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Singh Ajay
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India-124001.

Budhwar Vikaas
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India-124001.

Choudhary Manjusha
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, India-136119.

Correspondence
Budhwar Vikaas
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India-124001.

A comprehensive study on regulation on clinical trials of pediatrics in US, EU and India

Singh Ajay, Budhwar Vikaas and Choudhary Manjusha

Abstract
Children have different pharmacokinetic and pharmacodynamics responses as compared to adults. They can also be categorized in different age groups which show different Pharmacokinetics and Pharmacodynamics particularities. Therefore, it becomes necessary to see the effects of optimal dosages and formulations in various age groups of children. The child protection in research was recommended at the Belmont report (1979) first time. The necessity for written informed consent of the subject from a legally authorized representative of a child was described in the Declaration of Helsinki (1964). The United State of America was the first country which made the act for pediatric population clinical trials as the FDA Modernization Act (1997). After that the Best Pharmaceuticals for Children Act **(**BPCA, 2002) and the Pediatric Research Equity Act (PREA, 2003) were included in the U.S. regulatory framework. These acts cover the incentives for drug developers to conduct (after FDA Written Request) pediatric research and guidelines for conducting clinical trials in children. Similarly to enhance the protection of children in research 'Pediatric Regulation (EC) No 1901/2006' was established in Europe in January 2007. It came after the ICH Guidance 11 for conducting research on children. According to this regulation before conducting clinical trials in pediatric population pharmaceutical companies must have a Pediatric Investigational Plan (PIP) and which must be approved by the suitable competent authority. If it is approved six-month patent protection is given to pharmaceutical companies. In India there is no specific act for conducting clinical trials in the pediatric population. Only a section of schedule Y gives information about the requirements of the structure and content of study protocols, informed consent forms and documentation and the composition and functions of ethics committees and includes child patients as deserving special consideration as a vulnerable group. The present article compares the legal provisions and guidelines documented in the US, Europe and India concerned with the clinical trials regulations, incentives and compensation, informed consent etc. of pediatrics.

Keywords: The best pharmaceuticals for children act, the pediatric research equity act, clinical trials, pediatric use marketing authorization, pediatric investigation plan

1. Introduction
Children are not small adults. They have different pharmacokinetic and pharmacodynamics responses as compared to adults. These differences are mainly due to differences in body water and serum protein composition in the pediatric population. It is necessary to study the drug profile in different age groups of children and drugs available for adult may cause adverse effects in children. If the safety profile of drugs not checked in children, they cannot be benefited from these drugs [1]. Currently 'off label' drugs uses without determining their safety and efficacy in children from 50 to 90% sick children's prescriptions. The pediatric population may be subjected to unexpected adverse effects and under dosing effects without determining efficacy with lack of information and inappropriate pharmaceutical formulations [2].
The pharmaceutical companies cannot extrapolate to adult drug study data to child study data. Different body fat and muscular mass, underdeveloped blood-brain barrier, deficiency in some of the microsomal enzymes, thin stratum cornium layer, different composition of plasma proteins in children are some of the major attributes to this. Pediatric population can be divided into different age groups on the basis of different pharmacokinetics and pharmacodynamics parameters.

- From 0 to 27days "preterm and term neonates"
- From 1 to 23 months "infants"
- From 2 to 5 years "pre-school children"
- From 6 to 11 years "school children"
- From 12 up to 18 years "Adolescents" [3]

Therefore, it becomes necessary to conduct clinical trials in different pediatric age groups for establishing a suitable dosage form of the drugs, which can be used without causing harm to children.

It is acknowledged worldwide that children should be included in the clinical trials ethically. The Belmont report (1979) recommended protection of children in research first time. The Declaration of Helsinki (1964) described the necessity for written informed consent of the subject from a legally authorized representative of a child [5]. The process of taking Informed consent and assent is very difficult because both depend on the level of development of the child and their age. The varying ability of children to understand and adequately interpret the consequences of participation, requirement of minimal burden and an optimal harm/benefit balance are the challenges that come across during the time of making guidelines and laws for clinical trials in children [4, 6]. Inspite of these challenges, it is well recognized worldwide that a suitable program must be present in the research of drugs in the pediatric population. In the last two decades the opinion of both the United States (US) and the European Union (EU) about the involvement of children in clinical trials has been changed very much.

In India, there are no specific requirements for conducting clinical trials in the pediatric population. The conclusions come from adult dosing and safety and efficacy data published in other developed countries become a source of clinical practice with children in India. The requirements for the clinical trials in children, such as the composition and functions of ethics committees, informed consent forms and documentation, the structure and content of study protocols and includes child patients as deserving special consideration as a vulnerable group are given in schedule Y [7].

2. Clinical Trials of Pediatric Population in US

The FDA Modernization Act was introduced in 1997. In this act incentives such as exclusivity or patent protection was given for conducting pediatric clinical trials, while off-patent drugs were not included. But the manufacturers not accepted that the timing and other pediatric studies provisions were made mandatory for them by this act that time [8].

Today, the current U.S. regulatory framework includes:

- The Best Pharmaceuticals for Children Act **(**BPCA**)**, an additional six months of marketing exclusivity was given to the drug developer for conducting (after FDA Written Request) pediatric research [9].
- The Pediatric Research Equity Act (PREA), by this act it has become necessary for pharmaceutical companies to study the safety and efficacy of their products in children under certain conditions. The pediatric studies must be conducted for the drugs which were approved with the same use in adults before use in children. Unusually, mechanisms for studying on- and off-patent drugs and to test off-patent drugs were given in the Best Pharmaceuticals for Children Act:
  - Identifying those drugs which requiring study in pediatric populations.
  - Experts at the National Institutes of Health (NIH) and other organizations may develop study requests with collaboration with each other.
  - If manufacturers are declining to conduct studies on priority drugs, the National Institutes of Health (NIH) and other FDA organizations should conduct this study.

With enactment of PREA, it is not mandatory to submit plans for the pediatric research with a proposed timeline during the New Drug Application (NDA) submission. On July 9th, 2012a provision was included in PREA which stated that manufacturers must submit a Pediatric Study Plan (PSP) before the drug development process. Under PREA all activities are reviewed by a consultative body known as Pediatric Review Committee (PeRC) (this committee also reviews the activities come under BPCA) [10].

2.1Informed Consent

Informed consent is becoming more important when children are included in clinical trials as participants. It is the responsibility of parents to give permission and consent for enrolling their children in a clinical study and they should act in the best interest of their children. In the USA, only one parent consent is required for clinical research with negligible risk or having best interest for the individual child and consent of both parents is required for all other categories with a high risk profile. The process of informed consent for pediatric research can be divided in two parts: parental (or guardian) permission and child assent [11].

2.2 Parental Permission

The parental permission is becoming important to make legal to participation of children in research as we know children are unable to give informed consent. A parent is one who born to child biologically or one who adopts the child legally, while a guardian is one who authorized under the law to give consent on behalf of a child.

"Consenting Minors" is the term used for adolescents. A minor who can understand the medical procedures and the treatment of certain conditions such as pregnancy, drug abuse and venereal disease legally considered as a mature minor. The definition of children, which has been given in the regulation 21 CFR 50.3, is not applicable to these mature minors. It is also not applicable to the minors deemed as emancipated from state law because they may be able to give consent for themselves but refuse to do that due several reasons. At any time of the clinical study parent, child, emancipated minor, or mature minor can revoke their participation [12].

2.3 Assent from children

The assent of children is a part of the informed consent process. The informed assent form much likely work as the parent informed consent form. It gives answers of the basic questions related to clinical trial such as how long it will go on, what they will be asked to do, benefits to them and what the possible risks are. It ensures that children are informed about participating in the clinical trial to the level they are capable to understand even when consent rights are not present. The maximum age for giving assent is between 18 and 21 years which is considered as the age of majority. Though, individuals less than the age of majority may have a grant for their consent. In the USA, individuals may be considered as emancipated if they have got married, served in the military and with the effect of a court order or other reasons accepted by local statutory body. The age of 7 years has often been fixed for giving assent. Some experts agreed that it is the earliest age or time at which a child could form their particular intent. The age of 6 years is recommended by the International Conference on Harmonization (ICH) for giving assent [13].

2.4 Incentives and Compensation for Pediatric Research

The amount paid to every participant of the clinical study is not same it can vary with each of the participants from study to study as well as site to site, even for the same study conducting at the same institution. According to the American Academy of Pediatrics it is not necessary to give money to the children for their participation; drug developer can give appropriate gifts to them when they have completed the trials. The parents/authorized representatives can only have compensation for their time and expense from the researcher. The Pediatric Regulation 45CFR 46.116; 21CFR 50.25(a) requires that drug developer must give information in the informed consent form about whether compensation or medical treatment available for clinical trials related injury, whom to contact in the event of such injury and how to get further information. According to the pediatric regulation, the amount and plan of payments to clinical trials participants should be presented to the ethics board at the time of initial review as it is part of the ethics board process [14].

3. Clinical Trials of Pediatrics in EU

In EU provisions for conducting clinical trials on human subjects involving medicinal products have been given in Directive 2001/20/EC. On September 2004 article '4' was introduced in Directive 2001/20/EC. The article '4' gave the basis of including pediatric clinical trials during the developmental process of adult drugs and differentiate the ethics and methodology of pediatric and adult clinical trials. However, all the requirements for the protection of children were not satisfied with article '4' of Directive 2001/20/EC so it was considered insufficient for child protection [15]. Consequently to support the clinical investigation in pediatric population the European Pediatric Regulation (EC) No 1901/2006 was implemented in the January 2007. The Pediatric Regulation in Europe was preceded by the ICH Guidance 11 for conducting studies in the pediatric population. It also obligates pharmaceutical manufacturers to conduct clinical studies in children in accordance with an agreed Pediatric Investigational Plan (PIP) in return for six-month patent protection [16].

3.1 The main pillars of the EU Pediatric Regulation are:

- The Pediatric Committee (PDCO) was established at EMA.
- The Pediatric Use Marketing Authorization (PUMA) developed as a new type of Marketing Authorization, which is only accessible to off-patent drugs.
- It is made compulsory to the drug developers that they apply for a Pediatric investigation plan during the initial phase of the drug development process.
- The pediatric clinical studies are mandatory according to the approved Pediatric investigation plan that can also include a waiver or deferral.
- The off-patent drugs enlisted in 'Priority List' published by the PDCO of EMA should be awarded with appropriate incentives under the EU pediatric regulation [17].

3.2 Major Provisions of the European Pediatric Regulation:

Following are the directives which cover the regulations of pediatrics in Europe:-

3.2.1 Pediatric Investigation Plan (PIP): A PIP is the basic requirement which helps in drug development for the pediatric population. It should have all the information about the clinical trial program which will follow in the pediatric population. It has to be submitted after Phase 1 of the development process of new drug molecule when pharmacokinetic studies of adult are available for that drug molecule. The PIP must be approved by the PDCO; it can be modified if new information comes during the drug development process to apply to the PDCO.Table.1 classifies the pediatric age groups on the basis of ICH guideline 11 and FDA. Figure. 1 shows the flowchart of PIP approval process [21].

Table 1: Classification of pediatric age groups for the purpose of clinical trials [18].

ICH Guideline E11(1)		FDA		India
Preterm newborn infants		-		No such classification on record
Term newborn infants:	0 to 27 days	Neonate:	Birth to 1 month	
Infants and toddlers:	28 days to 23 months	Infant:	1 month to 2 years	
Children:	2 to 11 years	Children:	2 to 12 years	
Adolescents:	12 to 16-18 years (2)	Adolescent:	12 to <16 years	
(1) Followed by the EU, (2) dependent on region				

3.2.2 Incentives and rewards: Pediatric data must be submitted in accordance to an approved PIP for all regulatory applications for new medicinal products and for on-patent medicinal products with new pediatric use unless a waiver/deferral was granted to these products. The medicine is rewarded with six months of patent extension if it authorized in all E.U. Member States and its pediatric study results are included in the product label. Extra two years market exclusivity is given to the orphan-designated medicinal products under the E.U. Orphan Regulation if these products prove their application in pediatric population. PIP must be approved before getting any incentives and to receive marketing authorization [19].

Free scientific advice or protocol assistance is also given to any pediatric development question by the EMA if the drug is used in rare disease, but advice should be requested after PDCO decision or before submitting a PIP. The PDCO decision does not require for giving any scientific advice [20].

3.2.3 Pediatric Use Marketing Authorization (PUMA): Under the PUMA, EMA collects data from new clinical studies, pediatric clinical studies published in the literature and from studies conducted in other countries. The small and mid-size companies can use this data as a reference in developing products for children. With effect of this mechanism the EU Centralized Procedure can be used for applications if studies performed according to the approved PIP. Earlier regulation also cross-referenced by PUMA, which gives 10 years of market protection as an incentive for conducting clinical trials in the pediatric population [21].

3.3 Informed consent: According to Article 4(d) of the Directive 2001/20/EC (reference) the parents/authorized representative should not be pressurized by researchers during the process of getting informed consent from them. For example:

1. Parents/authorized representative must not be offered other financial incentives to enroll the child as a subject of clinical except compensation and costs.

2. The researcher should inform to the Parents/authorized representative about the possibility to withdraw informed consent.
3. The researcher should reassure to Parents/authorized representative that the child's treatment will not be biased by failing to participate or by removing participation from the trials.
4. Consent should be obtained from Parents/authorized representative in writing with Article 4 (a), (b) and (c) of the Directive 2001/20/EC at the same time as assent is looked from the child.

In all conditions, parents/authorized representatives should have knowledge about the rights to revoke their participation and their informed consent for clinical trials, without giving reasons. All these points mentioned above should be written clearly in the informed consent form [22].

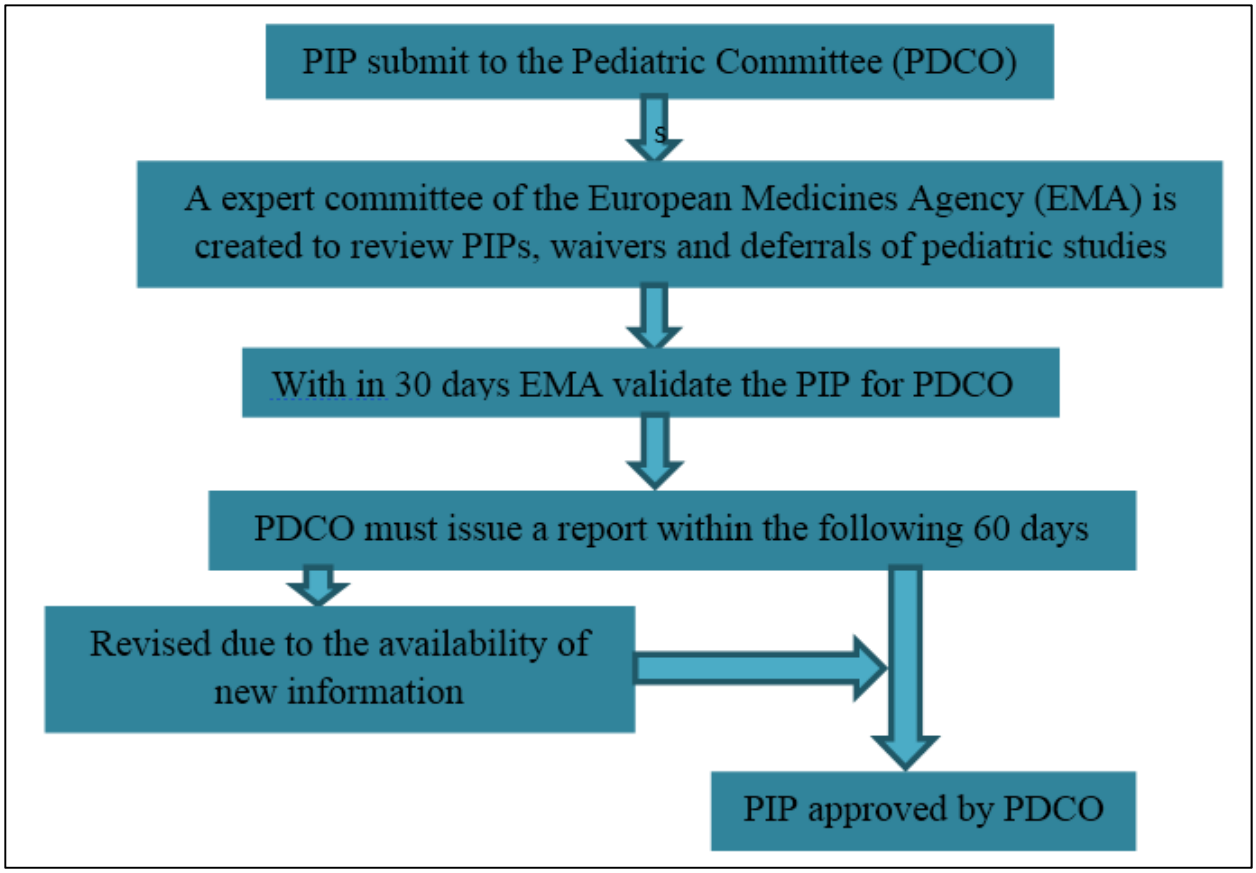

Fig 1: Flow chart of PIP approval process [21]

3.4 Assents from Pediatrics

Normally, to provide information separate information sheets and assent forms are created, which depend on the age range of clinical trials subjects. The child's ability to sign assent increases with their age; in the US, the age to give assent is permitted to be seven years, while in the EU, nine years are considered reasonable with no clear guidance. The clinical trials settings should be present in the situations where the child's dissention may be dominated by his participation, which likely to benefit the child (*e.g.,* Rare diseases or if no alternative treatments present or these are available in the form of research). According Article 4(d) of the Clinical Trials Directive either the parents/authorized representatives or children must not be offered for financial inducement requires that there must be no inducement except compensation for their time and expenses [23].

4. Clinical Trials of pediatrics in India

In contrast to India, in the United States, the Food and Drug Administration and European Medicines Agency (EMA) have well-established department of regulation of drug development for pediatrics. There are no specific requirements, *per se*, for the conduct of clinical trials on the pediatric population in India. The Indian clinical practice relies heavily upon safety and efficacy data published in other developed countries, or inference from adult dosing (7). During India import, manufacturing and sales of drugs and cosmetics (including those that are used in Ayurvedha, Siddha and Unnani systems of medicine) are regulated by the Drugs and Cosmetics Act 1940 (as amended up to 2013) and the Drugs and Cosmetic Rules 1945 (as amended up to 30 June 2005) regulate. The policies, procedures and requirements regarding the manufacturing and conducting clinical trials for new imported drugs in India are given in the Schedule Y of the Drugs and Cosmetic Rules 1945 and rules 122 A to E of this Act. According to the Schedule Y all applications for clinical research should fulfill the requirements of the Good Clinical Practice Guidelines established by Central Drugs Standard Control Organization, the requirements of the Declaration of Helsinki and the Ethical Guidelines for Biomedical Research on Human subjects made by Indian Council of Medical Research. Schedule Y gives detailed information about informed consent forms, protocols for the structure and content of study, documentation, ethics committee composition and its functions and to give special consideration to child patients as a vulnerable group [24].

The Schedule Y sections which give information about pediatric clinical trials are discussed below:

1. The pediatric studies timing depends on the type of disease being treated, the medicinal product, the safety and efficacy of available treatments and safety consideration during the development process of new drug. Evaluations should be generated in the appropriate age group of children for a drug before it is used in the pediatric population. When children are included in clinical development, it is good to initiate trials with older children, then proceed with younger children and then infants.
2. Except initial safety and tolerability data, all clinical trials data should be made in the pediatric population for the drug which will be used for diseases affecting pediatric patients exclusively and predominantly. The safety and tolerability data are usually obtained from studies conducting in adults. These studies would yield useful information but may expose adults to unknown risk.
3. If both adults and pediatric patients suffering from the same life-threatening disease and no or limited treatments are available for this, children should be included in the early phase of clinical trials of new drug or treatments for this life-threatening disease. In clinical trials the initial safety and evidence of potential benefits should be assessed earlier and lack of data should be justified in detail where this is not possible.
4. Pediatric studies should be conducted if the new drug shows potential for use in pediatric patients initially. If the drug safety profile is good in adults, clinical studies may be initiated at various phases of clinical study or after post marketing surveillance in adults. For use in children more data in pediatric population would be expected after market authorization if limited pediatric have been submitted data at the time of submission of application.

The relative bioequivalence studies and pharmacokinetic studies are performed in pediatric clinical trials. Data should be submitted with the new drug application if the new drug demonstrates major therapeutic advance for the pediatric population early in the drug development. For children a new drug should be evaluated clinically after the phase III of clinical trials in adults. If the drug has therapeutic evidence of a primary disease of the children, it can be studied earlier [25].

The Indian Council of Medical Research made ethical guidelines for the biomedical research on human participants state that before starting clinical trials in children the drug developer must confirm that children will not be included in clinical trials that could be carried out equally well in adults, assent must be obtained according to the child's competency, the proxy consent has been given by a parent or authorized guardian of each child and. A written or well signed informed consent must be obtained from the participants before participating in clinical trials. An impartial witness or authorized representative or guardian should be present throughout the whole informed consent process if the participant is not able to giving an informed consent, for example, children is unconscious or mentally or physically disabled (26).

Participants of clinical research may be paid for their time spent in research and for their inconvenience and should be compensated for their expenses. Essential free additional care or suitable medical appointment must be provided if the participant has need of treatment for complications (temporary/permanent) occurred during the research. Appropriate compensation has to be given to the participants in case of permanent disability. Institutional ethics committee (IEC) approved payments, compensation and medical facilities to be provided to research participants [14].

4.1 Indian Academy of Pediatrics (IAP)

In 1963, under Public Trust Act 'Indian Academy of Pediatrics' was registered as an Academy in Mumbai and now works as a professional body of Pediatricians in India. At that time 20300 people worked as a member of the Indian Academy of Pediatrics. Its Central Office is Mumbai Indian Academy of Pediatrics [27]. The Indian Academy of Pediatrics is bound to improve health and safety of the children. The main aim of Indian Academy of Pediatrics is to improve the knowledge of its members by giving expertise and scientific advice regarding the child's health. It also plays an important role in making of committees/task forces/boards for the safety of child by the government. The members of the Indian Academy of Pediatrics work as advocates of children and adolescents and their families and increase their knowledge about the whole process of clinical research such as informed consent, compensation, time period of research, risks and benefits associated with the research which can help the children to fight against the diseases they are suffering from [28]. Table 2. Describes major milestones of pediatric legislation in the US, EU and India and Comparison of Incentives given in US, EU and India for Pediatric Drug Development have been done in Table 3.

Table 2. Major milestones of pediatric legislation in the US, EU and India (23).

US		EU		India
Year	**Legislation**	**Year**	**Legislation**	**Legislation**
1994	Pediatric Labeling Rule	1997	EMEA Round Table	Schedule 'Y' of The Drug & Cosmetic Act 1945
1997	Pediatric Rule FDAMA: Food and Drug Administration Modernization Act	2000	Guideline ICH E11	
2002	BPCA: Best Pharmaceutical For Children Act	2002	Consultation Paper	
2003	PREA: Pediatric Research Equity Act	2006	Pediatric Regulation Agreed	
2007	FDAAA: Food and Drug Administration Amendments Act	2007	Pediatric Regulation Into Force	

Table 3: Comparison of Incentives given in US, EU and India for Pediatric Drug Development (22).

Item	US	EU	India
Protocol assistance	All scientific advice provided by FDA is free.	Free scientific advice available for pediatric studies.	NO
Criteria for waiver	Criteria for waiver: 1) pediatric studies impossible or highly impractical (e.g. number of pediatric patients very small or geographically dispersed); 2) ineffective or unsafe in part of pediatric population; 3) unlikely to be used in a substantial number of pediatric patients; or 4)age-appropriate formulation can't be made.	Criteria for waiver: 1) ineffective or unsafe in part of pediatric population; 2) disease does not occur in pediatric patients; or 3) product is not a "significant" advance over existing treatments for children.	NO
Market exclusivity for on-patent drugs	Provides six months of additional marketing exclusivity if studies in pediatric patients are completed in accordance with a written Pediatric Study Request issued by FDA, but only as an extension of another granted exclusivity. Results of all pediatric studies must be included in product labeling.	Provides six months of additional marketing exclusivity for products for which pediatric information has been added to labeling based on studies. Two years of additional marketing exclusivity are provided for orphan products for pediatric patients (in addition to the 10 years for orphan products for adults).	(7-8 Years)Time remaining after drug approval from patent life and no additional marketing exclusivity if studies in pediatric patients are completed.
Market exclusivity for off-patent drugs	No exclusivity is available for developing off-patent drug s*per se.*	10 years exclusivity is available for off-patent drugs developed for pediatric patients no extension of other exclusivity.	

5. Conclusion

It is necessary to carry out clinical trials in children to make sure that better treatments become available to them as they are physiologically different than adults. The regulatory authorities in the U.S. and the Europe have done good work in this direction to promote better medicines for children. The pediatric legislations have been made by both the country for pediatric drug development and the pharmaceutical companies have to deal with different requirements and special Obligations to receive the incentives. In India still there is no separate regulation for pediatric clinical trials, however some provisions are given in the schedule Y. The Indian health authorities also need to make separate legislation for clinical trial in children for their safety.

6. Acknowledgement

The Authors acknowledge the official websites of US, EU and India where latest authentic information regarding the regulations of pediatrics in their countries could be gathered.

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