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RESEARCH ARTICLE

ROLE OF REGULATORY BODIES IN PEDIATRIC PRODUCTS AND PEDIATRIC DRUG EXCLUSIVITY WITH SPECIAL REFRENCE TO US, EUROPE AND JAPAN

Shikha Saxena[*1], Divya Sadhna[1] and Nishi Singh[1]

Amity Institute of Pharmacy, Amity University, Sector 125, Noida-201313 ,Uttar Pradesh

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Corresponding Author

Shikha Saxena

Abstract

In the present scenario, children's are considered as small adults during administrating medication to them. The dose for children are usually given by crushing tablets, breaking tablets into halves and quarters, opening capsules, or for liquids, by proportionally reducing volume. More than 60% of all medicines used for children have never been tested and even lack authorization in the pediatric population. Several barriers may be encountered while working for the development of formulation for the pediatric population. The challenges include ethical issues, monetary concerns, type of formulation preparation, dosing, bioavailability and drug response measuring techniques. Due to diversity of children in different age groups, the consent, ethical implication and selection process, clinical studies in children differs from studies in adults. So as to obtain as much information as possible from data derived from trials in children, the modeling and simulation method is good option to support pediatric study design. The model based development of pediatric drug helps by aiming at efficiency. To encourage pharmaceutical sponsors to carry out clinical studies in the development of pediatric indications for drugs and biologics, Congress and United States Food and Drug Administration have granted perk of marketing exclusivity. India needs a pediatric legislation which should be built of a strong framework for pediatric drug development. There is a need to set a pediatric research committee which would lay down standard regulation for the pediatric drug development. Market exclusivity will encourage the sponsors to develop the pediatric specific drugs which would be safe and efficient.

INTRODUCTION

In the present scenario, children's are considered as small adults during administrating medication to them. Due to lack of guidelines specified for pediatric, the healthcare providers and caregivers estimate the dose for therapeutic use and for carrying out the clinical trials. The dose for children are usually given by crushing tablets, breaking tablets into halves and quarters, opening capsules, or for liquids, by proportionally reducing volume [1]. Inaccurate dosing occurs by following such method of reducing dose without understanding the basic concept of need of exact dose for pediatric population. This further leads to reduced efficacy due to under-dosing and/or compromise safety due to overdosing. The article by Le Cam, Y. entitled "Medicines for children: better, more and faster", reveals that more than 60% of all medicines used for children have never been tested and even lack authorization in the pediatric population. The trend is to test the drug in adults, even not necessarily in the same indication or same disease. The first step of developing a drug for particular population of patient is to know the pharmacokinetic and pharmacodynamic pattern. Pediatric population shows difference in pharmacokinetic and pharmacodynamic

responses as compared to adults. The variation in response is due to difference in serum protein composition and body water in the pediatric population. There are sufficient examples of adverse effect cases, occurred due to irrational use of drugs in children. There is a need for regulatory efforts which would protect children from harmful medications. The guidelines are required which would lay down the standards for clinical trial design for pediatric products. Like other drug product categories, pediatric products also require regulations for efficacy, safety, marketing and prescribing standards.

PURPOSE

This review article endows age classification of pediatric patients, ethical issues and clinical trial design for pediatric population. It also discusses the need for guidelines which would regulate the efficacy, safety, marketing and prescription of drugs for pediatric population. Comparison of European Union regulations, United States regulations and Japanese's regulations has also been done in this paper.

BACKGROUND

Pediatrics deals with the medicinal care for newly born children up to the age of 18. Pediatrics is the subdivision of medicine. The physiologies of children's are different from that of adults. Till the age of 18, physiology keeps on developing and hence requires different treatment method as compare to adults [2]. No standard treatment can be norm for all age groups. The age classification of pediatric patients along with special feature of that age is [3]:

Preterm newborn infants	• Unique spectrum of diseases • Unique response to treatment • Rapid development and differences in their body function
Term newborn infants (0 to 27 days)	• Volumes of distribution may be different than those in older pediatric patients • Blood-brain barrier is not fully mature • Oral absorption may be less predictable • Hepatic and renal clearance mechanisms are immature and rapidly changing
Infants and toddlers (28 days to 23 months)	• Rapid mental. Physical and immune development • Elimination of drugs from the body may exceed that in adults
Children (2 to 11 years)	• Large variation and variability in development • Onset of puberty is highly variable and heralds a time of accelerated growth and marked change which may alter response to medications and doses required
Adolescents (12 to 16-18 years)	• Sexual maturation • Medicinal products may intervene with the actions of sex hormones and impede development • Rapid growth and continued neurocognitive development

Table 1: Age Classification

The irrational use of drugs for children has lead to many unpleasant adverse effects cases. The point to be noted is that all these adverse drug reactions occurred at lower doses than in adults. The list of drugs along with the related adverse drug reactions (ADRs) are:

Drug	Adverse Drug Reaction
Over-The-Counter cough and cold medicine containing Dextromethorphan* [4]	Rapid heart rate Convulsions
Ciprofloxacin [5]	Risk of arthropathy
Non Steroidal Anti-inflammatory Drugs (NSAIDs) [6]	Gastrointestinal bleeding
Sodium valproate [7]	Hepatotoxicity

Salicylates [8]	Incresed risk of Reye's syndrome
Corticosteroids (long term use) [9]	Growth suppression/effect
Chloramphenicol [10]	Grey baby syndrome in neonates

*FDA discourages use of cough and cold medicines for children younger than age 2.

Table 2: Drugs and Related ADRs in children

The formulation is composed of active pharmaceutical ingredient and excipients. It is important to note that the selection of suitable excipients in a pediatric formulation is the most critical step of pharmaceutical development [11]. The excipients that induced ADRs in children are:

Ethanol toxicity [12]	Intoxication Lethargy Stupor Coma Respiratory depression Cardiovascular collapse (If used above permitted quantities)
Azo dyes [13]	Hypersenstivity
Propylene glycol [14]	Hyperosmolality Lactic acidosis
Antiasthmatic drugs containing Benzalkonium chloride [15]	Bronchospasm
Benzyl alcohol toxicity [16]	Metabolic acidosis Seizures Bradycardia Gasping respiration Hypotension Cardiovascular collapse
Aspartame [17]	Headache Seizures

Table 3: Excipients and related ADR's

The need for special consideration for pediatric population for prescription of medicine is essential. This will give better and reliable treatment to this special population. The guidelines and regulations for the pediatrics are available in other regulated and emerging market. The need of regulation for pediatric population for Indian market is now need to be fulfilled.

CHALLENGES FOR DEVELOPMENT OF PEDIATRIC DRUGS

Several barriers may be encountered while working for the development of formulation for the pediatric population. The challenges include ethical issues, monetary concerns, type of formulation preparation, dosing, bioavailability and drug response measuring techniques. It is quite obvious that without testing pediatric drugs, it would be impossible to understand that what safety signals to watch for and how to manage them. Apart from that, there would be pediatric population specific adverse event which would remain unknown [18].

Ethical issues: To be the part of research for the development of formulation, children need to consent to participate in studies, which is not possible. Three core ethical rules that would guide pediatric drug development are [19]:

(i) The enrollment of children in research should only be allowed only if it is necessary to reply an important scientific doubt about the health and welfare of pediatric population.

(ii) Complete analysis of the protocol of research should be done so as to calculate the benefit to risk ratio along with comparing it to alternates available for the treatment of specific condition for the research involving pediatric population.

(iii) If the research results in no direct benefit to pediatric population, it should be limited to that offering minimal risk.

Ethical considerations are and will remain important aspect of pediatric drug development studies. There is a need for the better definitions of risk categories, benefit to risk analysis, strategies to overcome adverse events and other concepts.

Monetary concerns: The major barrier for the pediatric favored formulation is the economic factor. This is due to the relatively small market size and deemed large risk. Apart from that, for the small companies, the cost of maintain the sale of pediatric drug is more [20]. Another issue is that, the pediatric population need is further categorized according to the need for different formulations and dosing for various age groups. High risk is involved in the testing of pediatric drugs in children. In case of adverse event encountered sponsors have to face product liability risk.

Dr. Giacoia enlisted solutions to the economic barriers for pediatric drug development studies. The following are the solutions ruminated by the Economics and Partnerships Working Group of the Pediatric Formulations Initiative:

- Developing global standards for oral liquid preparations, and expanding the market for such preparations by combining incentives for pediatric population.
- An effort to reduce cost, risk, and time to launch a drug in market.
- Using already existing formulations.
- Import approved pediatric drugs from other countries like Europe, United States after addressing legal, regulatory, and legislative issues.
- Limiting exclusivity, generating funding, and tax breaks.
- For priority extemporaneously formulated drugs, incentives may be rewarded.
- Establish public–private partnerships for drug categories like orphan drugs.

Type of formulation: Swallowing pills is not possible for children. They may spit out chewable tablets and even odor of the formulation would enable them to take the dosage form. This results in manipulation of formulations for the children which may be unsafe for them. Maximum formulations are in the form of oral liquid preparation, which are dispensed from droppers or teaspoon. They still lack accurate dose administration as tableware teaspoon varies in capacity from 4 to 7 mL. There is a need to identify regulatory issues that would affect the development and approval of drugs for pediatric population.

Dosing, Bioavailability and drug response: Due to very little information available for the action of drug in pediatric formulation, label information is not sufficient to follow the instruction. The available scientific literature to estimate dosing for children is not sufficient. There is available data which would prove that how pharmacokinetic and other functions are different in important ways among premature infants, full-term infants, children and adolescents. The dosing technique should either be based on weight or surface area; this remains point of discussion [21].

RESEARCH COMMITTEE FOR PEDIATRIC DRUG DEVELOPMENT

To begin with, a separate department is required which would deal with research, development, market authorization and adverse effect reporting specific for pediatric population. The adverse effect reporting system should be globally recognized so as to gather as much information for a particular drug product. Central Drug Standard Control Organization, India should take up step to lay down regulations and legislation for the benefit of this special population. The regulation which would summarize the regulatory requirements and strategies for the development of pediatric drug from industry perspective would help in resolving issues related to pediatric-specific drugs. Current requirement of the system is the complete study plan and conduct, dose consideration, sampling techniques, method for generation of data and analysis of data to generate knowledge about the pharmacokinetics and pharmacodynamics of a drug in children [22].

PEDIATRIC DRUG DEVELOPMENT: ESSENTIAL CONSIDERATIONS

While developing formulation for children, certain things are needed to be kept in mind. These are [23]:

- The minimal dosage frequency for children
- The particular dosage form should fit all or a full range
- The impact of the formulation should be minimal on the lifestyle especially for adolescents
- The excipients used in formulation should be non-toxic

- The administration of formulation should be convenient, easy and reliable
- The formulation should be easy to produce, elegant and should stay stable till the shelf life
- The drug should b commercially viable and formulation should be cost effective

All the information should be submitted to regulatory authority so as to get market authorization of the product.

IMPORTANT STUDY COMPONENTS FOR PEDIATRIC DRUGS

Due to diversity of children in different age groups, the consent, ethical implication and selection process, clinical studies in children differs from studies in adults. The significant study components involve:

- Efficacy studies
- Pharmacokinetics and Pharmacodynamic studies
- Pediatric assessment report- which would work as post marketing commitment
- Safety studies
- New dosage form strength studies
- Administration frequency

MODELING AND SIMULATION IN PEDIATRICS: BENEFICIAL METHODOLOGY IN DRUG DEVELOPMENT

So as to obtain as much information as possible from data derived from trials in children, the modeling and simulation method is good option to support pediatric study design [24]. The model based development of pediatric drug helps by aiming at efficiency. The modeling and simulation method helps in developing new drug in following ways:

- Obtaining pharmacokinetic information
- Estimating variability
- Identifying covariates
- Minimizing the number of samples
- Selecting sampling times and number of patients
- Extrapolation of the data obtain from adults and other children
- Investigating drug interaction and effect of impaired organs
- Using prior knowledge
- Compiling pre-clinical data and data obtained from adult's study report
- Using pharmacokinetic information so as to extrapolate efficacy
- Individualize the doses

This study methodology would minimize distress, pain and fear of involving children in research studies. It will not only minimize the study size but also maximize gain of knowledge in a pediatric population. Dosing recommendation and best design for pediatric study development would also be easy by following this method.

PEDIATRIC DRUG EXCLUSIVITY

So as to encourage pharmaceutical sponsors to carry out clinical studies in the development of pediatric indications for drugs and biologics, Congress and United States Food and Drug Administration have granted perk of marketing exclusivity. The benefit of market exclusivity can be availed only if certain provisions and requirements are met. The main aim of such legislation is to bring about the change in labeling of existing drugs for pediatric use specifically. A sponsor may ask for a waiver for the obligation to be submitted as a pediatric assessment for reasons such as in case of lack of data concerning safety, efficacy, or impracticability for a pediatric population. In such condition, FDA demands that the waiver should be included in the product labeling so that physicians should be informed before using the drug for an off-label pediatric purpose. By obtaining market exclusivity for particular product, the sponsor retains sole rights to all forms of a drug product line containing the active moiety [25].

CONTRADISTINCTION OF PEDIATRIC REGULATIONS AMONG E.U., U.S. AND JAPAN

Although, percussive goal of the U.S, European and Japanese pediatric legislation is similar: to ameliorate health of the children with the advancement in research and by providing schema for evaluation of safety and efficacy in pediatric population. There are adequate differences though among their legislation.

	E.U Pediatric Statute	**U.S Pediatric Statute**	**Japanese Pediatric Statute**

Statute	Governed by one regulatory provision: - Regulation 1901/2006/EC -Pediatric Investigation Plan (PIP) requirement(s) regulates Incentives and rewards for performing pediatric studies	Governed by two separate laws: -Pediatric Research Equity Act (PREA), which requiring pediatrics studies. -Best Pharmaceuticals for Children's Act for additional market exclusivity	Governed by ICH guideline E11: -Clinical investigation of Medicinal products in the pediatric population. [28]
Reviewing/ approving authority	-Pediatric Committee of the European Medicine Agency review and approve all PIPs [26]	-Specific division for the disease area review pediatrics development plans being studied [27] -Centralized FDA Pediatric Committee approves Pediatric Study -Requests are issued by FDA	-Ministry of Health, Labor and Welfare (MHLW) review and approve pediatrics development plans
Scientific Advice committee	European Medicine Agency	Food and Drug Administration	Pharmaceutical and Medical Device Agency (PMDA) [29]
Time frame	-After completion of pharmacokinetic studies in adults PIP submission is recommended -A positive opinion must be received by PIP prior to submission of a Marketing Authorization Application (MAA) -Any modifications require approval, after that PIP can be amended.	-Prior to or at the time of the NDA submission, PREA can stipulates submission of a Pediatric Development Plan -Written Request may be made by FDA or proposal may b accepted for a Written Request for any drug that conforms to the precondition of section 505A of the Federal Food, Drug and Cosmetic Act or the Amendments Act of 2007.	-There is no as such time frame for pediatric drug development. -But there are data exclusivity protections, referred to as "re-examination period after approval of new medicines production." -No marketing application is issued for generic drugs during this term -After that, Substantial Regulatory Data Exclusivity is given. [30] -Re-examination system time frame for pediatric drugs is 10 years plus term between generic drug application and its approval/price listing till expiration of exclusivity.
Exclusivity award	-Patent extension of six month is granted for pediatric studies which have been conducted as per PIP. -For drugs that have showed a significant clinical pediatric benefit for an already approved indication, one year patent extension is given. -For orphan products for which pediatric studies are	-BPCA issues six months of additional marketing exclusivity for the studies which are conducted in pediatric patients and are complete according to a written request issued by FDA.	-Japan grants a six-year protection for New Chemical Entities (data exclusivity) -It also issues four years of data exclusivity for certain improvements -Another grant is of ten-year period for orphan drugs (Data exclusivity)[31]

	conducted as per PIP, two years of additional marketing exclusivity is been granted.		
Policy for off-patent drugs	Off-patent drugs granted a Pediatric Use Market Authorization for Eight years for data protection and ten years for market exclusivity.	Additional exclusivity is not available for developing off-patent drugs for pediatric use.	There are ongoing plans organized by the MHLW (Ministry of Health, Labour and Welfare), which has a goal to facilitate a fast review of off-label pediatric drugs.

Table 4: Comparison of regulations among Europe, U.S and Japan

CONCLUSION

The goal of health authority is to promote better treatment and medicine for children. India needs a pediatric legislation which should be built of a strong framework for pediatric drug development. There is a need to set a pediatric research committee which would lay down standard regulation for the pediatric drug development. Starting from pediatric investigation plan till market authorization along with post market surveillance, specifically for pediatric drug products, everything needs to be regulated for the Indian market. Adjusting of the adult dose for children would no longer substitute the need of fully fledged pediatric regulation. Increasing cases of adverse drug reactions in children suggest that now there is a need for improvising the drug development technique for pediatric population. The guidelines and regulations specifying pediatric drug development should be developed in India. The perks like market exclusivity will encourage the sponsors to develop the pediatric specific drugs which would be safe and efficient.

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