PQRI Workshop: MIDD Approaches in Pediatric Formulation Development
Q&A from February 28, 2024

Question Asked	Response
To Dr. Petrea Cober: You mentioned viscosity having an impact on patient acceptability. What is classed as good vs bad in terms of viscosity and does the patient population affect the acceptability with different viscosities when dosing orally?	**COBER:** Excellent question. I have NOT seen a great study on the preferred viscosity for pediatric patients yet but maybe that is something for a future group to tackle. As a pharmacist and mother, my own practical experiences have shown that the thicker the viscosity the worse it is for patients to tolerate. I would think this would be even worse for those patient populations that have texture issues (e.g., autism spectrum disorder).
To Dr. Hardik Patel: Does the Agency have a Guidance on Biorelevant Dissolution Testing? Could this be a topic to discuss via the Emerging Technology Team?	**PATEL:** Some guidances discuss the use of biorelevant dissolution media tailored to specific dosage forms, such as chewable tablets. Nevertheless, ongoing efforts are underway to develop additional guidance or white papers to comprehensively address this matter.
FOLLOW-UP: Thanks for the response Dr. Patel. Can you provide a timeline about White Papers and/or Guidances. Also, please comment about the Emerging Technology Team approach to discuss the topics with the CDER BioPharm Experts. Thanks.	**PATEL:** Unfortunately, I lack information regarding the timelines for these efforts or the ongoing discussions between ETT and biopharmaceutical experts.
	WU: FDA and CRCG organized a workshop on Oct12, 2023. Session 3 is about PBPK Modeling to Support BA and BE Assessments in Pediatric Populations. A workshop report is also under planning. You may find some useful information there. Link: https://dev-crcg-db.pantheonsite.io/education-training/advances-in-pbpk-modeling-and-its-regulatory-utility-for-oral-drug-product-development/

To Prof. Sandra Klein: Is there any feedback from health authorities regarding this new (or different) biorelevant setup for pediatric dissolution testing? I am wondering how receptive a new setup would be -> even though it has been stated by previous presenters as well that testing specific for pediatrics is needed, and there is a gap. And any thoughts on what criteria would have to be fulfilled for acceptance. Thank you for a very nice presentation!	**KLEIN**: Hi and thanks for this question. We just published this approach by end of last year and unfortunately to date didn´t get any feedback from health authorities, maybe simply, since they were not aware of it. I hope todays presentation will raise awareness, since even though addressing GI physiology of different age groups and real-life dosing conditions, our approach focusses on standardizing biorelevant dissolution methods, so that the methods could finally also be applied in QC. With a good understanding of drug- and formulation characteristics, one should finally be able to pick out a set of test conditions that are likely to represent best and worst case dosing conditions for risk assessment. We have also already started to implement our data into a PK Sim based in silico model, but haven't published it yet. Results are very promising and industry is interested in our approaches. It would be great, if we would get the chance to work together with FDA to further refine the model.
FOLLOW-UP: Thank you for the very thorough response! Sounds promising. Looking forward to your future publication.	
To Dr. Andrea Moir: Great presentation. Thank you. Can you clarify when and how did you scale the paediatric dose for the TIM experiments? Also have you combined any of the dissolution techniques (simple dissolution or TIM) and results with PBPK modeling?	**MOIR:** As the TIM-1 system is currently scaled for adults we dosed the age appropriate formulation at the same dose as adults would receive for the adult formulation. Yes we have taken data from the dissolution tests into PBPK modelling and used this in combination with the dissolution and TIM-1 to build understanding.
To Dr. Andrea Moir: Please refer to Slide 16: When was the Type B Mtg with the Agency?	**MOIR**: I don't have a specific date but within the last year or so

FOLLOW-UP: Dr. Moir, I was only interested in the fact it was a recent Mtg. That's great.....since 2022. Excellent seminar. Thanks.	
GENERAL QUESTION: Has the CDER BioPharm Special Council been involved with the evaluation of the Pediatric Biorelevant Dissolution Testing development?	**WU**: Pediatric Biorelevant Dissolution Testing is an emerging area. FDA has funded research in this area and collaborations are conducted among different offices/disciplines.
FOLLOW-UP: Good to know, Dr. Wu. Is this INFO and contact INFO on the CDER Website??	**WU**: Here is the link about the research priorities that GDUFA support: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects. Awarded Projects can be found using this link as well.
To Dr. Petrea Cober: What's the acceptability of minitablets (2-3mm) in children < 6 years	**BURCKART**: Dr. Cober had to go to class, but check out several recent publications, such as: European Journal of Pharmaceutics and Biopharmaceutics 166 (2021) 126–134. **COBER:** This is an excellent article to discuss this question. Definitely check this one out.
FOLLOW-UP: Hi Gil, thanks for sharing the reference!	**BURCKART**: I think that this is a newer discussion at FDA than EMA, so these are important discussions with review groups.

To Dr. Petrea Cober: Also, are there any specific challenges that you have encountered during reconstitution of adult solid dosage forms for NG tube administration??	**COBER:** Most definitely. Two common ones I encountered in the NICU were the following: 1) Lansoprazole Solutabs down the NG tube. This dose form is marketed as an option for NGT/GT use in adults. While it does work for many pediatric patients, it is a challenge for neonatal patients. When dissolved prior to administration, the enteric-coated pellets/beads can "clog" the smaller NGTs in the neonatal unit. I actually saw a nurse crushing the tablet one time and asked her why she was doing that since the instructions specifically said not to crush the tablet since it contained enteric-coated pellets/beads. She said she did not realize that would be a problem for the smaller patient. Additionally, if you need a partial tablet it is very challenging. The tablets are very crumbly so to cut it in half is challenging. If you dissolve the tablet in a set amount of water to utilize the aliquot method, the pellets/beads seem to stick to the plunger of the oral dosage syringe and do not get to the patient. 2) Another challenge is ciprofloxacin administration. Ciprofloxacin suspension is not able to be placed down a feeding tube due to its viscosity. One therefore has to use the crushed tablet instead. This can be very challenging unless the patient's dose can be a half of a tablet or a whole tablet. To add to these challenges, the administration in someone who usually eats every 3 hours a milk-based diet, the concern for drug-nutrient interactions is high.
To Dr. Andrea Moir: Thank you Andrea, were any of the biorelevant and PBPK approaches submitted to support submissions to regulatory agencies and is there any feedback received?	**MOIR:** It is our strategy to engage with the regulatory agencies on modelling approaches and project specific interactions will continue through their development programs.

To Dr. David Good: Can you comment about your PEDS IVIVC approach acceptance via the FDA and EMA evaluation??	**GOOD**: Thanks for the question. All IVIVC/R work for peds and adult formulations were resolved in clinical adult populations. This was in advance of a ped product with target attributes being taken forward to clinical use in peds subjects. No specific clinical IVIVC study directly with peds subjects.
To Dr. David Good: Dr Good, very nice talk and presentation. Generally speaking, what are your thoughts on sufficient in vivo dataset for modeling - or feedback for a built model - with the challenges of getting having clinical data from pediatrics. Whether frequency of sampling or number of patients included in a study. thank you.	**GOOD:** Thanks for the question. At minimum it is preferable that peds modeling activities first apply the entire adult data set from PK studies with intensive sampling. This would hopefully include multiple product presentations and any unique routes of administration. As such would provide a well verified adult model covering various product release behavior. Subsequently, the peds data sets can be highly variable… generally with less intensive PK sampling and fewer subjects. However, this is where integration with a popPK model could help express observed PK for the purposes of mechanistic PBBM models.
FOLLOW-UP COMMENT: Ah, ok. So PBBM can be used to evaluate a population with a variety of parameters/factors/ ranges and assess which could be critical? Thank you for the response.	