Proposed BCS for pediatrics and implication on bioequivalence assessment

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Topic C. Pediatric BCS

- Regarding pediatric BCS, for which pediatric ages, if any, is the adult BCS adequate for biowaiver of pediatric products? With an eye towards a pediatric BCS to allow for biowaiver of pediatric products, suggest attributes and test methods for a pediatric BCS. What research is necessary for the development of a pediatric BCS?
- Assume a pediatric BCS is developed and differs from the adult BCS and that it is more restrictive (i.e. adult BCS allows more biowaivers than pediatric BCS across same drugs). For a compound/product that meets the adult BCS biowaiver criteria, but does not meet it for the pediatric BCS biowaiver criteria, how should bioequivalence be established?

Objective

- The objective was to classify five drugs into a potential pediatric BCS: dolasetron, ketoprofen, voriconazole, azithromycin and ciprofloxacin
  - Selected due to both oral and IV pharmacokinetic data for each drug available and cover the four BCS classes in adults
- Gandhi, S., Rodriguez, W., Khan, M., and Polli, J.E. (2014): Considerations for a Pediatric Biopharmaceutics Classification System (BCS): Application to Five Drugs. DOI: 10.1208/s12249-014-0084-0. AAPS PharmSciTech. 15:601-611.

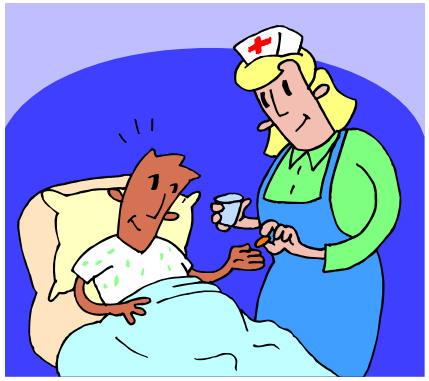
Drug Product Quality

TIME

Multiple Manufacturers ⟷ ANDA Approval → Abbreviated New Drug Application

SUPAC Formulation(s) ⟷ Supplements → Scale-up and post-approval changes

Further Development Formulation(s) ⟷ NDA Approval → New Drug Application



Clinical Trial Formulation(s) ⟷ Safety and Efficacy

Development Formulation(s) ⟷ Pharmacokinetics (PK)

Drugs

- Dolasetron
  - FDA approved in pediatrics for preventing postoperative nausea and vomiting
- Ketoprofen
  - reported to be safe and effective in children for post-surgical pain and the relief of pain and fever in inflammatory conditions (not labeled)
- Voriconazole
  - Common antifungal, but no efficacy and safety studies have been conducted in patients younger than 12 years
- Azithromycin
  - Common antibiotic, but no efficacy and safety studies have been conducted in patients younger than 6 months
- Ciprofloxacin
  - pediatric indications for treatment of anthrax and urinary tract infections

“Adult” Biopharmaceutics Classification System (BCS)

- Solubility (dose vs 250ml) and permeability (vs Fabs=85%)
  - High and low
  - e.g. Class 1 (HS and HP) and class 3 (HS and LP) are potentially eligible for “biowaiver”
- Additional
  - IR solid oral dosage forms
  - Rapid or very rapid in vitro dissolution (500ml); similarity
  - Stability in GIT (e.g. 1hr in gastric and 3hr in intestinal)
  - Excipients
    - None will affect drug absorption (Class 1); amount consistent with intended function
    - Test is qualitatively the same and quantitatively very similar (Class 3)

Summary of pediatric BCS classification and comparison to adult BCS classification

Drug	Adult BCS Class	Pediatric BCS Class
Dolasetron	1	3
Ketoprofen	2	4
Voriconazole	2	4
Azithromycin	3	3
Ciprofloxacin	4	4

Pediatric BCS permeability was elucidated from literature that did not include all pediatric sub-populations. All pediatric permeabilities were low.

Most conservative solubility applied from various sub-populations.

Sub-populations

- Neonates (0-1mo)
- Infant (1 mo-24 mo)
- Children (2yr-12yr)
- Adolescents (12 yr-16yr)

Dose

- Need a dose for BCS classification
  - General approach using common clinical dose equations
  - Doses from literature references
- Examples
  - Dolasetron tablets are available as 50mg and 100mg tablets. Label indicates oral dosing in terms of 1.8mg/kg within 1 hour before chemotherapy in pediatric patients.
  - Ketoprofen is commonly used in pediatric patients but not indicated. Only available in 25mg, 50mg and 75mg capsules. In literature references, ketoprofen was orally administered as either 12mg or 25mg doses to pediatric patients.

Pediatric solubility classification

- Dose number $$D_p = \frac{M_p / V_p}{C_p}$$
  - D_p is pediatric dose number, M_p is pediatric dose, V_p is pediatric reference volume, and C_p is pediatric drug solubility
  - Pediatric dose numbers greater than 1 were classified as low solubility
- Pediatric dose (Mp) was calculated using several different formulas, including Young's Rule, Clark's Rule, Modified Weight Rule, and Body Surface Area Method.
- Vp was calculated for each of four sub-populations
  - based on BSA, relative to the adult volume of 250ml and adult BSA of 1.73m^2

$$BSA\ (m^2) = \frac{\sqrt{Height\ (cm) * Weight(kg)}}{60}$$

Pediatric solubility classification

- Pediatric dose (Mp)

$$Young's\ Rule: \frac{Age(years)}{Age(years)+12} \cdot Adult\ dose$$

$$Clark's\ Rule: \frac{Weight(pounds)}{150pounds} \cdot Adult\ dose$$

$$Modified\ Weight\ Rule: \frac{Weight(kg)}{50kg} \cdot Adult\ dose$$

$$BSA\ Method: \frac{BSA\ of\ pediatric\ patient(m^2)}{1.73m^2} \cdot Adult\ dose$$

$$D_p = \frac{M_p / V_p}{C_p}$$

- Vp based on BSA, relative to the adult volume of 250ml and adult BSA of 1.73m^2
  - Vp = 34.7ml, 67.4ml, 127.6ml and 220.3ml, respectively

Ketoprofen pediatric dose number for various pediatric subpopulations

Dose Formula	Neonates (0-1mo)	Infant (1-24mo)	Children (2-12yr)	Adolescents (12-16yr)
Young's Rule	0.0415	0.494	1.20	1.02
Clark's Rule	0.703	0.948	1.10	1.41
Modified Weight Rule	0.960	1.29	1.50	1.93
Body surface area	1.67	1.67	1.67	1.67

Permeability

- Permeability classification based on absolute bioavailability. High permeability required >= 90% (per original/prior adult BCS)

$$F_p = \frac{AUC_{po} / dose_{po}}{AUC_{IV} / dose_{IV}}$$

- Dolasetron - 60.9%
- Ketoprofen - 46.9%
- Voriconazole - 69.4%
- Azithromycin - 61.6%
- Ciprofloxacin - 57.3%

Conclusions and issues identified

- Agreement in adult and pediatric BCS class for two drugs, azithromycin (class 3) and ciprofloxacin (class 4)
- Since all pediatric permeabilities were low, even when adult permeability class was high, there was discordance for the three drugs that have high adult permeability: dolasetron (class 3 in pediatric), ketoprofen (class 4 in pediatric), and voriconazole (class 4 in pediatric)
- Differences between adults and pediatric patients and hence a need for further development
- Adult BCS references a dose volume of 250ml, versus no fixed volume in the pediatric population
- Sub-populations exist within the pediatric population
- Different study designs for different drugs and limited literature resources available
- Significant challenges that will be encountered in developing this methodology