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A comprehensive study on the regulation of pediatric in U.S., Europe and India

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Abstract

Metabolism in a child is different from adults. Their response to drugs is different in both the ways, pharmaco-kinetically and pharmaco-dynamically. Considering this fact, there are specific regulations for pediatrics in US and EU. In US, pediatric exclusivity provisions were established in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA), and in 2002 the Best Pharmaceuticals for Children Act (BPCA) was introduced followed by the Pediatric Research Equity Act (PREA) in 2003. In Europe, the Pediatric Regulation (EC 1901/2006 Medicinal Products for pediatric use) came into force in January 2007. The article compares the current status of pediatric regulations in US and EU and emphasizes the need to develop specific guidelines for pediatrics in developing countries.

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Introduction

50–90% of drugs used in children today have never been actually studied in this population, and the results of drug studies done in adults are often extrapolated for use in children (Yewale and Dharampalan, 2012). Some severe adverse drug reactions in children with the drugs which were marketed in the world without any specific studies in children, made the practitioners and other healthcare professionals realize that children and neonates are different from adults and thus the response of any drug in their body would be different from adults. Although the laws and regulations governing the marketing, production, clinical trials, storage, stability etc. of drugs and excipients for pediatrics have been framed in the developed countries like US and EU, these regulations are relatively very new. The condition is still worse in India and other

developing countries. Every year an estimated 26 million children are born in India (Why is birth registration important? cited at http://www.unicef.org/india/resources_1650.htm) which suggests a huge demand for drugs and vaccines throughout the country. Still a little importance is given to the regulations of drugs and vaccines in these countries. Efforts to harmonize the pediatric regulations throughout the world, which would lead to hassle free export and import of pediatric dosage forms within the countries is also one of the biggest need of the hour.

Need for the separate Regulations for pediatrics

Ignorance or lack of knowledge of the differences in pediatric pharmacotherapy has led to various medicine-related tragedies in the past. These tragic side effects of drugs on children propelled much of the legislation that led to the creation of the Food and Drug Administration (FDA) and European Medicine Agency (EMA) in its modern incarnation. Medications that are generally safe and effective for adults may be unsafe or ineffective or both for some or all pediatric age groups or may require changes in dosing forms, calculations, or schedules to be safe and effective. Such disparities underscore the necessity for pediatric drug studies.

Behavior of the drugs both pharmacodynamically and pharmacokinetically is different in infants and small children when compared to adults. There are some gross differences in children and infant's physiology and anatomy. Underdeveloped blood brain barrier, liver, muscles, stratum corneum and differences in the constitution of body fluids and plasma proteins, subcutaneous fats etc. are some of the major differences contributing in different Absorption, Distribution, Metabolism, Excretion (ADME) of many drugs like sulphisoxazole, chloramphenicol, benzyl alcohol and digoxin etc. (Curley *et al.*, 2001). The Discussion begins with the examples of the some fatal consequences of the lack of drug studies with children, especially the youngest children. Some severe adverse drug reactions related with commonly used drugs in pediatrics are:

Sulphisoxazole (Kernictures)

The major disaster about drug use in children happened in 1956, when newborns receiving sulphisoxazole were found to be having more kernicterus (entry of bilirubin into the brain, causing yellow discoloration of brain tissue, seizures, and death). It occurs because infants have diminished glucuronosyl transferase activity, and therefore, less ability to glucuronidate bilirubin. Infants also have immature blood-brain barriers, which allow more of the free bilirubin to cross into and damage the brain. It displaces bilirubin from plasma proteins, thus increasing the free fraction of bilirubin in the plasma and enhancing the movement of bilirubin into the brain (Casavant *et al.*, 2010).

Chloramphenicol (Gray baby syndrome)

Gray baby syndrome is a rare but serious side effect that occurs in infants (especially in premature babies) following the intravenous administration of chloramphenicol, a

becteriostatic antibiotic. Gray baby syndrome was first reported in 1959, in neonates. Immature glucuronyl transferase activity is one of the reasons of gray baby syndrome; inadequate renal excretion of chloramphenicol and its metabolites is the other reason (Casavant *et al.,* 2010).

Benzyl alcohol

In 1982, a common excipient, benzyl alcohol, was blamed for the neonatal gasping syndrome and the deaths of premature babies. Used as a bacteriostatic preservative, it was given to children in a flush used to keep intravenous lines patent. The neonatal gasping syndrome consists of acidosis, respiratory distress, circulatory failure, intracranial bleeding, seizures, and death. Besides reminding us that excipients are not inactive, the neonatal gasping syndrome exemplifies the problem of differential metabolism of benzyl alcohol in babies. Neonates probably metabolize benzyl alcohol to benzoic acid, which accumulates and causes toxicity (Field *et al.,* 2012).

Hepatotoxicity associated with the use of sodium Valproate (Jackson *et al.,* 1984), increased risk of Reye's syndrome with the use of salicylates in children with viral infection (Busti *et al.,* 2010), growth suppression/effects on adrenal function with long-term corticosteroids (Dahl, 2006), gastrointestinal bleeds with NSAIDs (Anyanwu *et al.,* 2013), risk of arthropathy due to use of ciprofloxacin in children (Adefurin *et al.,* 2011) are some of the other adverse drug reactions in the children which lead to the serious disasters.

Benzalkonium chloride-induced bronchospasm from antiasthmatic drugs (Committee on Drugs, 1997), aspartame induced headache and seizures (Lipton *et al.,* 1989), saccharin-induced cross-sensitivity reactions in children with sulphonamide allergy (Committee on Drugs, 1997), propylene glycol-induced hyperosmolality and lactic acidosis (Huggon *et al.,* 1990) are some other adverse reactions which occurred due to irrational use of excipients in pediatric formulations.

This finally purposed the regulatory agencies throughout the world to seriously review these events and from separate guidelines for pediatrics. US and EU were amongst the pioneers with regard to step taken in this context. The framework of separate guidelines for pediatric started with the classification of pediatric age categories shows the Table 1.

Laws governing the Pediatrics in US

The US was ahead of Europe in recognizing the need for legislation to ensure that pharmaceuticals are developed for, and tested in, the pediatric population. Pediatric exclusivity provisions were established in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA), and in 2002 the Best Pharmaceuticals for Children Act (BPCA) was introduced followed by the Pediatric Research Equity Act (PREA) in 2003 (Bhatti *et al.,* 2011).

In 1979, Product label include pediatric use section rules were enacted. According to this rule, if the drug is approved for a pediatric indication, that indication must be described under the indication and usage section of the labeling, with dosing information provided

under usage and administration section. If there is no pediatric use, the labeling must state that "safety and effectiveness in the children below the age have not been established" (Labson, 2002). In 1994, Pediatric labeling rule were made, according to this rule, all sponsors of drug and biologics product examine available data on pediatric use and submit a supplemental application for a pediatric indication, if supported by the existing data. In cases where the sponsors determined that the existing data did not support pediatric use, labeling could simply state, that "safety and effectiveness in pediatric patients below the age of ( ) have not been established (Labson, 2002). In 1997, Section 111 of FDAMA established a new detailed statutory program to enhance the incentives for the sponsors of a new drug application (NDA) to conduct pediatric studies and collect pediatric use information at the FDA's request on new and already approved drugs. Companies that satisfy the requirement of section 505A earn six months of additional marketing "exclusivity" for a drug. This Act incorporates the provision of written request (Labson, 2002). In 1998, Pediatric rule require that a new product application contain a pediatric use section. This section briefly summarizes the pediatric studies conducted (Labson, 2002).

In 2002, Best Pharmaceuticals for Children Act (BPCA), replaced the FDAMA. It is not a mandate for the manufacturer. If the manufacturer also conducts a pediatric study of that drug, he will then receive a six-month extension to run after the initial Waxman-Hatch extension (Labson, 2002). In 2003, Pediatric Research Equity Act (PREA) came in force. PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Under PREA, sponsors submitting a new drug applications (NDA), Biological License Applications (BLA), or supplemental applications on or after April 1, 1999 must include assessments of safety and efficacy for all relevant pediatric populations for claimed indications (Bhatti *et al.,* 2011). In 2007, reauthorization of BPCA and PREA took place. The BPCA 2007 extends the provision offering additional patent exclusivity for on patent drugs being tested for pediatric use. In 2010, Biological Price competition and Innovation Act (BPCIA) incorporated the provision for the exclusivity of pediatric biologics. The BPCIA may extend by six months, respectively, the general four year marketing exclusivity and twelve year data Protection periods. If applicable, the BPCIA will also extend by six months the seven-year period of orphan drug exclusivity for such biologic (Kogan, 2011). In 2012, PREA and BPCA become permanent. Food and Drug Administration Safety and Innovations Act (FDASIA) also created new provisions governing deferral extensions under the PREA. FDASIA establishes that an "initial pediatric study plan" must be submitted not later than 60 days after the date of the end of Phase 2 meeting with FDA or other time agreed upon between FDA and the sponsor (Food and Drug Administration, n.d.). Table 2 shows the aforementioned legislation for children in chronological order and table 3

shows the list of medicine to which pediatric exclusivity has been granted till date.

Pediatric Regulation in European Union

The European Medicines Agency enacted Pediatric Regulation in January 2007. This legislation concerns the development and authorization of medicines for use in children aged up to 17 years and introduced sweeping changes into the regulatory environment for pediatric medicines (Mulberg *et al.*, 2013).

In 1997, the European Commission (EC) organized at the European Medicine Agency (EMA) a round table of experts to discuss pediatric medicines. In 1998, the Commission supported the need for international discussion on the performance of clinical trials in children in the context of the International Conference on Harmonisation (ICH) an organization working on the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and the US. Subsequently, the ICH guideline became the European guideline "Note for guidance on clinical investigation of medicinal products in the pediatric population" (ICH Topic E11), which has been in force since July 2002 (European Medicine Agency, 2007).

On 29 September, 2004, the EC released the first proposal for a Regulation on medicinal products for pediatric use. The Regulation was agreed on 1st June 2006 by the European Parliament. On 27 December 2006 the Regulation was published in the Official Journal of the European Union. It entered into force on 26 January 2007. The new pediatric legislation comprises Regulation (EC) No. 1901/2006 and the amending Regulation (EC) No 1902/2006 (European Medicine Agency, 2007).

The Pediatric Regulation (Regulation (EC) 1901/2006 as amended) establishes a new scientific committee of the European Medicine Agency (EMA), the Pediatric Committee (PDCO) (Medicine and Healthcare Regulatory Agency, n.d.). The Pediatric Committee's (PDCO's) main role is to assess the content of Pediatric Investigational Plan (PIPs) and adopt opinions on them (Rochhi *et al.*, 2010).

EMA, with the scientific support of the PDCO, developed a European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. The Agency's Management Board adopted an implementing strategy for the network on 15 January 2008. Every year, Enpr-EMA holds a workshop at the European Medicines Agency in London. Enpr-EMA works with international partners specializing in the regulation of medicines for children. It works with World Health Organization (WHO) and United State Food and Drug Administration (European Medicine Agency, n.d.).

The Pediatric Regulation establishes a new type of marketing authorization, called the Paediatric Use Marketing Authorization (PUMA), intended to stimulate the development of off patent products for use in the pediatric population. It has been designed to promote pediatric development of already

authorized products which are no longer covered by a Supplementary Protection Certificate (SPC) (Co-ordination Group for Mutual Recognition and Decenteralised Procedures-human (Co-ordination Group for Mutual Recognition Decentralised procedures-Human, 2012).

The incentives associated with the PUMA are:

- PUMA applications have an 'automatic access' to the centralised procedure (Article 31 of the Pediatric Regulation).
- PUMA benefits from the 8+2 year period of data and market protection (Article 38 of the Pediatric Regulation).
- PUMA applications submitted under the centralised procedure benefit from a partial exemption from the payment of the fees laid down in the Regulation (EC) No 297/95. This partial exemption applies to the submission of the PUMA application and some of the post authorization activities for 1 year as of the date of granting a PUMA (Questions and answers on the Paediatric Use Marketing Authorization (PUMA) cited at http://www.ema.europa.eu/docs/en_GB/document).

So far, no orphan medicinal product has benefited from pediatric regulation since the entry into force of the regulation (European Medicine Agency, 2014).

Table 4 shows the medicinal product authorized through central procedure since pediatric regulation came in force, which include a pediatric indication. Table 5 shows the list of products authorized under PUMA by EMA. Table 6 shows the differences and similarities in pediatric legislation of US and EU.

Regulations of Pediatrics in India and Other Developing Countries

Globally nearly nine million children under five years of age die every year, with pneumonia, diarrhea, and neonatal causes being the major killers (Yewale and Dharampalan, 2012). Large proportions of these victims belong to India and other developing countries. Many of these conditions could be treated with safe and effective medicines. India, with 1.21 billion people is the second most populous country in the world, representing almost 17% of the world's population. Every year, an estimated 26 million children are born in India (Jain *et al.*, 2013). This statistical data emphasizes the need for strict and mandatory laws for the marketing, manufacturing, packaging and labeling of drugs in India. Unfortunately this is not the case.

Pediatric population by itself is a spectrum of different physiologies with significant variation in pharmacodynamics and pharmacokinetics. Unfortunately, 50–90% of drugs used in children today have never been actually studied in this population, and the results of drug studies done in adults are often extrapolated for use in children (Yewale and Dharampalan, 2012). Many medicines in pediatrics are off label or unlicensed. In a review in UK, over an eight-year period (1993 to 2000), there were 81 medication-error

incidents involving at least 1144 children. There were at least 29 deaths, nine of which involved neonates. The most frequent type of medication error involved an incorrect dose (Cousins *et al.*, 2002).

Promoting appropriate and safe drugs for children is a global concern. In December 2007, WHO published its first ever model list of essential medicine list for children with more than 200 medicines, including HIV/AIDS treatment, vaccines, anesthetics, hormones, vitamins, and minerals. This serves as a reference for countries to develop national essential medicines lists, according to their specific public health needs. The list is updated every two years and has been recognized as a powerful tool to promote health equity. The second edition was published in April 2010 (Yewale and Dharampalan, 2012).

In India, the establishment of essential medicines lists for children in two states, Orissa and Chhattisgarh, is currently under way. The Indian Academy of Pediatrics is also reviewing a list for implementation at a national level. This will allow for better selection and procurement of child medicines based on specific needs. However there is still a long journey to be covered. In India, pediatric drugs are developed based on clinical trials and protocols for a healthy adult human. There are no specific drug development regulations for pediatrics. Indian clinical practice relies heavily upon safety and efficacy data published in other developed countries, or inference from adult dosing.

The Central Drug Standards and Control Organization (CDSCO) is the principal regulatory body, which functions under the Ministry of Health and Family Welfare, government of India. It ensures the approval, production, and marketing of quality drugs in India. It is a matter of great concern and disappointment that the Central Drug Standards and Control Organization does not have any guidelines/laws with regard to:-

1. Packaging and labeling requirements of pediatrics in India
2. Format for dossier required to be submitted for approval of pediatrics including biologicals e.g. vaccines, in India
3. List of excipients clamed to be safe for use in pediatric dosage forms and laws/directives governing the same in India
4. Manufacture, sale, packaging and labeling of pediatric cosmetics in India.

Provisions of manufacturing, storage, packaging and labeling of drugs and cosmetics for human use were framed in India under Drugs and Cosmetics act in 1940. Unfortunately this act does not contain any stringent guidelines for pediatrics even after amendments made in its provisions time to time since than (Yewale and Dharampalan, 2012).

Recommendations

1. There should be pediatric specific guidelines to address the ethical issues and clinical trials design, efficacy and safety compliance, marketing and prescribing of drugs in India

2. Development of the way to calculate pediatric dosing especially for drugs with different ADME in children and adults.
3. The financial grants sanctioned presently for research and development of pediatric formulations needs to be increased worldwide, which may ultimately lead to the availability of more and more fixed dose combinations for pediatrics in developing countries. This would prevent the unethical practice of prescribing the pharmaceutical preparations meant for adults, to small infants after their doses calculated superficially.
4. Harmonization between pediatric rules and regulations is required for their hassle free export and import throughout the world. It would also contribute towards rectifying the discrepancies like drugs banned in one country are being sold in the other *etc*.

ICH Guideline E11		**FDA**	
Terms	**Age**	**Terms**	**Age**
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	Adolescent	12 to <16 years

Table 1: Classification of Pediatric Age Categories as per ICH and FDA Guidelines *(*Zisowsky *et al.,* 2010)

Year	**Legislation**
1979	Product label include pediatric use section
1994	Pediatric labeling rule
1997	FDA Modernization Act (FDAMA)
1998	Pediatric rule
2002	Best Pharmaceuticals for Children Act (BPCA)
2003	Pediatric Research Equity Act (PREA)
2007	Food and Drug Administration Amendment Act (FDAMA); Reauthorization of BPCA and PREA
2010	Pediatric Exclusivity for Biologics (Biologics Price Competition and Innovation Act, 2010)
2012	Food and Drug Administration Safety and Innovations Act (FDASIA)

Table 2: History of Pediatric Regulation in US

S. No.	Drug	Date of Exclusivity	Sponsor	Indication(s)
1.	Abacavir	14/12/98	GSK	HIV
2.	Albuterol	27/8/08	GSK	Treatment and prevention of the bronchospasm in the children from birth to <4 years of the age with obstructive airway diseases
3.	Alendronate	28/4/03	Merck	Osteogenesis imperfecta
4.	Alfuzosin	7/9/10	Sanofi Aventis	Treatment of patients 2-16 years with elevated detrusor leak point pressure associated with known nuerological disorder (e.g., spina bifida)
5.	Almotriptan	13/1/09	Johnson & Johnson	Acute treatment of migraine in the adolescent, ages 12 to 17 years
6.	Amlodipine	27/11/01	Pfizer	Hypertension
7.	Amphetamine mixed salt	28/10/04	Shire	ADHD
8.	Anagrelide	25/5/04	Shire	Thrombocytopenia secondary to myeloproliferative disorder
9.	Anastrozole	14/11/07	Astrazeneca	Male pubertal patient with gynecosmatia and female pediatric patients with McCune –Albright Syndrome with progressive precocious puberty
10.	Aripiprazole	14/11/07	Otsuka	Schizophrenia; Bipolar depression
11.	Atomoxetine	18/12/01	Lilly	Attention Deficite Hyperactive Disorder
12.	Atrovastatin	22/2/02	Pfizer	Hypercholeserolemia
13.	Atovaquone/Proguanil	6/8/03	GSK	Prevention of malaria
14.	Azelastine	11/8/99	Asta	Itching associated with allergic conjunctivitis
15.	Balsalazide	23/8/06	Salix	Ulcerative colitis
16.	Benazepril	2/703	Novartis	Hypertension
17.	Bendamustine	24/5/12	Cephalon	Relapsed or refractory acute leukemia
18.	Betaxolol	28/2/07	Falcon	Treatment of elevated intraocular pressure
19.	Bicalutamide	19/9/08	Astrazeneca	Treatment of gonadotropin independent precocious puberty in boys with testotoxicosis
20.	Capecetabine	28/8/13	Hoffman La Roche	Non disseminated intrinsic diffuse brain stem gliomas
21.	Dexmedetomidine	12/3/13	Hospira	Loading and maintenance infusion for sedation in intubated and mechanically ventilated pediatric patients
22.	Difluprednate	21/3/13	Alcon	Treatment of post operative inflammation following cataract surgery
23.	Efavirenz	29/1/13	BMS	Treatment of HIV-1
24.	Entecavir	5/12/13	BMS	Chronic Hepatitis B virus infection
25.	Palonosetrone	10/4/14	Helsinn	Prevention of post operative nausea and vomiting and chemotherapy induced nausea and vomiting
26.	Sapropterin	13/3/14	Biomarine	Treatment to reduce blood phenylalanine level
27.	Vigabetrin	3/10/13	Lundbeck	Intractable complex partial seizures and and infantile spasm
28.	Namenda (memantine hydrochloride)	18/6/2014	Forest Laboratories	moderate to severe confusion (dementia) related to Alzheimer's disease.
29.	Namenda XR	18/6/2014	Forest Laboratories	moderate to severe confusion (dementia) related to Alzheimer's disease
30.	Rebeprazole	4/12/12	Eisai	Healing & maintenance of GERD & improvement of GERD symptoms in children 1-11 years of age

Table 3: List of medicine to which pediatric exclusivity has been granted till date in USA (Food and Drug Administration, n.d. updated 16 April, 2014)

Sr. No	Name of Medicinal Product	Year of authorization	Requirement to fulfill Pediatric Regulation at first authorization	Indication is pediatric-only or 'mixed' (adult and pediatric)
1.	Altargo (Retapamulin)	2007	No	Mixed
2.	Atriance (Nelarabine)	2007	No	Mixed
3.	Cervarix (Human papillomavirus vaccine (types 16, 18)	2007	No	Mixed
4.	Cyanokit (Hydroxocobalamin)	2007	No	Mixed
5.	Elaprase (Idursulfase)	2007	No	Mixed
6.	Optimark (Gadoversetamide)	2007	No	Mixed
7.	Cystadane (Betaine anhydrous)	2007	No	Mixed
8.	Diacomit (Stiripentol)	2007	No	Pediatric only
9.	Increlex (Mecasermin)	2007	No	Pediatric only
10.	Avamys (Fluticasone furoate)	2008	No	Mixed
11.	Privigen (Human normal immunoglobulin)	2008	No	Mixed
12.	Vimpat (Lacosamide)	2008	No	Mixed
13.	Mycamine (Mycamine)	2008	No	Mixed
14.	Kuvan (Sapropterin)	2008	No	Mixed
15.	Mepact (Mifamurtide)	2009	No	Mixed
16.	Vedrop (Tocofersonal d-alpha tocopheryl polyethylene glycol succinate	2009	No	Pediatric only
17.	Synflorix (Pneumoccocal polysaccharide conjugate vaccine)	2009	No	Pediatric only
18.	Prevenar 13 (Pneumoccocal polysaccharide conjugate vaccine)	2009	Yes	Pediatric only
19.	Menveo (Meningococcal group and conjugate vaccine)	2010	Yes	Mixed
20.	Vpriv (Velaglucerase alfa)	2010	Yes	Mixed
21.	Fluenz (Influenza vaccine (live attenuated, nasal)	2011	Yes	Pediatric only (Waiver)
22.	Buccolam (Midazolam)	2011	Yes (PUMA)	Pediatric only
23.	Votubia (Everolimus)	2011	Yes	Mixed
24.	Colobreathe (Colistimethate sodium)	2012	Yes	Mixed
25.	Xaluprine (Mercaptopurine)	2012	No	Mixed
26.	NovoThirteen (Catridecacog)	2012	Yes	Mixed
27.	Efavirenz Teva (Efavirenz)	2012	No	Mixed
28.	Kalydeco (Ivacaftor)	2012	Yes	Mixed
29.	Desloratadine Actavis (Desloratadine)	2012	No	Mixed
30.	Fycompa (Perampanel)	2013	Yes	Mixed

Table 4: Medicinal products authorized centrally since 2007, which include a pediatric indication (European Medicine Agency, 2013)

Name of Drug	Approval Date	Manufacturer's Name	Indication	Reference
Buccolam (Midazolam)	11 August, 2009	ViroPharma	Prolonged, acute, convulsive seizures in pediatric patients from the age of 3 months to 18 years	European Medicines Agency, 2011
Hemangiol (Propranolol	21 February, 2014	Pierre Fabre Dermatologie	proliferative infantile haemangioma	European Medicines Agency, 2014

Table 5: EMA approved PUMA medicinal product

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	US BPCA	**US PREA**	**EU (PIP)** (For patented, SPC covered medicines and new unauthorized product)	**EU PUMA** (exclusively for off patent and pediatric use medicinal product)
	Optional	Mandatory	Mandatory	Optional
	Written Request	Pediatric Assessment	Pediatric Investigation Plan	Pediatric Investigation Plan
Waiver	Provision of waiver is absent	Yes	Yes	Yes
Deferral	Provision of deferral is absent	Yes	Yes	Yes
Plan discussions Begin	End of Phase 2 of clinical trial to post approval	End of Phase 2 of clinical trial to NDA/BLA approval	Completion of adult PK (End of Phase 1)	Completion of adult PK (End of Phase 1)
Final plan approval	Variable	With NDA/BLA approval	Prior to MAA filing	Prior to MAA filing
Reward	Patent exclusivity	Patent exclusivity provision is absent	SPC or market exclusivity (Orphan drugs)	8+2 years data/ marketing protection, brand name can be retained
Drugs	Yes	Yes	Yes	Yes
Biologics	Yes (BPCI 2010)	Yes	Yes	Yes
Biosimilars	Yes	Yes	No	No
Orphan drugs	Yes	No	Yes	No
Off patent	Yes	No	No	Yes
Generics	No	No	No	No
Homeopathic	No	No	No	No
Decision authority	Review Division	Review Division	Pediatric Committee	Pediatric Committee

Table 6: Comparison of BPCA, PREA, PUMA (Mulberg *et al.,* 2013)

Abbreviations	
ADME	Absorption, Distribution, Metabolism, Excretion
BLA	Biological License Applications
BPCA	Best Pharmaceuticals for Children Act
BPCIA	Biological Price competition and Innovation Act
CDSCO	Central Drug Standards and Control Organization
EMA	European Medicine Agency
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovations Act
ICH	International Conference on Harmonisation
NDA	New Drug Applications
PREA	Pediatric Research Equity Act
SPC	Supplementry Protection Certificate
WHO	World Health Organization

Conclusion

Regulations of drugs for pediatrics are very settle throughout the world. Although US and EU are amongst the pioneers in initiating the framework for regulating the approval, sale, production, storage, clinical trials and packaging/labeling of pediatric dosage forms, yet a long journey is yet to be covered in this direction. History has witnessed many disasters relating to the adverse drugs and excipients reactions on mass scale in pediatric populations. Many drugs which are considered safe in adults are banned for pediatrics in some countries but still being used for the same in other countries. In fact most of the third world countries consider children and neonates as small adults and therefore the laws governing the medicines for adults are extrapolated in children in major part of the world. Further there is no harmonization between the countries across the globe. The enforcement departments in all the countries would have to frame new laws for pediatrics. This would not only enhance the export-imports of pharmaceuticals within the countries but assure better health care for pediatrics at the same time.

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