Clinical Pharmacology Considerations for Pediatric Formulations: Case Studies in Antiviral and Anti-infective Products

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Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products Workshop

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Disclaimer

- The opinions expressed in this presentation are my own and do not necessarily represent the views of the FDA.

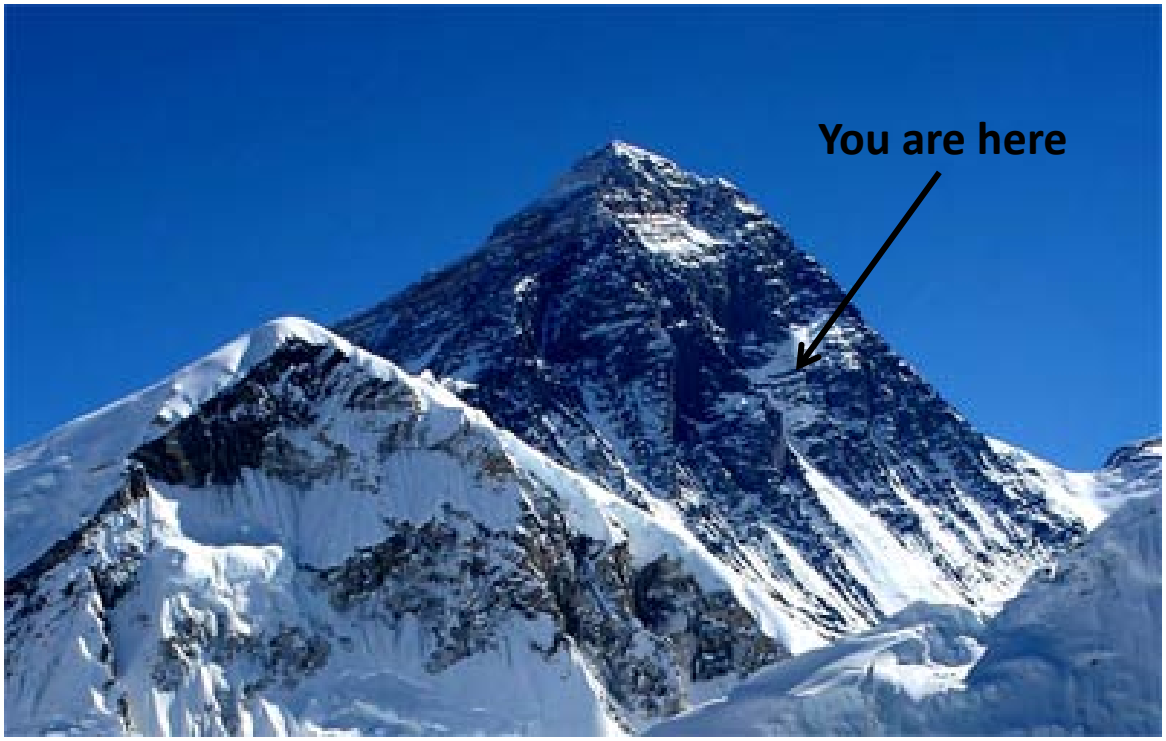
Introduction

A lot of work in advancing drug development in pediatrics has been initiated/done:

- Two laws (PREA and BPCA) have been enacted and reauthorized that will continue to increase the number of studies conducted in children
- Progress in the areas of biomarkers, PK-PD relationships in children, *in silico* modeling have all contributed to a greater understanding of response to treatment in children

Introduction

But a lot of work is still left to be done!



Formulation issues remain a challenge for many pediatric programs…

The Ideal Formulation

- The ideal pediatric formulation should:
  - have non-toxic excipients
    - Amprenavir case—propylene glycol
  - allow for flexible titration of dosing
    - Limited for fixed dose combinations
  - be stable in various light, humidity, and temperature conditions
    - Extemporaneous formulations
  - be palatable
    - Powder formulations—have you guys tried this stuff?
  - be easy to administer
    - Haha, yeah right

Pediatric Formulation Issues

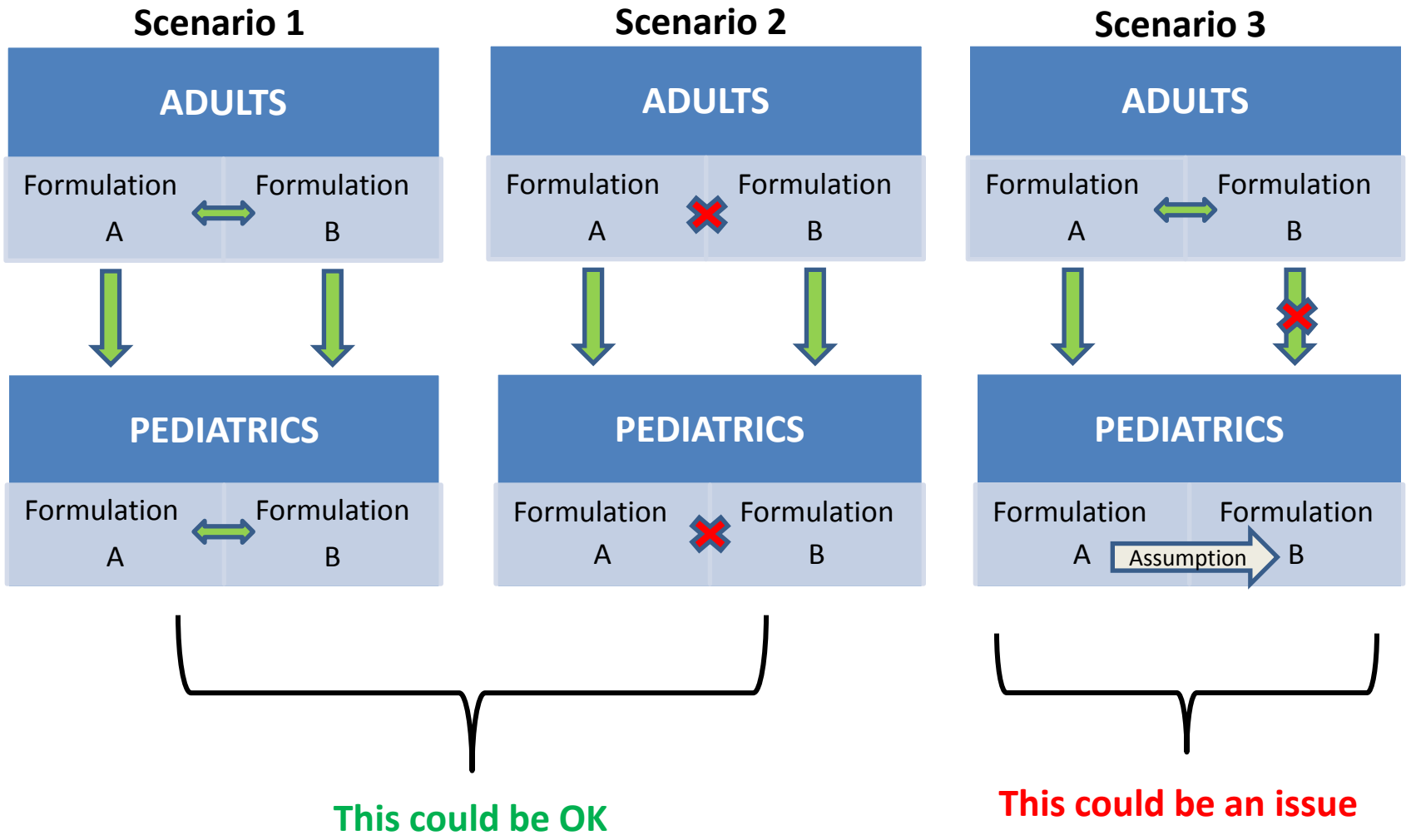
-have translatable bioavailability between adults and pediatrics

- Lamivudine case:

Pharmacokinetics of Antiretroviral Drug Varies With Formulation in the Target Population of Children With HIV-1

P Kasirye[1], L Kendall[2], KK Adkison[3], C Tumusiime[4], M Ssenyonga[4], S Bakeera-Kitaka[1], P Nahirya-Ntege[5], T Mhute[6], A Kekitiinwa[1], W Snowden[7], DM Burger[8], DM Gibb[2] and AS Walker[2]; on behalf of the ARROW Trial Team

Translation of Relative Bioavailability



Lamivudine

- The ARROW trial (conducted in Africa) offered a rare opportunity to obtain BA comparison data in children in a PK substudy:
  - children with HIV-1 infection weighing 12 to <15 kg
  - had been taking zidovudine, lamivudine, and abacavir oral solutions during the trial and were ready to switch from oral solution to tablet formulations
  - intensive PK assessments while children were on oral solution and then again after the switch to tablet

Lamivudine

- Results showed divergence from what was previously known about bioavailability of solution vs. tablets in adults
  - Peds: 37% lower bioavailability for the solution as compared to tablet
  - Adults: BE shown in NUCA1003 in 12 HIV-infected adults, with GMR (90% CI) for tablet vs. solution being 0.98 (0.98–1.00) for $AUC_{0-\infty}$ and 0.98 (0.98–1.01) for Cmax

Lamivudine

- From section 12.3 (under Special Populations):

  "The relative bioavailability of EPIVIR oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown."

Current Paradigm

A Randomized, Open-Label 3-Way Crossover Study to Investigate the Relative Bioavailability and Bioequivalence of Crushed Sildenafil 20 mg Tablets Mixed With Apple Sauce, Extemporaneously Prepared Suspension (EP), and Intact Sildenafil 20 mg Tablets in Healthy Volunteers Under Fasting Conditions

Xiang Gao[1a], Marie-Noella Ndongo[2], Tina M. Checchio[3], Jack Cook[3], Barbara Duncan[4a], and Robert R. LaBadie[3]

Single-dose pharmacokinetics of pediatric and adult formulations of etravirine and swallowability of the 200-mg tablet: results from three Phase 1 studies

Thomas N. Kakuda[1], Cindy Berckmans[2], Goedele De Smedt[2], Ruud Leemans[3], Lorant Leopold[1], Monika Peeters[2], Steven Nijs[2], Veerle Vyncke[2], Rodica van Solingen-Ristea[2] and Richard M.W. Hoetelmans[2]

Relative Bioavailability of Pediatric Oral Solution and Tablet Formulations of Trametinib in Adult Patients With Solid Tumors

Donna S. Cox[1], Alicia Allred[1], YanYan Zhou[1], Jeffrey R. Infante[2], Michael S. Gordon[3], Johanna Bendell[2], Suzanne Jones[2], Howard Burris III[2], and Keith Orford[1]

Bioequivalence of Enalapril Oral Solution for Treatment of Pediatric Hypertension and Enalapril Tablets

Brady S. Moffett[1], Anthony R. DiSanto[2], Orlando Espinosa[3a], Jingguo Hou[3b], and Peter Colabuono[4]

Pharmacokinetics, Pharmacodynamics, and Comparative Bioavailability of Single, Oral 2-mg Doses of Dexamethasone Liquid and Tablet Formulations: A Randomized, Controlled, Crossover Study in Healthy Adult Volunteers

Christian Queckenberg, MD[1]; Bertil Wachall, PhD[2]; Valerie Erlinghagen, MS[1]; Paola Di Gion, MD[1]; Dorota Tomalik-Scharte, MD[1]; Mona Tawab, PhD[3]; Kathleen Gerbeth, PhD[3]; and Uwe Fuhr, MD, PhD[1]

Extemporaneous Formulations for Pediatric Patients

- Why/when used?
  - An age-appropriate formulation is needed for pediatric patients (i.e., oral solution or suspension) and one is not commercially available
  - Alternatives may be too cost-prohibitive
- How?
  - In some instances, the information is found in the USPI
  - Otherwise, USP monographs or published references
- Clinical pharmacology considerations?
  - At times, a relative BA study is not conducted; assumed to be similar between the solid oral dosage form and the extemporaneous formulation

Valacyclovir

- One example of detailed instructions for an extemporaneous formulation being contained in a drug's USPI

2.3 Extemporaneous Preparation of Oral Suspension

Ingredients and Preparation per USP-NF: VALTREX Caplets 500 mg, cherry flavor, and Suspension Structured Vehicle USP-NF (SSV). Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) should be prepared in lots of 100 mL.

Prepare Suspension at Time of Dispensing as Follows:

- Prepare SSV according to the USP-NF.
- Using a pestle and mortar, grind the required number of VALTREX 500 mg Caplets until a fine powder is produced (5 VALTREX Caplets for 25 mg/mL suspension; 10 VALTREX Caplets for 50 mg/mL suspension).
- Gradually add approximately 5 mL aliquots of SSV to the mortar and triturate the powder until a paste has been produced. Ensure that the powder has been adequately wetted.
- Continue to add approximately 5 mL aliquots of SSV to the mortar, mixing thoroughly between additions, until a concentrated suspension is produced, to a minimum total quantity of 20 mL SSV and a maximum total quantity of 40 mL SSV for both the 25 mg/mL and 50 mg/mL suspensions.
- Transfer the mixture to a suitable 100 mL measuring flask.
- Transfer the cherry flavor* to the mortar and dissolve in approximately 5 mL of SSV. Once dissolved, add to the measuring flask.
- Rinse the mortar at least 3 times with approximately 5 mL aliquots of SSV, transferring the rinsing to the measuring flask between additions.
- Make the suspension to volume (100 mL) with SSV and shake thoroughly to mix.
- Transfer the suspension to an amber glass medicine bottle with a child-resistant closure.
- The prepared suspension should be labeled with the following information "Shake well before using. Store suspension between 2° to 8°C (36° to 46°F) in a refrigerator. Discard after 28 days."

*The amount of cherry flavor added is as instructed by the suppliers of the cherry flavor.

Vancomycin

- USPI for Vancomycin HCl for injection, fliptop vial. Contains instructions for making an oral formulation.

For Oral Administration

Oral vancomycin is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and for staphylococcal enterocolitis. Vancomycin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dosage in pediatric patients is 40 mg/kg of body weight in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g. The appropriate dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via nasogastric tube.

Conclusions (my soap box)

- Pediatric formulations present unique challenges to drug development
- A lot of progress has been made; even more is needed (particularly in the area of prediction)
- Recognizing where the challenges and areas of need are, is the first step in making further progress

Questions?