PEDIATRIC FORMULATION DEVELOPMENT: THE MOST COMMON QUESTIONS I GET ASKED

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Q & A:

1: Question: What is the best/right dosage form for our pediatric development?

Answer: There are a number of considerations, but one of the most crucial decision points is defined by the minimum dosing age. Chewable/ODTs and minitablets are popular choices but are not appropriate for patients < 2year olds. For these younger patients, a liquid type of dosage form is usually targeted. For reference, the EMA published a reflection paper, "*Formulations of Choice for the Pediatric Population*," which provides some additional information on the subject.

2: Question: Are there significant difference between the U.S. and European requirements for pediatric development?

Answer: There are a number of regulatory differences surrounding the timings for various filing activities, as well as requirements for the pediatric study plan. From a formulation development stand point the European commissions tend to expect additional justifications surrounding excipient usage and selection, especially pertaining to preservatives, flavors, and sweeteners.

3: Question: Are there major differences in the acceptability of formulation components according to the patient's age?

Answer: There are some pretty significant differences related to the acceptability of excipients; and also major differences around body surface area, intestinal volume, and metabolism based on patient age. As a general reference there are "landmark" changes observed at 0-30 days, 30 days-6 months, < 2 years, and 2-5 years. Consideration should also be given to regulatory acceptance based on where the sponsor intend to seek a filing when selecting excipients; not all countries hold every excipient in the same status.

4: Question: Where can I find information concerning excipient acceptability and/or usage in pediatric formulations?

Answer: This information is decentralized but referencing the "Allowable Daily Intake" (ADI) and eIIG Database are good places to start. The information included in these resources is not specific to pediatrics though so excipient selections should also be vetted by verification of pediatric safety and history of prior use. Some information can be found in the STEP Database concerning pediatric safety studies for excipients.

5: Question: What are some of the differences between a pediatric development program, and something targeted for adults?

Answer: Obviously, dose range and dose accuracy are more important for pediatric development and requires a formulation with higher uniformity compared to adult formulations. But as I specialize in liquid/PFOS and semi-solid dosage forms, we spend significant additional effort to evaluate and select formulation components. This includes reviews of toxicology and regulatory status. We also have a data base of pediatric package inserts which helps sponsors establish the history of safety and prior use. There are also usually additional studies to justify preservatives, dose accuracy/uniformity, and formulation stability to satisfy EU compliance that are not needed for adult formulations. The FDA and EMA also tend to ask for a palatability study to justify/establish use of sweeteners and flavors. It is also important to note that the selection of the target label claim should take into consideration the dose volume and should include awareness of acceptable delivery volume per the pediatric age group.

A Word from the Author: *It is important to carefully consider the patient population and minimum age before committing to a development path. Another area where I have observed sponsors struggle or hit unexpected program/clinical delays is from regulator justification during filings. In short, skipping steps to speed up development timelines can be a problem on the back end. This may make it sound daunting, but with proper planning, background knowledge, and upfront effort, these programs can fly. On that subject I have provided a number of references below for additional information.*

Program success is important to me personally. I truly find developing products that help children grow up happy and healthy one of the most rewarding parts of my profession.

U.S. Acts and Guidances

-Best Pharmaceuticals for Children Act (BPCA) – voluntary incentive.
-Pediatric Research Equity Act (PREA) (Public Law No: 108-155)
FDA Guidance to Industry - Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans
-Pediatric Review Committee (PeRC) (Public Law No: 107-109)

U.S. Statutes and Regulations

-FDA Reauthorization Act (2017): See Title V for Pediatric Changes
-FDA Safety and Innovation Act (2012): See Title V for pediatric drugs and devices
-Food and Drug Administration Amendments Act of 2007: See Title IV for full text of the Pediatric Research Equity Act of 2007 and Title V for full text of the Best Pharmaceuticals for Children Act of 2007.
-PREA Retrospective Review (PDF - 281KB) 1/14/2010
-Rare Pediatric Disease Priority Review Voucher Program Section 908 of FDASIA

FDA Guidance Documents

-Guidance for Industry (Draft): How to Comply with the Pediatric Research Equity Act.
-Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act.
-Pediatric Oncology Studies in Response to a Written Request
-General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products.
-Content and Format of Pediatric Use Supplements.
-Nonclinical Safety Evaluation of Pediatric Drug Products.
-Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients.

Non-FDA and EU Guidance Documents

-ICH- E11 Clinical Investigation of Medicinal Products in the Pediatric Population.
-American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations" (April 2010)
- EU Regulations (EC) #1901/2006 and 1902/2006; medicinal products for pediatric use.
- EMA reflection paper; Formulations of Choice for the Pediatric Population, 2006

PRESENTOR BIOGRAPHY

Travis Webb is a Principal Scientist with the Product Development Group and has a Master of Science in Pharmaceutical Chemistry from the University of Florida and has worked in the pharmaceutical and biotech industry for 18 years, with a focus on oral formulation and analytical development. He has worked on over thirty pediatric programs, bringing 4 products to market, 1 currently on submission, and several in various clinical stages in the U.S. and Europe over just the last 5 years.

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