Asian Journal of Medical and Pharmaceutical Sciences
Journal Home Page: www.pharmaresearchlibrary.com/ajmps
ISSN (Online): 2348-0165 | Publisher: Pharma Research Library
A. J. Med. Pharm, Sci., 2024, 12(1): 26-29
DOI: https://doi.org/10.30904/j.ajmps.2024.4637

Regulatory aspects on drug development for pediatric Populations

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A b s t r a c t

The study aimed to investigate the current regulations guarding the approval and maintenance of the pediatric drugs. This review gives an overview of the regulatory aspects for pediatric drug development and their influence on practical and scientific considerations when conducting clinical studies in children. M&S as an efficient means to extract knowledge from the data will be discussed subsequently, rounding off the process of pediatric study planning, conduct, and evaluation. Numerous regulatory documents are available to guide pharmaceutical companies through the specific procedures and to answer specific scientific questions regarding study design and conduct. Since pediatric drug development is a very complex area, many questions remain open, and close collaboration and communication between industry and health authorities is essential. Numerous regulatory documents are available to guide pharmaceutical companies through the specific procedures and to answer specific scientific questions regarding study design and conduct. Since pediatric drug development is a very complex area, many questions remain open, and close collaboration and communication between industry and health authorities is essential. The paediatric population requires special considerations for prescription of medicines due to their under developed physiologic systems. Any negligence of this very aspect can lead to often deleterious side effects. For these very reasons there is a need to develop guidelines and regulations in India, similar to other regulated and emerging markets, for the welfare of the paediatric population.

Keywords: Paediatric population, regulatory documents, pediatric drugs, U.S. and E.U.

A r t i c l e I n f o

***Corresponding Author:**	**Article History:**
N.V.V.S. Swami	**Received** : 10 Sept 2023
Department of Regulatory affairs,	**Revised** : 28 Oct 2023
K.G.R.L College of Pharmacy,	**Accepted** : 24 Dec 2023
Bhimavaram, Andhrapradesh	**Published** : 18 Jan 2024

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Citation: N.V.V.S. Swami, *et al. Regulatory aspects on drug development for pediatric Populations*. *A. J. Med. Pharm, Sci.*, 2024, 12(1): 26-29.

C o n t e n t s

1. Introduction

Over the past decade, regulatory legislations for drug development in pediatric patients were passed worldwide, dramatically increasing the number of drug stested in and labeled for children. Both, the Food and Drug Administration (FDA) in the United States (U.S.), and the European Medicines Agency (EMA) in the European Union (E.U.), established approaches that have been successful in generating important new information about the safety and efficacy of drugs used by children [1,2]. Transparency and accountability of pediatric drug development has improved and the amount and quality of pediatric information was increased by an elevated number of clinical trials in children in recent years. The progress was achieved by combining requirements for pediatric drug development with incentives for the pharmaceutical industry to (at least partly) cover the additional investment for testing drugs in children. There was and still is effort needed to harmonize the regulatory framework for pediatric drug development,

but as of today pharmaceutical companies are still facing the problem that the regulatory requirements differ between FDA and EMA and that the development of a new drug in the pediatric population has to be in line with requirements from both authorities. Enforced by the authorities-in particular he EMA-pediatric aspects have to be integrated early in the development process of a new drug and the general strategy has to be part of the overall development program[1].

2. Materials and Methods

Regulatory Aspects of Pediatric Drug Development

U.S. perspective

Historically, only a small fraction of all marketed drugs have had clinical trials performed in pediatric patients and a majority of marketed drugs were not labeled for use in pediatric patients. Accordingly, many drugs were administered to children in an off label fashion without adequate understanding of appropriate dose, safety, or efficacy.

The first initiative took place in 1994 when the Pediatric Labeling Rule was issued, requiring drug manufacturers to survey existing data and to determine whether those data are sufficient to support additional pediatric use information in the drug's labeling. Under the Pediatric Labeling Rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the label change.

The Pediatric Labeling Rule allowed the labeling of drugs for pediatric use based on extrapolation of efficacy in the adult population and additional pharmacokinetics, pharmacodynamics, and safety studies in pediatric patients, but only if the course of the disease and the response to the drug were known to be similar in children compared to adults. Although this rule was designed to improve pediatric labeling, only a small number of well designed and well conducted studies subsequently resulted.

The submission of information could be deferred, e.g., if pediatric studies should not begin until information on adults had been collected, or incase the collection and filing of pediatric data would delay the availability of a product that provides a significant therapeutic advantage in adults. The requirement would be waived for some or all pediatric age groups if, e.g., the product did not represent a meaningful therapeutic benefit over existing treatment or the product would likely be unsafe or ineffective in pediatric patients.

Main Pillars of E.U. regulation

In general, the objective of the E.U. regulation is to improve quality and ethical research into medicines for children, increase the availability of authorized medicines for children, and to increase available information on medicines for children without unnecessary studies in children and without delaying authorization for adults.

Pediatric Investigation Plan (PIP): A PIP is the basis for development and authorization of a medicinal product for the pediatric population subsets (i.e., the different age groups, see. It has to be submitted upon availability of adult PK studies, i.e., at an early phase of development of a new compound (after Phase 1). The PIP has to be agreed upon and/or amended by the PDCO and is binding for the company. If new information becomes available during the development, it is possible to apply to the PDCO for a modification of the agreed upon PIP[2].

Comparison of U.S.(FDA)and E.U.(EMA) regulations

The primary goal of the E.U. and U.S. legislations is identical: to improve children's health through advancements in research and to provide a frame work for evaluation of efficacy and safety in the pediatric population. The U.S. and the E.U. legislation show substantial differences though. The E.U. legislation unifies the incentives and requirements under one legislation and the changes occurred in a shorter time frame: since July 2008 (18 months after entry into force), all applications for new marketing authorization must contain results of studies conducted in compliance with an agreed PIP unless a waiver or deferral was granted; since January 2009 (24months after entry into force) all applications for new indications, new routes of administration, or new pharmaceutical forms must contain results of studies in compliance with the PIP unless a waiver or deferral was granted[3].

3. Results and Discussion

Modeling and Simulation in Pediatrics

The regulatory guidance documents cover various practical and ethical considerations for pediatric studies, but nevertheless, performing clinical trials in children remains a challenge and many special requirements and considerations have to be addressed up front. Obviously, specialized tools that can help in designing and analyzing pediatric studies need to be considered and explored.

Optimal design

The evaluation and optimization of the study design becomes more and more important due to the limited number of studies, the low number of individuals and samples leading to the need of optimized and thus most informative sampling times. Prior information (e.g., PK in adults including covariates and the distribution of covariates of pediatric patients) can be employed to evaluate a sparse sampling strategy[4].

Pediatric formulations

The oral route of administration is commonly used for dosing to children and, therefore, many medicines should be available in both, liquid and solid oral dosage forms, in order to target a wide age range. Liquid formulations, for instance, are most appropriate for younger children who are unable to swallow capsules or tablets. Parenteral formulations are commonly used in neonates and extrac are should be taken with respect to drug concentrations and choice of excipients.

Current Scenarioin India:

In India, paediatric drugs are developed based on clinical trials and protocols for a healthy adult human. There are no specific drug development regulations for paediatrics. Indian clinical practice relies heavily upon safety and efficacy data published in other developed countries, or inference from adult dosing. Lack of paediatric specific guidelines has led healthcare providers and caregivers to estimate the dose (either for therapeutic use or for carrying out clinical trials) by breaking tablets into quarters and halves, crushing tablets, or opening capsules, or if it is liquid, by proportionally reducing volume. Administering medicines in this way is difficult and can cause in accurate dosing, which may result in reduced efficacy (due to under dosing) and/or compromise safety (due to over dosing). Children are not small adults. They have different pharmacokinetic and pharmacodynamic responses as compared to adults. These differences are mainly due to differences in body water and serum protein composition in the paediatric population. In addition, children, particularly newborns, may suffer from illness specific to their age group that requires medicines not available for adults[5].

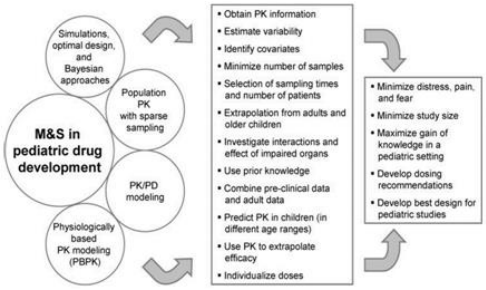

Figure 1: M & Scan help in different ways to reach this goal

Discussion:

The combination products that are discussed here are the drug-elutingstents. The first drug eluting stent was approved by the FD Ain2003 and was a Johnson & Johnson Cord is Corporation product. In the span of 10 years from 2003 to 2012, 16 drug eluting combination products were approved and released in to the market. Six leading medical device manufacturing companies are producing these combination products. Of these 16 stents, Cook's product Zilver PTX drug-eluting peripheral stent was withdrawn from the market. Cook identified the reason for this as then on conformance of the design criteria for the inner component of the delivery system. On the whole, only one product has been recalled from the market out of the 16 products, or withdrawal rate is 6.25% in10 years. Except for the recall of Zilver PTX, all of the other issues are minor and can be rectified with the proper marketing of the companies and better post market surveillance of the FDA. Sixty Class III medical devices have been approved by the FDA between 2010 and 2012 and 15 devices were withdrawn from the market due to various reasons, during the same period for a withdrawal rate is 25%. Of the 209 New Chemical Entities that were approved by the FDA between 2010 and 2012 are 209 two were removed from the market as of June 2013. The withdrawal rate is currently ~1%[6].

The frequency of the market withdrawal of combination products, devices and drugs is approximately 6%, 25% and 1%, respectively. While the numbers are very small with limited time on the market, it appears that the withdrawal rate for the combination product used as an example falls between that for devices and drugs. It appears that the FDA has not found the review of combination products appreciably more difficult than that of the other classes as judged by market success. Further data will be required to make a more definitive statement as further marketing history is generated for this new product type[7].

4. Conclusion

The health authorities in the U.S. and the E.U. show a strong commitment to promote better medicines for children. The pediatric legislations have built a complex framework for pediatric drug development and the pharmaceutical industry has to deal with different requirements and special obligations to receive the incentives. The preparation of the PI Pisa major task for each clinical development team and pediatric aspects have to be integrated early in development. The regulatory authorities reviewed a substantial number of pediatric evaluations in recent years and pharmaceutical companies become familiar with the pediatric regulations. Numerous regulatory documents are available to guide pharmaceutical companies through the specific procedures and to answer specific scientific questions regarding study design and conduct. Since pediatric drug development is a very complex area, many questions remain open, and close collaboration and communication between industry and health authorities is essential. Surprisingly, the number of companies using the free pediatric scientific advice is low compared to the number of submitted PIPs. Although the pediatric scientific advice is not binding, an open discussion about the pediatric strategy up front can improve information exchange and reduce the time for the entire PIP procedure. Even though the guidelines cover various important aspects, the pediatric strategy is highly dependent on the properties of the drug, on the disease, and on the pediatric population and has to be defined carefully for each drug and indication. Similarly, pediatric studies vary widely and many procedural and scientific considerations (e.g., age categories, dose finding, PK sampling, pediatric formulation) are indispensable and an extraordinary challenge for each study team.

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