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Review Article

CURRENT SCENARIO AND REGULATORY FRAMEWORK OF PAEDIATRIC DRUGS IN THE UNITED STATES (US) AND EUROPE WITH A BRIEF PERSPECTIVE TO INDIA

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ABSTRACT

Since from decades, healthcare professionals were unable to provide suitable information for prescribing medicines for the treatment ofpaediatric population. Many depended on off-labeled drugs by manipulating the adult dosage form, simply by crushing the tablets or diluting the syrups. Even though there iseminent differences between children and adults, most of the drugs that have been developed for adults are simply used for children without necessary studies. This kind of practice is therapeutically successful for the drugs which have a wide therapeutic window and thus are relatively safe.There exist some barriers in developing paediatric drugs. Major regulated nations have identified these barriers and have developed specific regulations that will enhance the paediatric drug development. This includes the Best Pharmaceuticals for Children's Act (BPCA), Paediatric Research Equity Act (PREA) of the United States and the Paediatric Investigation Plan (PIP) of Europe. This article highlights the global situation of paediatric medicines and their regulations in Europe and United States (US) with a brief perspective to India.

Key words: Paediatric drugs, Regulatory framework, United States, Europe, India.

INTRODUCTION

In very early history, the children were literally excluded from medical discussions. From several years, physicians and parents were paralyzed with lack of information for prescribing treatment to children. Many were compelled to rely on off-labeled drugs by manipulating the adult dosage form simply by crushing the tablets or diluting the syrups. Even though children and adults have some similar medical needs, they should not be regarded as small adults or homogenous group in themselves. Since their bodies respond to medicines differently, they need medicines appropriate to their age, body weight and physiological condition. In spite of these well-known differences, most of the drugs, devices, and biologics that have historically been developed for adult products are simply used in children without adequate studies. This practice is clinically successful for the majority of drugs which are relatively non-toxic and have a wide margin between therapeutic and toxic doses. Hippocratic texts from the third century BC stated that "children are not just little adults"[1].According to statistics of World Health Organization (WHO), nearly 7.6 million children under the age of five die every year [2]. At present, between 50 to 90% of daily prescriptions for sick children use 'off-label' drugs, that is their effects on children have not been studied and they are not licensed for use in children[3]. Some 70% of the world's under-five deaths in 2010 occurred in only 15 countries, and about half of this in only five countries: India, Nigeria, Democratic Republic of the Congo, Pakistan and China due to lack of essential medicines [4].

The study of drugs in paediatrics was discouraged mainly due to concern of harming children in clinical trials and because of the lack of technical expertise, infrastructure, funding and non-availability of sponsors.But the impacts of these barriers lead to the use of off-labeled unlicensed medicines with insufficient information on dosage regimen and absence of information on warnings of adverse effects. It is not surprising that paediatric patients are exposed to potentially dangerous medication errors at a rate three times higher than that for adult patients[5].Some of the notable examples for off-label prescription for paediatric use are Albuterol for asthma, Phenergan for allergy, Ampicillin for infections and Prozac for depression disorders[6].Regulations from Europe and the US came in to force to enhance the safety of medicines for children by increasing research, development and authorization of medicines based on specific paediatric experience, without subjecting the paediatric population to unnecessary clinical trials.

Current Paediatric medicine market: Paediatric medicine market previously the most under-valued segment is now emerging as the fastest growing sector. The main key drivers for the growth of the market are: 1) Rising incidence and prevalence of chronic conditions pertaining

to children, 2) Supportive regulations in major markets like in Europe and the US by providing paediatric exclusivity provision (incentives), and 3) Strong pipeline of paediatric drugs in development. The US represents the largest regional market, Europe trails behind and Asia-Pacific is projected to be the fastest growing regional market. Anti-infective drugs represent the largest segment[7]. Major players in the market having more than five paediatric exclusivity granted includes Astrazenica, Merck, Sanofi, GSK, Novartis, Pfizer, Abbot, Bristol-Mayer, Roche, Alcon, Glaxo, Schering, MC Niel, Wyeth, Allergan [8, 9]etc.

Paediatric Age Classification: Paediatricsis a special population, which includes premature, newborn, infant/toddler, children and adolescents; the age ranges defined by different regulatory authorities for these groups are provided in Table.1.

Table.1.Age ranges defined for the Paediatric population by various Regulatory bodies[10, 11, 12]

Classification	FDA	EMA	CANADA
Premature	No category	< 36 weeks of gestation	Before the 37th week of gestation
Newborn ,term	Birth to 1 month	0-27 days	0 to 27 days
Infant and toddler	1 month-2 years.	28 days - 23 month.	From 28 days to 2 years of age, 2 years plus 1 day to 11 years of age and 11 years plus 1 day to 18 years of age considered as children
Children	2-12 years	2-11years	
Adolescents	12-16 years	12-18 ears	

Clinical trials in Paediatrics: As per the recent regulations, drug development programs should usually include the paediatric patient population when a product is developed for a disease or condition in adults and is anticipated to be used in the paediatric population. The conduct of clinical trials in paediatrics and timing to initiate the trials is according to ICH E11 guidance document "Clinical Investigation of Medicinal Products in the Paediatric Population"[13].This document provides the general ethical issues to be considered during clinical trials in paediatrics. Special measures are needed to protect the rights of paediatric study participants from undue risks which are a collective responsibility from investigator, ethical committees as well as from parents. Ethical committee should include paediatric experts when trial is needed in children for evaluation of trial protocols. Paediatric

subject is legally unable to provide consent therefore should rely on parents/legal guardian for consent for study participation. Based on the maturity level, assent can be given by the paediatric population. For minimizing risk and distress, protocols and investigations should be designed specifically for the paediatric population and study should be conducted in a familiar environment.

UNITED STATES LEGISLATION

Globally, the first initiation for regulating paediatric medicines was made by the US.The major regulatory milestones for paediatric drugsare provided in Table 2.

Table.2.Major milestones and highlights in Paediatric regulations of the US

Year	Regulation (act)	Highlights[1,6]
1994	Paediatric rule	Revised 21 CFR 201.57(f) (9) with added subsection (iv) for paediatric Use.
1996	Food and Drug Administration regulation.	FDA Guidance on "Content and Format of Paediatric Use Section"
1997	Food& drug Administration Modernization Act	Initial paediatric incentive program.
1998	Paediatric Rule	Mandated paediatric studies under particular circumstances
2002	Best Pharmaceuticals for Children Act (BPCA) replaced FDAMA	Applies to drugs and biologics. Study of off patent drugs Studies are voluntary Paediatric exclusivity
2003	Paediatric Research Equity Act (PREA) replaced Paediatric rule	Applies to drugs &biologics. Clinical studies are made mandatory

Reauthorizationof BPCA and PREA 2007: The acts PREA and BPCA have a shared goal of providing new paediatric information and drug labeling, and encouraging the appropriate use of medication to treat paediatrics**.** In 2007, as a part of the FDA Amendments Act of 2007 (FDAAA), Congress reauthorized PREA and BPCA in order to increase paediatric studies for use in paediatrics.[14] PREA (Section 505B of Federal Food, Drug, and Cosmetic Act)applies to new drugs, biologics; this act requires that sponsors conduct paediatric studies according to paediatric plan, unless FDA grants a waiver or deferral. A waiver removes the requirement of some or all studies to be completed, and a deferral allows the sponsor to conduct a study by a specified date after the product has been approved for marketing and these are mandatory under PREA[15]. However BPCA (Section 505A of FederalFood, Drug, and Cosmetic Act)is voluntary for the sponsor. The provisions apply to both new drugs/biologics, drugs already on the market and also for off patent drugs. Under

BPCA, sponsor conducts paediatric studies requested by FDA through "written request" (WR) or through proposed"paediatric study request" (PPSR) from sponsor. Studies submitted in response to the written request may qualify an application for paediatric exclusivity. This market exclusivity generally delays entry of generics of the product and is known as Paediatric exclusivity. Paediatric exclusivity can only be granted to those products that are "on-patent" that is, those that have patent protection.To qualify for paediatric exclusivity, the paediatric studies must also satisfy the requirements PREA under section 505A of the act[16].Paediatric Review Committee (PeRC) will review all written requests and reviews studies submitted by sponsor under the section 505A of FFDCA (Federal Food Drugs and Cosmetics Act) and make a recommendation on exclusivity determinations[17].

Data submission: Protocols for the Paediatric studies should be provided in investigational new drug application (IND) and clearly mark the submission "study protocol submitted for paediatric exclusivity study. The regulation in 21 CFR 312 covers procedures and requirements for Investigational New Drug (IND) applications. Once the IND is reviewed, sponsor may initiate the clinical trials[15, 16]. The results of paediatric studies conducted under PREA and BPCA are submitted to FDA in an application as New Drug Application (NDA) or supplemental NDA. The study reports should be according to 21CFR 314.50 for New Drug Application requirements and 21 CFR 601.2 for Biological Licensing Application requirements. The application should contain paediatric administrative information. If waiver/deferral was submitted, then reasons for submission should be clearly justified and application should also include paediatric study results and suggested labeling changes.[15,16] The labeling should include paediatric labeling information according to 21 CFR 201.57.[18]FDA reviews the application under priority within 180 days to come to agreement with the sponsor on labeling change. Deferral studies will be reported as post marketing requirements under 21 CFR 314.81 and 601.70. FDA recommends that the application be submitted 15 months prior to the end of the innovator market exclusivity for the product in order to be considered for paediatric exclusivity.

Supportive Measures: These supportive measures are to attract the industries and to enhance the research and development (R&D) in the paediatrics drug development. These measures includes 1) An additional marketing exclusivity of 6 months will be added to the patent of drug product for which the sponsor submits the paediatric studies. Accordinglynew drugs will receive 6 months exclusivity including its 5 years. For an already marketed product, submitting a supplemental application will receive additional 6 months extension to already covered patent. If the drug is designated under section 526 for a rare

disease and if sponsor had conducted the studies according to BPCA, the period referred is deemed to be seven years and six months rather than seven years[16], 2) A free scientific advice for paediatric studies and priority review process for marketing application. 4) BPCA includes provisions to allow for the funding of paediatric studies of on-patent drugs that the sponsor declined to study, by the Foundation for the National Institutes of Health (FNIH). It also allow for the conduct of studies of "off-patent" products, which no longer have market exclusivity, through the National Institutes of Health (NIH[14].

EUROPE LEGISLATION

In the past, many medicines authorized in Europe were not studied adequately in children. Between 1995 and January 2006, a total number of 258 active substances wereapproved for adult indication, which was also used for paediatric needs, but was not tested in children (44% with a paediatric indication, 32% with a potential paediatric indication).Based on this the EU had also implemented a similar approach like in the US for the regulations for paediatric medicines.[19]

Paediatric Regulation 2007: All applications for marketing authorization for new medicines (Article 7 applications) that were not authorized in the EU before 26 January 2007 have to include the results of studies carried out in children of different ages according to Paediatric Investigation plan (PIP).The PIP is a process begins with the design, which is a document upon which the development and authorization of medicinal products for the paediatric population is being based, is submitted by a pharmaceutical company to the paediatric committee (PDCO) at the European Medicines Agency (EMA).This requirement also applies when a company wants to add a new indication, a new pharmaceutical dosage form or route of administration for a medicine that is already authorized and patented. Medicines that are already authorized but no more covered by patent protection,that is off- patent medicines (Article 30 applications) can receive a "Paediatric Use Marketing Authorization" (PUMA), if it is specifically developed for children by conducting studies according to PIP.PUMA applications are submitted on a voluntary basis. The PUMA application has direct access to centralized procedure. The PDCO grants deferrals for some medicines, allowing a company to delay development of the medicine in children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO also grants waivers when development of a medicine in children is not needed or inappropriate[19,21]. PDCO also checks whether the companies comply with the agreed studies listed in each PIP with specific time lines. These checks are necessary before the company can apply for a marketing authorization (via centralized/decentralized or mutual recognition procedures and national procedures). PIPs can be modified if new

information becomes available during the medicine's development& companies need to apply to the PDCO under EMA for these modifications[19,21,22].

Data submission: The marketing application is considered valid only if it includes the results of a PIP or a decision of the EMA granting a product-specific or class waiver or granting a deferral. The results of the studies should be reflected in the Summary of Product Characteristics (SmPC) and package leaflet of the medicine concerned. Data submission is according to EU Common Technical Document (CTD). The data for off patent drugs is reviewed under priority assessment. Marketing authorization holders that have received a deferral on a PIP should submit an annual report to the EMA[23].

Supportive measures: The supportive measures given by the European legislation are similar to that of the US. Companies that has developed the medicines for the paediatrics will benefit from an extension of the "Supplementary Protection Certificate" (SPC) by 6 months. Orphan medicinal products will receive a total of 10 + 2 additional years of market exclusivity (market exclusivity for orphan medicinal drugs=10 years).PUMA benefits from the 8+2 year period of data and market protection (Article 30 of the Paediatric Regulation). Another supportive measure is the funding of paediatric studies. The Seventh Framework Programme for Research and Technological Development (FP7) is the EU's main instrument for funding research in Europe. Running from 2007 to 2013, the program has a budget of 53.2 billion Euros.The legislation also provides for free scientific advice for the development of a PIP.Applications for waiver, deferral andPIPsare assessed by PDCO without fee.Initiatives are taken at national level by some member states for funding the development of medicinal products for paediatric use. These includes Belgium, Finland, Germany, Hungary, Italy, Malta, Netherlands and the United Kingdom[19, 24].

HEALTH CANADA INITIATIVE

Health Canada has been actively encouraging paediatric medicinal product development, both domestically and internationally, through drafting a Canada-specific Addendum to ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population. Sponsors are encouraged with extended market exclusivity by six months for conducting paediatric clinical trials. The Office of PaediatricInitiatives(OPI) was established in 2005 to co-ordinate the development of paediatric information through the regulatory system. Health Canada encourages the innovators to include the paediatric data to increase knowledge about the use of the drug in paediatric populations. The additional knowledge must be publicly available through additions to the labelling and product monographs. The paediatric study results

should be submitted in new drug submission or as supplemental new drug submission[25].An additional six-month extension will be applied if an innovator includes results of paediatric clinical trials along with its 8 year data protection. To qualify for an extension, the clinical trials must have been conducted in at least one of the three groups of paediatricpopulations[26].

INDIAN PERSPECTIVE

Schedule Y of Drugs and Cosmetic (D&C) rules discusses the regulatory requirements for conducting clinical trials for children while developing the paediatrics dosages forms[27]. The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments in the appropriate age group.If the new drug is for diseases predominantly affecting paediatrics, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data. If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early. If the new drug has a potential for use in paediatric patients, paediatric studies should be conducted. In cases where there is limited paediatric data at the time of submission of application, more data in paediatric patients would be expected after marketing authorization.If the new drug is a major therapeutic advance for the paediatric population – the studies should begin early in the drug development, and this data should be submitted with the new drug application. For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about paediatric, ethical, clinical and psychosocial issues. The use of a Data and Safety Monitoring Board (DSMB) that includes paediatric experts is recommended.

DISCUSSIONS

From the above information, it is clearly understood that the objective of the regulation is to improve the health of the children. Based on the successful experiences in the US, a similar approach is made in Europe in 2007. In the EU, legislation is unified and there is only one, whereas in the USit is regulated by two laws. During the period of 1998 to present, many studies were conducted that resulted in new paediatric labeling. The new labels include important new information regarding safety and effectiveness in dosing/pharmacokinetics.

Compared to initial years of regulation, paediatric R&D and the number of companies that utilized free scientific advice also have increased. It is also worth mentioning here that the development of off-patent medicines through funding

program and number of exclusivities also has increased which reflects the industries approach towards paediatric medicine development. In the EU, total scientific advice requests are 332 and total protocol assistance requests are 68.The US paediatric plan of PREA is comparable to EU PIP, where both outline the design of paediatric studies. Both the EU and US legislations include facilitating measures in form of waivers and deferrals. The main driving force and attractive reward is the 6-months extension of patent if it satisfies the conditions of EU PIP and written request (WR) of the FDA. Health Canada also offers a similar supportive measure of 6 months patent extension. But this is applicable only to drugs under patent protection. This attracts an innovator, by recovering the cost of testing through the 6 month patent extension but may impact the generic drug firms for loss of revenues. The number of paediatric exclusivities granted in EU during 2000 and 2010 are shown in Figure 1.

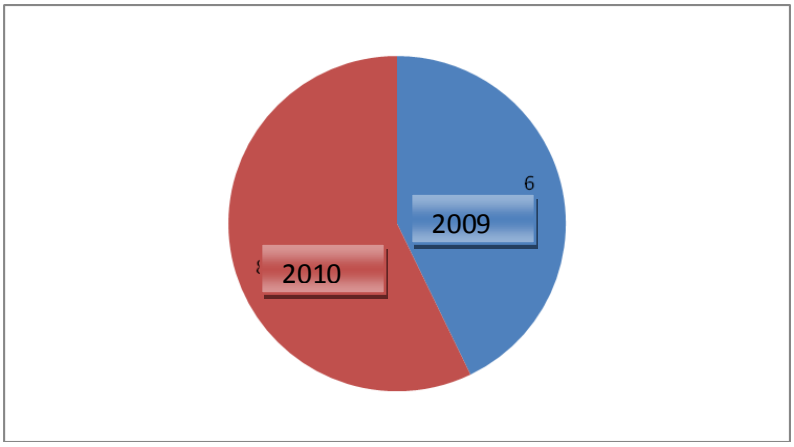

Fig.1.Number of exclusivities in the EU during 2009 and 2010

The funding programs [11,16,29], research networks, provision for free scientific advice, transparency of studies and constitution of specific paediatric committee etc., are the major pillars for the US and EU legislation. Even though there is no specific law in India, the clinical trials for paediatrics are required to be designed with special ethical concern and had adopted the ICH E11 guideline for conducting the paediatric trials. The part of Schedule Y of D&C rules of India, encourages the paediatric trials.

CONCLUSION

Even though there are some barriers for paediatric testing, these regulations provide long term benefits, and clearly identify authorized paediatric medicines and untested medicines. Physicians will benefit from an increased transparency with reduction in the ADRs, which in turn

increases the revenues for the companies. In order to overcome complexity in development of paediatric plans/programs the regulatory authorities in the US and EU has provided the regulatory guidance documents along with numerous supportive measures to encourage the industries in developing the paediatric medicines. Similar initiatives needed globally to enhance the development of better medicines for children without subjecting them to unnecessary clinical trials. Some recommendations for effective paediatric regulation for India are: 1) Allow a provision to utilize the evaluation reports on clinical data of paediatrics from international agencies like the US and EU. 2) Shorten the review time for faster availability of paediatric medicine to market. 3) Government funding and increasing the budget of R&D for paediatric drugs. 4) Similar supportive measures for generic drugs that is seen with the US and EU. 5) A new registration path without combining with the normal procedures. 6) The regulatory authorities as well as pharmaceutical companies in India must pay attention towards safety & effectiveness of paediatrics drugs by a specific regulation.

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