PEER REVIEWED

Reaching the Marketplace

Understanding the Complexities of Paediatric Drug Development and Manufacturing

Bringing a paediatric drug product to the marketplace can be very complex and also incredibly important as it increases the limited treatment options available for children, especially for niche and novel medications. The formulation development and manufacturing of paediatric medications poses unique challenges compared to that of adult medications. Developing safe, effective, and age-appropriate drug formulations for children requires a careful consideration of factors such as taste, dosage form, dosing accuracy, and palatability. Adhering to strict guidelines and best practices in the manufacturing process enables pharmaceutical companies to ensure that their paediatric patient is receiving the medication exactly as intended. Exploring the key challenges encountered in the formulation development and manufacturing of paediatric medications enables us to address and continually improve the healthcare outcomes of children.

Paediatric medications prompt a very specific set of challenges. They are required to reach across a broad age and developmental range, must be easy to swallow correctly, while being palatable to the patient, as well as being administered with ease at the point of care. Hence, these medications have very stringent guidelines that regulate their development, manufacturing, and packaging. Having the knowledge and expertise to navigate the regulatory complexities it is therefore essential to making sure that when the drug product reaches the marketplace it can be held to the highest quality, integrity, and safety standards.

One of the significant challenges in paediatric formulation development is ensuring palatability and taste-masking. As children are often sensitive to taste, this can create difficulties in administering medications due to their aversion to bitter and unpleasant flavours. Ensuring that medications are palatable is also crucial in supporting adherence and compliance and foster treatment plan effectiveness. Making use of various techniques such as flavouring, sweeteners, or encapsulation to mask the bitterness and enhance palatability is therefore essential. However, the taste-masking techniques can be complex and may affect the stability and bioavailability of the medication.

To establish the suitability and effectiveness of a medication such as mini-tablets, formulation scientists must conduct food-drug interaction studies. Food exposure assessments covering the dose range are carried out for multiple exposure times, mimicking in-use practices performed by parents and guardians. Carrying out this research is vital in establishing the effect that the food has had on the physical structure, assay, impurity and dissolution profile of a medicine. These studies should be carried out on new and aged mini tablets, demonstrating consistent characteristics throughout the shelf life of the drug to ensure effectiveness. In addition, the formulations must consider factors such as age-appropriate flavours, allergies, and other potential interactions. Finding the right balance between effectiveness, safety, and palatability is essential in paediatric medication development

The paediatric patients span a wide age range, from newborn to adolescents, each with unique anatomical and physiological characteristics. Ensuring the safety and effectiveness of medications across various age groups requires extensive testing to account for all the developmental differences and side effects that can occur. As children's bodies metabolise drugs differently at various stages of their development, formulation scientists need to have a thorough understanding of age-specific pharmacokinetics and pharmacodynamics.

It is also essential to consider age-appropriate dosage forms that are easy to administer, safe, and suitable for any given developmental stage of a child. Infants and young children may require liquid formulations, while older children may have the ability to swallow tablets or capsules. Developing child-friendly formulations, such as mini-tablets, powders and granules, liquids, and orodispersible tablets calls for extensive research and formulation optimisation.

Recent clinical studies have shown that for children aged between six months and six years, mini-tablets provide equal acceptance rates when compared with sweet-tasting syrup formulations, similar to those that have been historically used for paediatric patient populations.[1] The industry is also experiencing an increase in demand for the more traditional powder/granule formulations, which are filled into sachets or bottles for re-constitution at the point of care. However, there are additional technical considerations associated with the development of these specialised formulations. These can range from developing formulations with the right flow characteristics, to analytical studies designed to demonstrate the in-use stability for re-constituted formulations, or the compatibility of the formulations with various foods and other methods or routes of administration to the patient such as the nasogastric tubes.

Accurate dosing is critical for paediatric medications, as under-dosing can result in therapeutic failure, and over-dosing can lead to adverse and sometimes perilous effects. However, dosing accuracy is equally challenging due to the variations in body weight, age, and developmental stages of children. Formulations must be continually tested during their manufacturing process, to ensure uniform blend consistency throughout the batch. The weight of formulations should also be checked, and in some cases counted, throughout the manufacturing and packaging process, to warrant accuracy in dosage forms.

There should be a focus on simplifying dosing calculations, providing appropriate measuring devices, and offering a range of dosing strengths to facilitate accurate administration at the point of care. A range of varied packaging solutions enables a pharmaceutical company to select the most suitable delivery method for their treatment. Child-safe, tamper-evident packaging solutions such as sachets, bottles, and blister packs are ways of safeguarding young

children and at the same time complying with all the regulatory guidelines, while still remaining user-friendly for adults. All packaging should be checked and weighed, such as weighing bottles prior to, and after filling for example, to maintain accuracy throughout the process. Solid oral dose medications delivered in specific weighed solutions such as stick packs and sachets allow pharmaceutical companies to have a higher level of control that the correct dosage amount will be administered to the patient without under or over-dosing occurring.

As is the case with adult formulations, paediatric formulations, also need to maintain stability and potency over their intended shelf life. Various factors such as temperature variations, light exposure, and moisture can affect the stability and effectiveness of medications.

Developing stable formulations that retain efficacy and palatability throughout their shelf life is especially challenging for liquid dosage forms. Extensive stability studies should be carried out to assess the physical, chemical, and microbiological stability of paediatric formulations under different storage conditions.

Selecting the correct packaging for a drug product is also key in ensuring the intended shelf life is upheld. Moisture-resistant and dosage specific packaging aids maintaining the desired therapeutic properties of the medication by protecting the drug product from external factors. Paediatric medications often require an extended shelf life to accommodate their storage and administration over prolonged periods of time, therefore their packaging must also be able to complement this purpose. For instance, an orodispersible tablet will require moisture-resistant packaging, making it unaffected by where it's stored and able to retain its intended efficacy.

The fact that paediatric patients have different physiological characteristics from adult patients has an impact on drug safety and pharmacokinetics. Children's physiological and developmental differences from adult's present unique challenges in drug development. Factors such as metabolism, maturity of organs, body composition, and cognitive development, all have an influence on drug response and safety. Therefore, understanding these variations is crucial for developing safe and effective paediatric medications.

Preclinical and clinical studies enable the development of safety profiles to ensure that the medication does not pose potential risks to paediatric patients. They aim to provide data that helps to guide the dosing recommendations and inform many formulation decisions. However, there is a limited availability of paediatric clinical trial data which poses a challenge in development. This is partly due to ethical concerns regarding clinical trials in children. Regulatory agencies have strict requirements for paediatric-specific studies, which leads to a lack of comprehensive information on dosing, safety, and effectiveness in

paediatric populations. Hence, formulation scientists must rely on the extrapolation of data from adult patient studies and pharmacokinetic modelling to bridge the knowledge gap and inform decisions.

The development of paediatric medications involves navigating various complex regulatory requirements. Regulatory agencies have specific guidelines for paediatric drug development to ensure patient safety and efficacy. For example, EMA Paediatric regulation (26 January 2007) sets out "to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately and improving the availability of information on the use of medicines for children. It aims to achieve this without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults".[2] While being extremely important, compliance with these guidelines can be time-consuming and costly, and require obtaining informed consent from parents and guardians. Balancing the potential benefits of new drugs against the risks involved entails careful assessment and stringent ethical guidelines. These factors, in turn, result in a limited number of approved paediatric formulations. Familiarisation with the current guidelines from the early phases of development leads to a clearer and definite adherence and is crucial to improving access to safe and effective medications for children.

Many pharmaceutical companies choose to engage with a contract development and manufacturing organisation due to the high level of knowledge required and the restrictions surrounding paediatric treatments. Outsourcing to a provider who has a track record in paediatric medication production means that the knowledge base, technical experience, and equipment trains are already in place. The benefit of using an end-to-end single source provider also enables a seamless transfer of knowledge from early phase development through to manufacturing, and into commercialisation; along with providing access to dedicated teams of scientists, project managers, quality, regulatory, artwork, and packaging experts that are focused on the product and the end-user. This helps to manage costs and ensure that regulatory requirements are adhered to the highest standard throughout the process. Engaging with an established and experienced provider can be key to marketplace success during the development and launch of paediatric medications, especially when it is the first

paediatric treatment that a pharmaceutical company is looking to produce.

Formulation development and manufacturing of paediatric medications is a complex task that requires careful consideration of a multitude of factors that are highly specific to the demographic. The challenges related to taste and palatability, dosage form selection, dosing accuracy and safety, drug delivery, and regulatory hurdles, all need to be met and overcome to ensure optimum outcomes for the patient. Developing a comprehensive understanding of paediatric pharmacokinetics, physiology, and patient needs can contribute to improving the development of paediatric specific medications. Making sure the correct dosage form is selected for the appropriate route of administration to the patient, and stringent testing as well as check-weighing are performed throughout the manufacturing process, guarantee that safe and effective medications are delivered at the point of care. The main responsibility lies with the pharmaceutical company (and CDMO if used) to ascertain that all testing has been rigorously carried out, the regulatory standards are met, and the medication is provided in child-safe packaging that clearly defines dosage by age and/or weight, dosage method, and usage instructions.

Most importantly, by working through the complexities with the patient and caregiver in mind, pharmaceutical companies are able to develop effective and patient-friendly formulations that provide a wider availability of dosage forms and improve the treatment options available for children.

REFERENCES

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Tom Hegarty

Tom Hegarty, Director – Operations, Manufacturing for Almac Pharma Services, has worked in the pharmaceutical industry for over 25 years fulfilling various technical, operational and managerial roles. During this time, he has worked for large multinational and smaller regional based companies. His current responsibilities include pharmaceutical formulation development, technical support and strategic capital investment projects.