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HARMONIZATION AND COMPARATIVE STUDY OF REGULATION ON PEDIATRIC DRUGS IN US, UK AND TANZANIA

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ABSTRACT

Substantiation based medicine and healthcare constitutes the pillars of optimal medical care. Though there are deficits in understanding the quality and efficacy of Pediatric therapies, as prime criteria study of regulation requisite for conducting Pediatric clinical trials. Many efficacy data are unreliable. Over 60% of medicines used in children have not been licensed for use in Pediatric population. Efficacy of the Pediatric drugs is determined through extrapolating the data generated from adult's clinical trials. Evidently it was considered that it is complicated to conduct clinical trials in Pediatric population due to ethical consideration and recruitment issues, Harmonization of regulatory requirements will hopefully lead to a reduced clinical trial burden and an escaping of the overexposure of children to untested medicines. The present study focuses on the harmonization of regulation for Pediatric clinical trial and for the drug registration in US, UK and in Tanzania and it will be more helpful for the developing countries.

INTRODUCTION

The use of off-label prescription ingrained in clinical practice, Pediatric drug regulation introduced by the European Union, together with the renewal of the Pediatric Rule by the Food and Drug Administration on the requirements for Pediatriclabelling, imposes special attention to dose selection in Pediatric clinical trials.Ethical, practical and even economic considerations have caused the evaluation of efficacy and safety of drugs in children to be based on empirical extrapolations from clinical trials in adults. Dose choicein Pediatric populationis determined by differences in the pharmacokinetics and pharmacodynamics, disease or a combination of these factors.[1]

PEDIATRIC CLINICAL TRIAL:[2,3]

Pediatric clinical trials are more challenging as compare to the adults, because parents have to make decisions about trial participation on behalf of their child. Main benefit of Pediatric clinical trials is access to new treatments that might not be routinely available. And the risk associated with the Pediatric clinical trial is discomfort, inconvenience, pain, and effect on growing or developing organs and size or volume of biological samples.

Extrapolation of efficacy from adult data or other data to the Pediatric population can simplifyPediatric drug development and help to increase the number of approvals for Pediatric use and also helped to maximize the use of existing information to increase the efficiency of Pediatric drug-development programs while maintaining the goal of increasing the number of safe effective medicines approved for Pediatric use on the basis of scientifically robust data.

PEDIATRIC DRUGS AND CLINICAL TRIALS REGULATION IN US[4-10]:

The Regulation for Pediatric clinical trial in US has the stated aim to protect children and improve their health through the conduct of formal clinical research in order to increase access to new medicines and to derive data to guide the prescriber in the use of medicines in the Pediatric population.In US as per Pediatric research equity act (PREA) before conduct of Pediatric trials Pediatric study plan (PSP) is mainly required for conduct clinical trials in Pediatric population.PSP contains protocol for conduct clinical trial in these populations.

Content of and Process for Submitting Initial Pediatric Study Plans and Amended

Pediatric Study Plans:

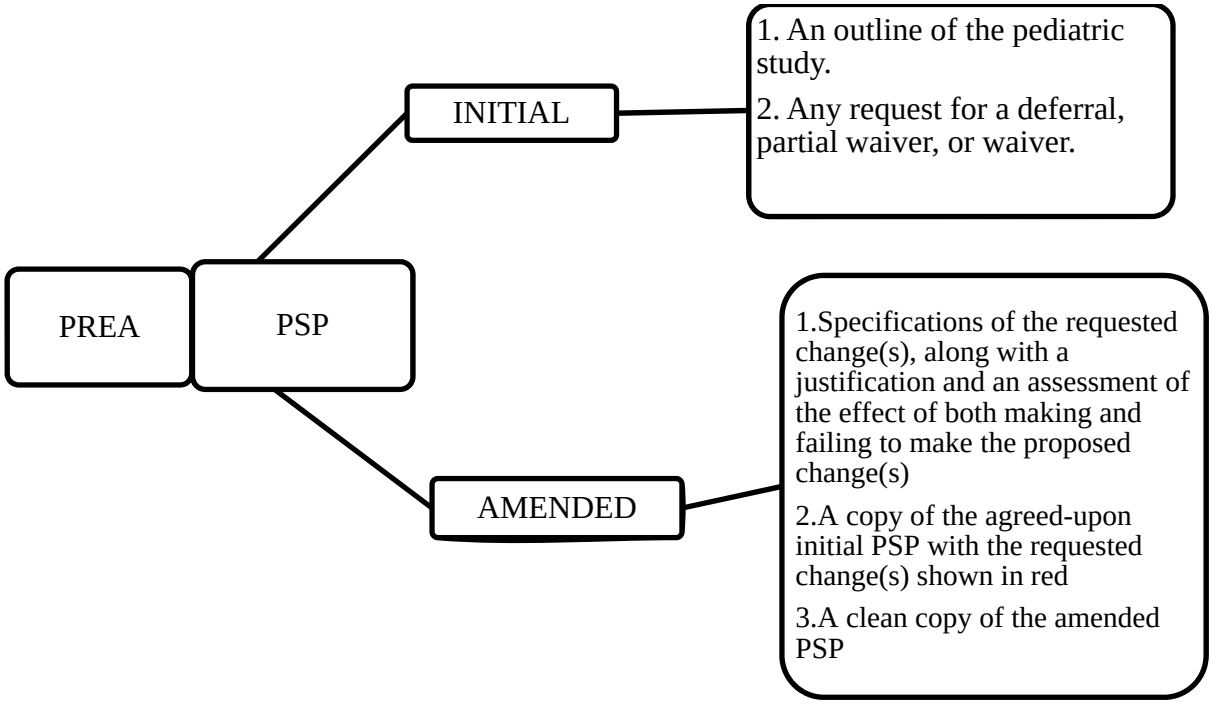


Figure 1: Content of Initial Pediatric Study Plans and Amended Pediatric Study Plans

PREA requires the conduct of Pediatric studies for certain drug and biological products. Particularly PREA requires new drug applications (NDAs) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a Pediatric assessment except the applicant has obtained a waiver or deferral. PREA was signed into law on December 3 2003. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of Pediatric use information in drug product labelling."Pediatric assessment" and "Pediatric studies" term are used interchangeably and the term "Pediatric assessment" describes the requisite submissions under PREA

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and Pediatric populations. Products intended for Pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant Pediatric population. PREA does not require applicants to conduct separate safety and effectiveness studies in Pediatric patients in every case. When study reports are submitted as part of an application the content and format must meet the relevant general requirements for submission (21 CFR 314.50 for NDA requirements).

WAIVERS AND DEFERRALS:

FDA authorized by PREA to waive the requirement to submit the Pediatric assessment, based on established criteria, for some or all Pediatric age groups. a full or partial waiver can be granted by FDA for the requirements on its own initiative or at the request of an applicant. If an applicant requests a waiver, the applicant should provide written explanation for the waiver and evidence to support the request documents.

Regulatory efforts to protect children from harmful medications began in the early part of the 20th century. Many of the initial laws were established in response to specific incidents involving products that caused harm. There are two regulations for the Pediatric drugs in US.

1. Best Pharmaceuticals For Children Act (BPCA)
2. Pediatric Research Equity Act (PREA)

BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA):

It is related to Pediatric drug enlargement and testing of off-patent drugs fell into three categories identifying and prioritizing drugs needing study. Developing study requests in association with experts at national institute of health (NIH), FDA, and other organizations conducting studies on priority drugs after manufacturers decline to do so. The NIH must publish a priority list of needs in Pediatric therapeutics, including drugs or indications that require study, every 3 years. The NIH can submit a proposed Pediatric study request (PPSR) to the FDA. A PPSR is a draft Written Request (WR) that gives details about the clinical trials needed to improve Pediatric labelling.

In this regulation Pediatric development programme is optional, and written request documents are mainly used. Orphan drugs are included in this and give six months data exclusivity for the Pediatric drugs.

PEDIATRIC RESEARCH EQUITY ACT (PREA):

Federal Food, Drug, and Cosmetic Act amended by PREA and Under this act the FDA can necessitate Pediatric studies of a product for which a New Drug Application is submitted, if the agency determines the product is likely to be used in a substantial number of Pediatric patients, or if it would provide meaningful benefit for children over existing treatments. For new applications to evaluate the safety and efficacy of a drug Pediatric assessment is required. In PREA the Pediatric drug development is mandatory and Pediatric study plan documents are

mainly used. Orphan drugs are excluded. This act not gives any kind of exclusivity for Pediatric drugs. Review of the Pediatric data is standard in this act.

PEDIATRIC DRUGS REGULATION IN UK [11, 12]:

Regulation [1901/2006] aims to facilitate the development and accessibility of medicinal products for use in the Pediatric population, to ensure that medicinal products used to treat the Pediatric population are subject to ethical research of high quality and are appropriately authorized for use in the Pediatric population, and to improve the information available on the use of medicinal products in the various Pediatric populations. These objectives should be achieved without subjecting the Pediatric population to unnecessary clinical trials and without delaying the authorization of medicinal products for other age populations.

Overall objectives of the Regulation,

1. To improve the health of the children of Europe by increasing the research, development and authorization of medicines for use in children
2. Without subjecting children to unnecessary clinical trials
3. Without delaying the authorization of medicinal products for other age populations

General objectives,

1. Facilitate the development and accessibility of medicines for use in children
2. Ensure that medicines used to treat children are subject to high quality ethical research
3. Ensure that medicines used to treat children are appropriately authorized for use in children
4. Improve the information available on the use of medicines in various Pediatric populations

Major Provisions of the UK Pediatric Regulation and its amendment require that manufacturers submit a Pediatric Investigation Plan (PIP) for all new products and line extensions (new indication, new formulation, new dosage form, etc.) for existing products. The regulation also specifies that PIPs must state which Pediatric age groups will be studied. Waiver or deferral for age groups not intended for studies should be requested as part of the PIP. The Marketing Authorization Application (MAA) must “cover all subsets of the Pediatric population, and thus must contain data for use in each of the different Pediatric age groups unless waived or deferred.

PDCO (Pediatric committee) an expert committee of the European Medicines Agency (MHRA), created by the Pediatric Regulation to review PIPs, waivers and deferrals of Pediatric studies.

The regulation also provides incentives for doing studies in Pediatric patients. If a product has been granted a "supplementary protection certificate," i.e., a certificate providing additional years of exclusive marketing in the form of an extension of patent protection (as a result of the present application or an earlier application for use in adults), a six-month extension of the supplementary protection certificate can be given as a reward for the expense of conducting studies in Pediatric patients, even if the study results do not support a Pediatric indication.

PEDIATRIC DRUGS REGULATION IN TANZANIA:[13]

Data on the appropriate use of medicinal products in the Pediatric population should be generated unless the use of a specific medicinal product in Pediatric patients is clearly inappropriate. The Pediatric development programme should not delay completion of adult studies and availability of a medicinal product for adults.During clinical development, the timing of Pediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Since development of Pediatric formulations can be difficult and time consuming, it is important to consider the development of these formulations early in medicinal product development. Justification for the timing and the approach to the clinical programme needs to be clearly addressed with TFDA at an early stage and then periodically during the medicinal product development process.

In Tanzania all drugs are regulated by the Tanzania food and drugs cosmetic act 2003. For the regulation of Pediatric clinical trial Tanzania mainly follows ICH E11 guideline. Regulation mainly provides the details about Fees to be paid by product dealers, Training and Consultancy Services, Duty to collect fees, Fees and Charges neither refundable nor transferable, Offence, Penalty, RevocationEstablishment of the Tanzania Food and Drugs Authority, Functions of the Authority, Powers of the Authority, Sources of fund and its management, Appointment and tenure of the Director General, Establishment of the Ministerial Advisory Board., powers and functions of the Board, Establishment of Directorates and appointment of Directors andother employees of the Authority, Transfer of staff and their rights, Establishment of Technical Committees of the Authority, Establishment of the Laboratory, Appointment of Analysts, Exemption from taxation, Control of manufacturing, importation, export, sell etc.

HARMONIZATION [14-18]

The harmonization is mainly required to change the environment of drug development for Pediatric population and to encourage, and to facilitate high-quality and ethical clinical research for children within the developing country. The framework of incentives and rewards for pharmaceutical companies established for the development of drugs for Pediatric use are compared. It appears that the well developed country i.e US and the UK have both developed specific regulations for Pediatric drug development while developing country Tanzania has not Pharmaceutical companies are encouraged to develop Pediatric assessment, including Pediatric clinical trials, which are described in a Pediatric plan, submitted to the relevant drug regulatory authorities. A system of rewards for Pharmaceutical companies submitting an application for marketing authorization containing Pediatric use information has been put in place to cover the supplementary investment for testing drugs in children. Subject to conditions, these rewards consist in a 6-month extension of the patent or supplementary protection.

Apart from special cases, the Pediatric investigation plan (PIP) in the UK is required to be prepared and submitted to the competent authorities after availability of adult pharmacokinetic studies (after phase I) as per regulation 1901/2006, which means at an near the beginning phase of a new drug development plan. But in case of US, the Pediatric study plan is required later during the phase II or III clinical trials (as per PREA). In practice, it has become difficult for pharmaceutical industries to develop a practicable clinical program for Pediatrics including timelines for studies in children that satisfy both UK and US drug regulatory authorities.

Pediatric committee is not established in Tanzania on other hand Pediatric committee (PDCO) is well established in UK as per regulation 1901/2006, their roles and duties are to review and assess Pediatric plans, to issue recommendations, to advise pharmaceutical companies on the content and format of Pediatric data to be methodically collected and analyzed, and to avoid exposure of children to unnecessary or superfluous clinical trials.

Additionally US and UK Pediatric drugs regulation both having the goal to integrate the Pediatric drug development into the standard development. These goals have been reached in many therapeutic areas nevertheless some areas like therapeutics for neonates and infants as well as therapeutics for rare diseases and long-term studies are still neglected.

The US and UK Pediatric drugs regulation have built a complex framework for Pediatric drug development. To guide pharmaceutical companies through specific procedures many of regulatory documents are available to assist in specific scientific and procedural questions. However, for a global Pediatric drugs development approach the assistance through these documents is not up to the mark due to significant differences in regard to the regulatory requirements and prospect. The most important differences are regarding the legal scope.

The Pediatric Research Equity Act (PREA) requires studies for drug under review and proposed adult indication whereas the UK Pediatric regulation requires studies on all Pediatric indications and conditions for which the medicinal product may be helpful. Different Pediatric medicinal product groups are covered by the scope of the regulation.

Whereas orphan drugs (OD) are not covered by the US Pediatric drugs regulation but by the UK the reverse is true for biosimilar. Additional important differences are timing of the Pediatric development plan submission and the timing and consequences of the corresponding fulfilment check. Since the compliance check is not a pre-requisite for the validation of a NDA in the US the medicinal products can be in advance available in the US than in the EU at least for the adult population.

New orphan drugs are fast available in the US than in the UK for the adult population, since Pediatric studies are not required under PREA for orphan drugs. Nowadays the Pediatric drug development respectively the Pediatric clinical trials are globally associated. First so the number of participants is easily and efficiently reached and secondly in order to fulfil the clinical demands for the future worldwide Marketing Authorizations. The establishment of the Parallel Scientific Advice procedure for the exchange of different views on scientific issues between EMA and FDA is a welcomed option in order to get an understanding for the specific US and UK expectations already early in the product development phase. The harmonization of the regulatory framework for Pediatric drug development can be reached through continuous refinement and harmonization of international standards and guidelines together with the establishment of a global Pediatric research infrastructure through internalization of clinical research institutions and networks.

For receive meaningful data from Pediatric clinical trial and to minimize the regulatory trouble the harmonization of the US and UK Pediatric plan template or the establishment of a common

core document combined with a harmonized process for interactions with US and European country it could be an option which should be followed up in the upcoming time. Ethical and practical considerations in conducting Pediatric research should be the basis for establishment of a harmonized standard. The studies should also be required for orphan indications in Pediatric population per UK 1901/2006 regulation. UK also encourages the development of the off patent medicines.

PEDIATRIC CLINICAL TRIAL REQUIREMENTS:

General Approach

Evaluate all possible indications based on the mechanism of action of product:

1. Literature review, data from other development programs, proof of concept studies, etc.
2. Consultation with Pediatric experts to assess each indication
3. Determine what data would be needed to initiate studies in Pediatrics, for developmental toxicities that may require juvenile animal studies.

Consider the type of information to be collected in Pediatric clinical trials

1. If efficacy can be extrapolated, PK and safety may be sufficient
2. Existing safety data may potentially be used to support safety
3. Estimation of the potential sample size of a Pediatric trial must be made to determine the type of trial design that may be used (e.g., small sample size may be overcome with large treatment effects or longer study period)

Development of program should include:

All indications considered, Justification for inclusion or exclusion of specific indications, what additional data are needed (always support with facts), Feasibility of studies, General approach to clinical studies (e.g., use of extrapolation)

There should be separate Pediatric drugs review committee. That reviews the Pediatric plans.

Expertise includes Pediatrician, Expert of chemistry, Statistics, Legal pharmacology, Safety, expert of Toxicology, from Ethical committee.

To request a waiver/Deferral, applicant should provide:

1. Product name, applicant name, and indication
2. Age group(s) included in waiver request
3. Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority.
4. Evidence that the request meets the statutory reason(s) for waiver of Pediatric assessment requirements
5. Applicant Certification

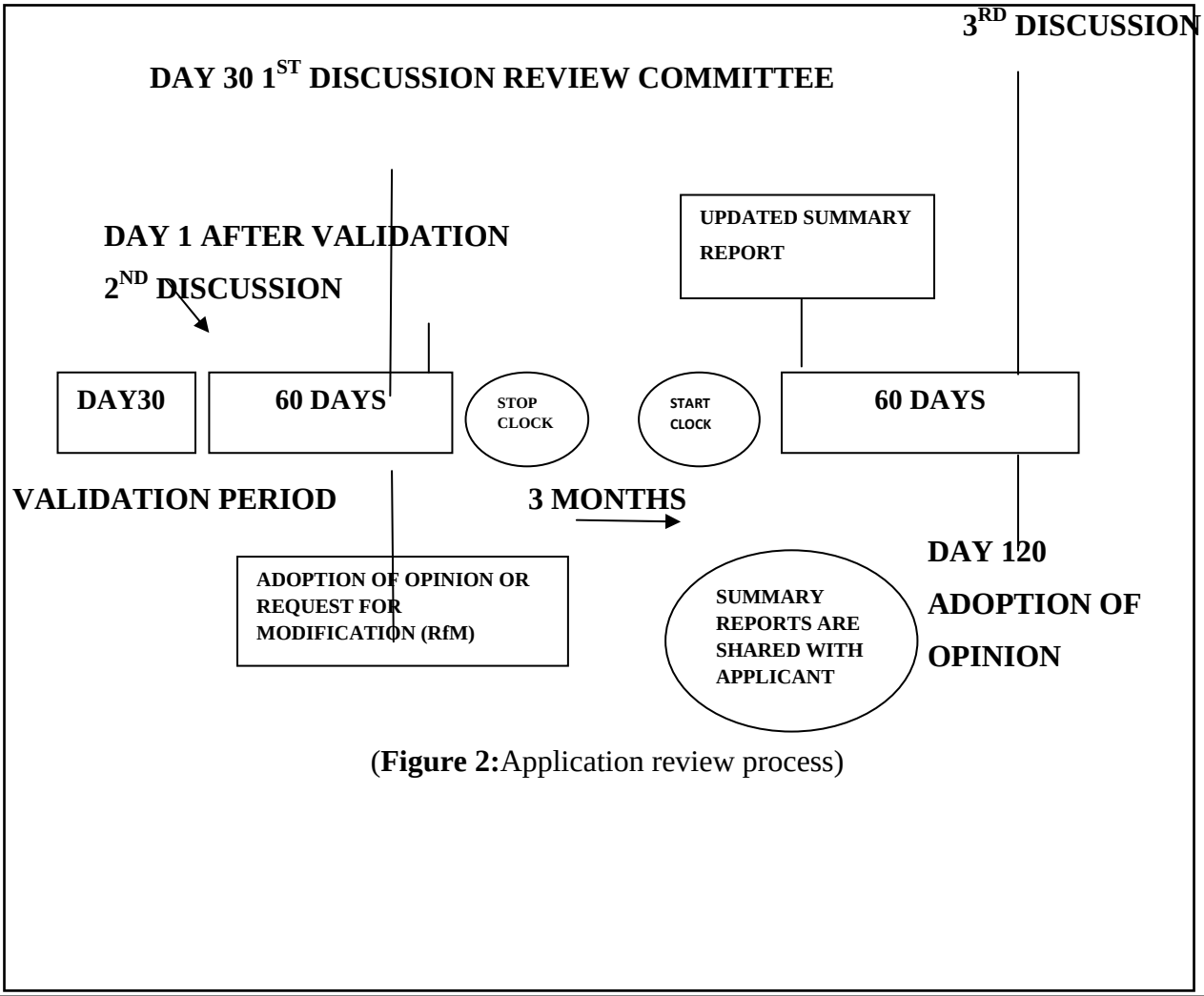
Regulatory authority may waive requirement for studies in some or all Pediatric age groups if:

1. Necessary studies are impossible or highly impracticable;
2. There is evidence strongly suggesting that the drug would be ineffective or unsafe in all Pediatric age groups; or
3. Drug does not represent a meaningful therapeutic benefit over existing therapies for Pediatric patients, and is not likely to be used in a substantial number of Pediatric patients.
4. A partial waiver may also be granted if the sponsor can demonstrate that reasonable attempts to produce a Pediatric formulation for that age group have failed

During the review of the marketing application the following steps should be carried out for the complete review.

1. Validation of the application (within 30 days)
2. Adoption of opinion or request for modification (within 60 days)
3. After 3 months updated summary report should be given and it should be shared with applicant.
4. Adoption of final opinion should be carried out within 120 days

APPLICATION REVIEW PROCESS



(**Figure 2:**Application review process)

In the protocol of Pediatric clinical trial the details of all measures of pharmaceutical and clinical development should be given to support the authorization of drugs for children.Pediatric legislation promotes gradual improvements: earlier availability of new adult drugs, better dose calculation, and improved drug safety.

US legislation balances mandatory requirements and incentives. EU emphasis is on mandatory requirements. The European Medicines Agency (EMA) will not register a new drug without a Pediatric investigation plan (PIP) agreed with its Pediatric committee (PDCO). PIPs should be submitted end of Phase I; their negotiation takes almost a year. The EU PIP procedure keeps many people busy: 66 PDCO members, 30 EMA Pediatric coordinators and administrators; employees of 27 EU authorities; and people in industry, CROs, and consultancies. Even companies that develop drugs specifically for children must negotiate a PIP. The UK legislation originated in good intention; run by a bureaucracy with much power and little control, it starts to affect drug development. Companies will avoid therapeutic areas with extreme PDCO requests. Even the UK ombudsman criticizes EMA/PDCO for lack of transparency.

We need a Harmonization that facilitates, promotes, and rewards basic and applied research for better medicines, and children should benefit.Blind trust into industry or academia or unlimited power to bureaucrats is not the right path.

COMPARISION OF REGULATION FOR PEDIATRIC DRUGS IN US, UK AND TANZANIA

TABLE 1: COMPARISION OF REGULATION FOR PEDIATRIC DRUGS IN US, UK AND TANZANIA

PARAMETERS	**US**	**UK**	**TANZANIA**
Drug Regulatory Authority	United States food and drug administration (USFDA)	Medicines and Healthcare products Regulatory Agency (MHRA)	Tanzania food and drug administration (TFDA)
Review Authority	Centre for Drug Evaluation and Research (CDER), Centre	Pediatric committee (PDCO)	TANZANIA FOOD AND DRUGS AUTHORITY

	for Biological and Evaluation Research (CBER)		
Age of Pediatric Population	Age criteria as per USFDA Guideline. **Neonate**: Birth to 1 month **Infant**: 1 month to 2 years **Children**: 2 to 12 years **Adolescent**: 12 to <16 years.	**ICH guideline E11** **Newborn infants:** 0 to 27 days **Infants and toddlers:** 28 days to 23 months **Children:** 2 to 11 years **Adolescent:** 12 to 16-18 years	**ICH guideline E11** **Newborn infants:** 0 to 27 days **Infants and toddlers:** 28 days to 23 months **Children:** 2 to 11 years **Adolescent:** 12 to 16-18 years
Regulation for Pediatric drugs	BPCA (Best Pharmaceuticals for Children Act), PREA (Pediatric Research Equity Act)	1901/2006	Tanzania Food And Drugs Cosmetic Act
Marketing Application Documents Format	For the new drug application of Pediatric drugs in US that iscalled written request (WR).	For the new drug application of Pediatric drugs in UK that is called marketing authorization	For the new drug application of Pediatric drugs in Tanzania that is called marketing authorization

		application (MAA)	application MARKETING APPLICATION
Development of Regulation	Regulations for Pediatric drugs are fully developed i.e PREA for marketing authorization requirements and BPCA gives six months data exclusivity for the Pediatric drugs.	Regulations for Pediatric drugs are not fully developed. Regulation no 1901/2006 is developed for the marketing authorization requirements and for the Pediatric clinical trials requirements.	Regulations for Pediatric drugs are not fully developed as compare to US and UK.
Waiver	As per US Pediatric clinical trials regulation they gives waiver in some cases for the clinical trial. (AS PER PREA)	As per US Pediatric clinical trials regulation they gives waiver in some cases for the clinical trial. (1901/2006)	Not applicable
Deferral	As per US Pediatric clinical trials regulation they applicant can defer the Pediatricclinical trial in some cases	As per US Pediatric clinical trials regulation they applicant can defer the Pediatricclinical trial in some cases	Not applicable

	(AS PER PREA)	(AS PER 1901/2006)	
Drugs	Regulation applicable for all Pediatric drugs	Regulation applicable for all Pediatric drugs	Regulation applicable for all Pediatric drugs but not gives details about combination of Pediatric drugs.
Orphan Drugs	Regulation applicable for all orphan drugs and also gives exclusivity for orphan drugs.	Regulation applicable for all orphan drugs and also gives exclusivity for orphan drugs	Not applicable
Biosimilars	Regulation for Pediatric drugs in US included bio similar drugs	Regulation for Pediatric drugs in UK not included bio similar drugs	Not applicable
Rewards	Best pharmaceutical for children act (BPCA) provides marketing exclusivity for Pediatric drugs.	The regulation 1901/2006 provides rewards for doing studies in Pediatricpatients. If a product has been granted a "supplementary protection	Not applicable

		certificate," i.e., a certificate providing additional years of exclusive marketing in the form of an extension of patent protection	
Approval Of Plan	variable	prior to marketing authorization application (MAA) filing	prior to marketing application filing
Pediatric Plan Required	later during the phase II or III trials	After Phase I	After Phase I
Discussion of Plan	Discussion of PediatricStudy Plan takes Place At The END OF PHASE II	Discussion of Pediatricinvestigation Plan takes place at the end of adults clinical trial (PHASE 1)	Discussion of PediatricPlan takes place at the end of adults clinical trial (PHASE 1)
Pediatric Clinical Trial	PEIATRIC STUDY PLAN (PSP) document is used	PEDIATRIC INVESTIGATION PLAN (PIP)	ICH E11
Clinical Trial Review Board /Ethical	Institutional review board and Independent	Institutional review board and Independent ethics	National ethical committee (NEC)

Committee	ethics committee (IRB/IEC)	committee (IRB/IEC)	
Type of Exclusivity	Pediatric Exclusivity (Marketing Exclusivity)	Pediatric Exclusivity or SPC Extension (Marketing Exclusivity)	Not applicable
Exclusivity period	**6 Months** (adds to existing exclusivity)	**6 Months** (adds to existing exclusivity)	Not applicable
Pediatric orphan drug Exclusivity period	Additional **SIX MONTH** exclusivity to existing orphan drug exclusivity	Additional **2 years** exclusivity to existing orphan drug exclusivity	Not applicable
Regulation that support exclusivity	**21 CFR § 355a, BPCA**	**1901/2006**	Not applicable
Exclusivity rights condition	▪ General exclusivity extension added to the end of any non-patent exclusivity Adds to the life of patented drug products listed in the Orange Book	▪ Available for patented Pediatric drugs Additional six-month extension to existing patent term extensions(SPCs)	Not applicable

CONCLUSION

In conclusion, Pediatric research has been increasing in volume and it has become a global phenomenon. Clinical studies in Pediatric population required careful planning and resourcing if the goals of the initiatives from regulators, governments, and health organizations are to be achieved. Incorporation of Pediatric drug development in the planning process and assessment of the return on investment is significant. The creation of PIPs requires an understanding of the clinical requirements in children and what studies are feasible. Harmonization of regulatory requirements will hopefully lead to a reduced clinical trial burden and an escaping of the overexposure of children to untested medicines. Clinical study risk assessment and contingency planning and the careful placement of the studies taking into account cultural, regulator, and clinical practice differences between US, UK and Tanzania will ultimately determine the success of Pediatric development.

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ABBREVIATIONS

BPCA: Best Pharmaceutical for Children Act
CFR: Code of Federal Regulation
CBER/CDER: Central for Biological Evaluation and Research/ Centre for Drug Evaluation and Research
EMA: European Medicines Agency
FDA: Food and Drug Administration
ICH: International Conference of Harmonisation
IRB/IEC: Institutional Review Board/ Independent Ethics Committee
MAA: Marketing Authorization Application
MHRA: Medicines and Healthcare products Regulatory Agency
NDA: New Drug Application
NEC: National Ethical Committee
NIH: National Institute of Health
PDCO: Pediatric Committee
PIP: Pediatric Investigation Plan
PPSR: Proposed Pediatric Study Report
PREA: Pediatric Research Equity Act
PSP: Pediatric Study Plan
RFM: Requirement For Modification
SPC: Supplementary Protection Certificate
TFDA: Tanzania food and Drug Administration
US: United States
UK: United Kingdom
USFDA: United States Food and Drug Administration
WR: Written Requests

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