PQRI Workshop: MIDD Approaches in Pediatric Formulation Development

Q&A from February 29, 2024

Question Asked	Response
To Dr. David Harris: Hi Dr. Harris, for those reconstitute drugs, I wonder how manufacture assure the accurate dose being delivered?	**HARRIS**: Thanks for the question. Human Factors studies are needed to show the parent can follow the dosing instructions, and analytical testing is needed to confirm the delivered dose meets label requirements. Rinses of the mixing cup may be needed to achieve complete dosing - the analytical studies will inform this. And these steps are more challenging if the parent needs to dose only a portion of the constituted liquid; more analytical testing needed to show uniform dosing can be achieved. Beyond that, normal manufacturing controls need to be applied to ensure each dosage unit (e.g., sachet or tablet) meets specifications / compendial requirements.
FOLLOW-UP: Thank you for your answer. It is very common to dose a portion of the constituted liquid, e.g. suspension. Hopefully, the manufacture can resolve this issue.	**HARRIS**: Yes, I agree that approach is often needed to achieve flexible dosing. It requires that the user be accurate in measuring the liquid for constitution, and measuring the dose, and it requires the liquid be uniform (e.g., may need a suspending agent). The "manufacturing" solution would be to make more different unit doses available, but that increases cost-of-goods and some lead time would be needed to deliver new doses if the dose changes mid-study.
The STEP database is a fantastic tool, however not all excipients (e.g. co-processed excipients) are documented on the STEP database. Where would you recommend obtaining relevant efficacy and safety data for excipients not on the database?	**YAO**: Good question. I can't recommend a single method or approach to obtaining information about the safety of excipients. Much will depend on nonclinical information and we sometimes (but not always) will ask for juvenile toxicity studies in animals if there is a potential concern related to an excipient. In general, we recommend that you review all of the excipients that are proposed and consider if they are really necessary and whether there is information that support the quantity you have proposed is safe for all pediatric populations who will receive the formulation.

To Dr. Lynne Yao: Dr. Yao: Are there any studies relating the taste perception of children of various ages to the taste perception of adults?	**YAO**: I know that this is an area of research. I believe Dr. Cummins may be discussing some of this. But you raise an important point about how we study taste and how can studies in taste help us to develop products that may be better as masking taste or are tasteless.
To Dr. Nikoletta Fotaki: Thanks for the great presentation. What will be the goals of the European Peadiatric Formulary initiative in reference to the use of vehicles? Thanks	**FOTAKI:** "As far as I am aware monographs are published in this Formulary https://paedform.edqm.eu/home. So, vehicles would be noted."
To Dr. Julia Pinto: Thank you very much for the great overview. One question regarding example A: What was the reason that an in-use period of 2 hours was granted even though the drug product was stable over 24 hours in soft foods up to pH 5. Was it meant to be a security buffer or was it just not necessary to grant more than 2 hours? I am wondering what would be a reasonable buffer to take into account when granting the in-use time. Thank you in advance.	**PINTO**: In this case, the Sponsor voluntarily conducted the study out to 24 hours. However, the drug was for a single administration. The Sponsor proposed and we agreed to the 2 hour limit.
For Dr Julia Pinto: Is loss of potency over time in a vehicle sufficient to indicate stability risk of that vehicle or does a degradation, related substance, analytical method need to be used to show the stability? If loss of potency is acceptable, then what is an acceptable range, 90-110% of target or wider?	**PINTO**: Typically loss of potency is sufficient to rule out a particular vehicle. Typically outside of the 90-110% range would be considered a flag.

For Drs. Pinto/Fotaki: Can we really generalize "foods" of a certain type (e.g., test one "apple sauce" product and generalize to all apple sauces)? Physicochemical properties vary between brands, markets etc. Instead, why not focus on testing extremes (e.g., pH) rather than in the vehicle itself? "How bad can things go?" is a good motto for stability testing. (Note, here I refer only to chemical stability such as Assay/Deg., not effects on bioavailability/dissolution etc.) I look forward to discussing this more in the breakout session!	**PINTO**: Good question. I have seen data demonstrating the differences noted in the stability results with different brands of applesauce. From FDA perspective, we recognize that it is not always feasible to ask for different types of applesauce be tested. We try to make a risk assessment based on testing extremes (like a wide pH range).
For Dr. Lynne Yao: What was the FDA's rationale to have the PIP at end of Phase 2 (understand sooner is better than later) given the extent of detail the FDA has requested (excipients, quantity of excipient, stability data)? At the end of phase 2, industry is just establishing doses to test in Phase 3 and generating data for the phase 3 adult dosage form. At this time there is very little data to predict what the pediatric dose might be much less having data (stability data on a quantitative unit formula) for a pediatric formula. Thank you.	**YAO**: Yes, good question. I acknowledge that sometimes there is not enough information to provide a fully developed pediatric program. Nevertheless, the THINKING about the pediatric development program must be started before adult development is completed so FDA has required the submission no later than 60 days after EOP2 meeting. While it is true that in some programs (particularly new programs in adults) that not much is known, in many cases, there is available information from previous programs in adults and maybe even other pediatric programs. The importance is that developers need to start thinking and providing those thoughts in the PSP. Amendments to a PSP can be made as more information becomes available. I hope this helps to explain FDA's rationale.
FOLLOW-UP: Dr. Yao. Thank you for your response and reminder regarding amendments.	
Is the STEP database widely accessible?	**YAO**: Yes, here is the link: https://step-db.ucl.ac.uk/eupfi/appDirectLink.do?appFlag=login

For Dr. James Cummins: A valuable offshoot of the bitter blocker experiment could be to build correlation (or establish absence thereof) of taste perception between children and adults.	**CUMMINS**: This is a great idea. The taste field typically starts with adult taste panels (which our project is doing), but we have to understand that correlation between adults and children.
For Dr. Viera Lukacova, are the physiological parameters in slide 11 including variability?	**LUKACOVA**: Yes, they are included when available in literature (or if we can derive them reliably from in vivo data). The variability was not shown specifically in that slide, but the values are included in the program and used in population simulation - they will be displayed when you are setting up the population simulation.
For Dr. Stephan Schaller: Nice presentation. I just want to let you know that we published one paper by pksim for pediatric absorption. Evaluation of Physiologically Based Pharmacokinetic Models to Predict the Absorption of BCS Class I Drugs in Different Pediatric Age Groups Xiaomei I Liu 1, John N van den Anker 1 2, Gilbert J Burckart 3, André Dallmann 4 Affiliations expand PMID: 34185902 DOI: 10.1002/jcph.1845	**SCHALLER**: Thanks! I will make sure to take this up as an example