate</td>
<td>birth to 1 month</td>
<td>1 to 7/14</td>
<td>5/11 to 21</td>
</tr>
<tr>
<td>Infant</td>
<td>1 month to 2 years</td>
<td>7/14 to 21</td>
<td>22 to 32</td>
</tr>
<tr>
<td>Children</td>
<td>2 to 12 years</td>
<td>21 to 29F/35M</td>
<td>43 to 140F/170M</td>
</tr>
<tr>
<td>Juvenile</td>
<td>12 to 16 years</td>
<td>29F/35M to 49F/70M</td>
<td>150F/180M to 250F/260M</td>
</tr>
</tbody>
</table>

M: male
F: female

POTENTIAL SPECIES

Rodent
- Rat
- Mouse

Alternative rodent models
- Hamster
- Guinea pig
- Transgenic

Nonrodent
- Dog
- Nonhuman primate
- Rabbit

Alternative nonrodent models
- Sheep
- Mini-pig
### ROUTES OF ADMINISTRATION

<table>
<thead>
<tr>
<th>DOSE ROUTE</th>
<th>SPECIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rat</td>
</tr>
<tr>
<td>Oral gavage</td>
<td>1</td>
</tr>
<tr>
<td>Intravenous (bolus)</td>
<td>4 to 15</td>
</tr>
<tr>
<td>Intravenous (infusion)</td>
<td>28</td>
</tr>
<tr>
<td>Inhalation</td>
<td>7 to 10</td>
</tr>
<tr>
<td>Parenteral (IM/SC)</td>
<td>1</td>
</tr>
<tr>
<td>Dermal</td>
<td>10</td>
</tr>
</tbody>
</table>

? = Unknown

IM = intramuscular
SC = subcutaneous

### EVALUATIONS

- Routine toxicology evaluations
- Evaluations of the development of organ systems of concern
  - Cardiovascular
  - Central Nervous System
  - Gastrointestinal
  - Pulmonary
  - Immune
  - Renal
  - Reproductive
  - Skeletal (growth)
- Reversibility (post-dosing development)
  - Consider endpoints to be assessed

### ROUTINE EVALUATIONS

<table>
<thead>
<tr>
<th>EARLIEST DAY (Post-Partum)</th>
<th>SPECIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Rat</td>
</tr>
<tr>
<td>In-Life (clinical signs, body weight)</td>
<td>1</td>
</tr>
<tr>
<td>Food consumption</td>
<td>22</td>
</tr>
<tr>
<td>Clinical Pathology</td>
<td>1</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>21</td>
</tr>
<tr>
<td>Toxicokinetic sampling</td>
<td>1</td>
</tr>
<tr>
<td>Organ wt, macroscopic &amp; microscopic observations</td>
<td>1</td>
</tr>
</tbody>
</table>
ORGAN SYSTEMS OF CONCERN

- Behavior/neurology
- Reproduction
- Skeletal (growth)
- Cardiovascular
- Gastrointestinal
- Pulmonary
- Immune system
- Renal
- Behavior/cognition
- Reproduction
- Skeleton (growth)
- Development up to one year
- Development up to five to 12 years
- Development up to adulthood

GROWTH & PHYSICAL DEVELOPMENT

- Parameters
  - Body weight
  - Physical development
  - Skeleton

- Physical Development
  - Rats, mice and dogs (minipigs, rabbits)
  - Tooth eruption, eye opening
  - Vaginal opening
  - Preputial separation, testes descent
  - Anogenital distance (rodents)

SKELETON: TIER I ASSESSMENTS

- Growth
  - Physical measurements
    - Crown-rump length,ibia measurements (rat)
      - Height, length (dog)
      - Bone length (femur, tibia)
    - In-vivo radiographs
    - Ex-vivo direct
    - rat, dog, nonhuman primate

Radiographic Measurements
- Male Rat Pups
SKELETON: TIER II ASSESSMENTS

• Bone strength
  – Bone mineral content (BMC)
  – Bone mineral density (BMD)
  – Architecture (histomorphometry)

• Bone densitometry (BMC and BMD)
  – Dual-energy X-ray (DEXA) absorptiometry
  – Peripheral quantitative computed tomography (pQCT)

• Biochemical markers of bone turnover
  – Osteocalcin, Procollagen type I N-terminal propeptide, C-telopeptide, N-telopeptide

REPRODUCTION

• Sexual maturation
  – Vaginal opening, preputial separation and testes descent
  – Rats, mice and dogs

• Estrous cycles
  – Rats and mice

• Functional
  – Mating, gestation, parturition and lactation
  – Rats, mice, rabbits, dogs and mini-pigs

• Hormone Assays
  – LH, FSH, estradiol, progesterone, prolactin and testosterone
  – Rats, mice and rabbits and dogs

IMMUNOLOGY/RENAL

Immunology

• Toxicology Screen (Tier I)
  – Hematology
  – Immunohistopathology

• Immunology Screen (Tier II)
  – Phenotyping
  – Natural killer cell activity
  – T-cell dependent anti-body response (TDAR) to Keyhole Limpet
  – Hemocyanin (KLH)

• Species
  – Rats, mice, cynomologus (dogs)

Renal Function

• Pre-weaning: urinalysis
• Post-weaning: urinalysis, function tests

• Clinical pathology parameters

• Histopathology parameters
PULMONARY/CARDIOVASCULAR

Lung Function Testing
- Dogs and rats
- Respiratory minute volume
- Tidal volume
- Respiratory rate

Cardiovascular Function
- Dogs and rats
- Blood pressure, direct – telemetry
- Blood pressure, indirect – paw (tail) cuff
- ECG

NEUROTOXICOLOGY

FDA/EMA Requirements for CNS Function

Reflex ontogeny/Sensorimotor function
- Reflex tests (e.g., auditory startle response)
- Functional/observational battery components

Locomotor activity
- Motor activity test
- FOB components

Reactivity
- Auditory startle habituation
- FOB components

Learning and memory
- Water maze
- Passive avoidance

Rats

<table>
<thead>
<tr>
<th>Test</th>
<th>First Day Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td></td>
</tr>
<tr>
<td>Negative geotaxis</td>
<td>From 8 to well-developed</td>
</tr>
<tr>
<td>Motor activity</td>
<td>12</td>
</tr>
<tr>
<td>Startle habituation</td>
<td>22</td>
</tr>
<tr>
<td>Learning and memory:</td>
<td></td>
</tr>
<tr>
<td>Passive avoidance</td>
<td>22</td>
</tr>
<tr>
<td>Water maze</td>
<td>22</td>
</tr>
<tr>
<td>Sensory development</td>
<td>22</td>
</tr>
<tr>
<td>Auditory startle:</td>
<td></td>
</tr>
<tr>
<td>Hearing/auditory response</td>
<td>From 12 to well-developed</td>
</tr>
</tbody>
</table>

TERMINAL PROCEDURES

Macroscopic Observations
- Neuropathology (CNS and PNS)
- Bone Pathology, Mechanics
- Organ morphology (e.g., lung)

Electron microscopy (e.g., CNS)

NEUROPATHOLOGY
- Whole-body perfusion with glutaraldehyde
- CNS: Paraffin embedding, special stains
- PNS: Plastic embedding, semi-thin sectioning, toluidine blue staining
TAKE HOME MESSAGES

1. The choice of a suitable excipient in a pediatric formulation is one of the key elements of the pharmaceutical development.

2. When selecting an appropriate excipient for pediatric medicines it is important to consider the overall function of the excipient, the safety profile based on acute or repeat exposure, and allergies and sensitization as well as the acceptability/palatability of the formulation, short-term vs. long-term use, and the clinical condition.

3. Good intentions in pediatric formulations have been demonstrated to go bad.

4. Toxicological studies may be necessary if the use of an existing excipient in a pediatric medicine cannot be justified on the basis of available information sources.

5. Each study must be designed on a case-by-case basis to meet the needs of the pediatric development program.

REFERENCES


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