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Comparative evaluation of Pediatric Drug Regulation in US, Europe and India

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Abstract

Profuse number of drugs are being labeled and tested for children for over a decade. This is mainly due to legislation and regulations passed globally which regulates and evaluates the area of pediatric drug development. (1) The challenges faced by the researchers were the right infrastructure for conducting pediatric trials on a global scale, whether or not the current regulations were working for children and adolescents. Successful propositions have been established to generate crucial information about pediatric drug safety and efficacy by Food and Drug Administration (US FDA) as well as European Medicines Agency (EMA). (2-4) These approaches have resulted in improved accountability and transparency of drug development for Pediatric use. It is high time and also the need of the hour for regulatory guidelines to be laid down by CDSCO, Central Drug Standard and Control Organization (India) so that drug development process and protocol can aim pediatric patient concerns as well. (4-8) This paper aims to review compare the Pediatric Drug Regulations of three different countries i.e. USA, Europe and India.

Keywords: Review, Guidelines/Legislations, ICH E11, Pediatric, Drug/Medicine, FDA, EMA, CDSCO, PIP, PSP, BPCA, PREA, Clinical Trials

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1. Introduction

Pediatric population being considered as more vulnerable, unlike adult pediatric drug clinical studies are completely distinct thus organizing and conducting pediatric studies requires special attention and consideration of ethical and practical facet. (9) This is due to the fact that the pediatric population denotes a range of different physiologies, and children must not be treated as "small scale and tiny men and women" (Abraham Jacobi, 1830-1919). (10) The spectrum extends from the very small preterm new born infant to the adolescents. There are fundamental changes in body proportions and composition that go along with growth and development. (11-13) The process of maturation is one of the major differences between the pediatric and the adult populations. (14) The developmental changes in physiology and therefore, in pharmacology, influence the efficacy, toxicity and dosing regimens of medicines used in children, thus having different pharmacodynamic and pharmacokinetic responses. (15) It becomes obligatory to conduct clinical trials in various paediatric age groups to set up a suitable dosage form of the drugs, that can be used without causing harm to children. (16)

It is accepted globally that children should be included in the clinical trials ethically. (17) For over last one decade, regulatory legislations for developing drugs for paediatric patients were passed worldwide, energetically increasing the number of drugs being tested in and labelled for children. (18) The Food and Drug Administration (FDA) in USA and the European Medicines Agency (EMA) in the Europe established constitution that have been great in generating crucial new information about the safety and efficacy of drugs used by children. (19-22) Transparency and accountability of paediatric drug development has upgraded and the standard of paediatric information enlarged by an increased number of clinical trials in children lately. (23)

In earlier times, in India, pediatric drugs evolved based upon the clinical trials and protocols for a healthy adult human. (24) There were no specified drug development regulations or directives for pediatrics. Indian clinical practice heavily relied upon the safety and efficacy data produced in other developed countries, or conclusion from adult dosing. (25-27) Deficiency of pediatric specified guidelines led healthcare providers and parents

to guess the dose by breaking tablets into quarters and halves, crushing tablets, or opening capsules, or if it is liquid, by partly decreasing the volume. This was a strenuous way to administer medicine and caused imprecise dosing, which led to lower efficacy (due to under-dosing) and/or compromise safety (due to over-dosing). (27-30)

Although there are no particular regulatory guidelines laid down by the regulatory body of CDSCO regarding Pediatric Drug Development in India which has eventually resulted in irrational use of drugs in children. (31)

USA: According to general principles of ICH E11 guidelines of FDA, paediatric patients should receive medication that have been suitably evaluated for their use. (32) Timely development of information on the proper use of medicinal products in paediatric patients of various age groups and the development of paediatric formulations of those products are the major requirements of safe and effective pharmacotherapy in paediatric patients. (33) Advancement of formulation chemistry and in paediatric study design will help ease out the development of medicinal products for paediatric use. (34) Paediatric patient population should be included in Drug Development plans when a product is being developed for a disease or condition in adults and it is expected that the product will be used in the paediatric population. (35) Acquiring information of the effects of medicinal products in paediatric patients is crucial objective. But this should be done without compromising the welfare and health of paediatric patients engaged in clinical studies. This responsibility is and has to be shared by regulatory authorities, health professionals, companies/pharma industries and society as a whole. (36)

The main USA Paediatric Drug Development laws include PREA (Paediatric Research Equity Act), BPCA (Best Pharmaceuticals for Children Act) a Title V of FDA Safety and Innovation Act (FDASIA). Both Drugs and Biologicals are covered under PREA and BPCA. (37)

2. Paediatric Research Equity Act (PREA)

It necessitates pharma industries to evaluate safety and effectiveness of new drugs/biologics in paediatric patients (Paediatric Evaluation). Under PREA studies are compulsory for drugs as well as biologicals. (38) It necessitates studies only on indication(s) under review Orphan indications exempt from studies from PREA but Paediatric studies should be labelled. PREA is brought to action by filing an application for New active ingredient, New dosage regimen, New dosing form, New route of administration or New indication. Under Paediatric Assessment the data generated from paediatric studies aids manufacturing appropriate formulations for each age group and other data, to assess the safety and effectiveness of a drug/biologic for the claimed indications in all applicable paediatric subpopulations and supports dosing and administration for each paediatric subpopulation for which the drug or biological product is safe and effective. (39)

Prior to filing application in PREA, PSP (Paediatric Study Plan) should be built. Paediatric Study Plan defines the paediatric study(ies) the sponsor intends to conduct. The intent of the PSP is to motivate sponsors to recognize paediatric studies as early as feasible in product development and when suitable, to conduct those studies before submitting the NDA/BLA. FDA firmly encourages PSP to be submitted before initiating Phase 3 studies. PSP should be submitted no later than 210 days prior to submission of application. (40)

3. Best Pharmaceuticals for Children Act (BPCA)

It provides a financial incentive to industries to willingly conduct paediatric studies. Studies correlate to entire moiety and may expand indications, also studies may be asked for orphan indications and paediatric studies must be labelled. (41) BPCA particularises need for knowledge that may produce health benefits in the paediatric population. It allows FDA to request paediatric studies of approved and/or unapproved indications also. (42) A sponsor may plea the FDA to issue a written request by submitting a Proposed Paediatric Study Request (PPSR). PPSR should consist of rationale for studies and study design, detailed study design, appropriate formulations for each age group. FDA may issue a written request without a PPSR. Sponsors who submit studies to fulfill a written request may be eligible to receive paediatric exclusivity. (42)

4. Title V of FDA Safety and Innovation Act (FDASIA)

This act reauthorized PREA & BPCA immutably. Under this act there have been modifications in PREA such as new ability to allow extensions for the submission of deferred studies, obligation to submit Paediatric Study Plans and Issuance and publication of non-compliance letters. Revision to BPCA includes addressing neonates in Written Requests. (43)

Europe: The Paediatric Drug Regulation was enforced in the European Union (EU) on 26 January 2007 with its mail aim to improve the health of children in Europe by promoting the availability and development of medicines for children aged 0 to 17 years. (44)

The directive focuses to ensure that medicines used in children are of supreme quality, ethically investigated and analysed and authorised suitably and enhancing the availability of facts and data on the use of medicines for children. It targets to attain this without putting children through needless trials or holding up the authorisation of medicines for use in adults. (45)

The Regulation made a big distinction into the regulatory domain for paediatric medicines, outlined to safeguard the heath of children in Europe. The principal difference was the formation and functioning of the Paediatric Committee to provide scientific judgement on **paediatric investigation plans (PIPs**), developmental plans for the medicines to be used in children. (46)

The European Network of Paediatric Research at European Medicines Agency (**Enpr-EMA**) is a network of research networks, analysts and centres with known

expertise masters in executing clinical studies of children. (46)

The Legislation fairly changed the regulatory domain of paediatric medicines in Europe. The chief influence was the formation of the **Paediatric Committee (PDCO**), which is responsible for harmonizing the Agency's work on medicines for children. The Committee's major responsibility is to direct and regulate the studies that pharma industries must conduct on children as part of paediatric investigation plan (PIPs). (47)

A ten year report on implementation of Paediatric Regulation was produced by European Commission in October 2017. The report manifests rise medicines available for children in many therapeutic areas in the past ten years, most importantly in rheumatology and infectious diseases. Nonetheless, it also revealed that small progress has been made in diseases that only affect children or where the disease manifests biological differences between children and adults, especially rare diseases. To overcome this, the Commission and EMA and its PDCO have formulated action plan to improve the implementation of the Regulation. (48)

On international front, the Agency performs its duties closely with its international partners on medicines for children. Regular meetings with the United States (FDA) within the paediatric cluster are held to interchange knowledge on applications and subjects associated with development and to assist development plans for paediatric medicines. (49) EMA also participated in "Make Medicine Child Size", an initiative by WHO. It is also associated with Paediatric Medicines Regulators' Network (**PmRN)** which is a network of national medicines regulatory authorities established by the WHO in 2010, encouraging the availability and quality of medicines for children. (50-54)

INDIA: Having discussed about two developed countries, its time to compare a developing country like India with developed nations such as US & EU in terms of Paediatric Drug Regulatory Guidelines. India has always been a favourite spot to conduct clinical trials because of large patient population, low fees and ethical mouldability. In India Central Drug Standard and Control Organization (CDSCO) is the main regulatory body that regulates approval and distribution of drugs in our country. Unfortunately, we don't have separate laws dedicated to medicines for children except for some amendments made in Schedule Y of Drugs and Cosmetic Act and Rule. (55)

Recently made been amendments by CDSCO to Schedule Y of Drug and Cosmetic Act and Rule regarding Pediatric Clinical Trials includes that the schedule of paediatric clinical studies in the new drug development program will depend on the medicinal product, safety considerations, the kind of disease being treated, and safety and efficacy of accessible treatments. (55) Assessment should be made in the suitable age group for a drug that is anticipated to be used in children. Clinical studies done in children for drug development should start with older children and then extend to small children and infants. If the new drug is for diseases chiefly or exclusively affecting children, clinical trial data should be produced in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk. If the new drug is proposed to treat fatal or life-threatening diseases, happening in both adults and children, for which there exists no or little therapeutic alternative, early involvement of paediatric population should be done in clinical trials. (56)

In spite of these amendments, there still feels a constant need for a regulatory department to come up so that the paediatric population doesn't end up become experimental guinea pigs for the clinical trials

In the past also there have been many undesirable yet avoidable Adverse Drug Reactions (ADRs) in children for the same drug which produces mild or even atypical side effects in adults. For instance, hepatotoxicity in children due to Sodium Valproate for treatment of seizures, Gastrointestinal bleeding due to the use of NSAIDs in children, grey baby syndrome due to chloramphenicol. Not only active ingredients but there have been unpleasant experiences due to excipients used in formulation also such as headache and seizures induced by Aspartame, bronchospasm induced by benzalkonium chloride-induced from anti-asthmatic drugs. (56)

The paediatric population is an endangered group with remarkable dissimilarity in their physiological, developmental and psychological portrait in contrast to adults. There is an utmost requirement to regard and contemplate these developmental differences throughout the drug research and drug development process.

Table 1. Legislative Comparison

US		EU		India
Year	Legislation	Year	Legislation	Legislation
1994	Paediatric Labelling Rule	1997	EMEA Round Table	Schedule Y of The Drugs & Cosmetic Act 1945
1997	Paediatric Rule FDAMA	2000	Guideline ICH E11	
2002	BPCA	2002	Consultation Paper	
2003	PREA	2006	Paediatric Regulation agreed	
2007	FDAAA	2007	Paediatric Regulation enforce	

5. Conclusion

Undergoing through the global scenario of Paediatric Drug Regulations, the paediatric population needs

particular considerations for prescribing medicines due to their immature and underdeveloped physiologic system. Therefore, it is high time and also need of the hour to include a paediatric drug development regulation by CDSCO as done by other nations, which in future will give more effective outcome without impacting the safety of the children. Pharmacovigilance in paediatrics should be upgraded by creating awareness among medical professionals. There should be a surveillance carried out by the members of regulatory bodies to check proper availability and labels of drugs available in market for the use in children. Ignorance of this particular can direct to often detrimental after-math. Therefore, it is a necessity to construct regulations and guidelines in India, same as to other regulated and emerging markets, for the well-being and safeguarding the paediatric population of our country.

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Conflict of Interest

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