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Regulatory Challenges and Strategies for Pediatric Drugs in the EU and US

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Abstract:

The immense use of unlicensed and off-label medicines in pediatric care points to serious regulatory, ethical, and clinical issues. A subtlety in pediatric drug development and its regulation has been carried out, making it clear the big gap that exists between adult and pediatric pharmacotherapy. In fact, up to 50% of medicines prescribed for children across Europe fall into these categories, for the most part due to a paucity of drugs specifically approved for use in the pediatric population. This only goes to put pediatric patients at unnecessary risks of encountering drug side effects and inefficacies. This underscores the critical need for tailored drug development.

The main changes to the regulatory framework for the European Union (EU) and the United States (US) have been to respond to these new challenges with the implementation of landmark legislation aimed at the safe and effective administration of medicines to children. The Paediatric Regulation of the EU and the Pediatric Research Equity Act (PREA) of the US regulate full Pediatric Investigation Plans (PIPs) and, in fact, even give companies some incentives to make such studies happen. This regulatory approach aims at bridging the gap by ensuring that new and pre-existing medicines are systematically tested for pediatric use, hence expanding the rational arsenal of clinically validated pediatric drugs.

These advancements are not challenge-free, though, and the present article has pointed to some of those challenges that are yet to be cleared. The latter includes complexities in trial design, ethics surrounding enrolling children into clinical trials, and continuing use, in the market, of off-label medications. In this regard, innovative trial designs, like adaptive pathways and model-based approaches, may offer more flexibility and efficiency in collecting pediatric-specific data.

The review goes on further to reveal the ethical dimensions in conducting pediatric drug trials, whereby it highlights the fact that the business interests of the drug trials should be, in every way, subordinated to the health and well-being of the child participants. It discusses the importance of monitoring long-term safety and the role of pharmacovigilance in protecting pediatric patient populations. In conclusion, though, in an attempt at regulation, there has been a significant amelioration of the landscape of pediatric pharmacotherapy, substantial work remains. Some ways are better cooperation between the regulatory bodies, improvement of legislative frameworks, and increasing the quality of the ethical conduct of pediatric trials. This points to the urgency for a joint international effort to ensure that children, a very vulnerable group, have access to the best and safest therapeutic interventions that are most effective.

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1. Introduction

Unlicensed medicines are any medicinal products where there is no product license, or the product is used outside the terms of its product license. It is estimated that approximately 50% of medicines prescribed for children are unlicensed or used off-label mainly due to the lack of availability of suitable licensed medicines. At best, the quality, safety, and efficacy of unlicensed/unlabeled medicines are not known as they have not been subject to quality, safety, and efficacy assessments specific to a particular use in a defined population. This is particularly the case for older medicines and generic products where no testing on children has been done and there is a dearth of information, but it is also a problem for recent innovative medicines where there may be little information outside of the licensed indications. Overall, the widespread use of off-label and unlicensed medicines in the European Union was less than optimal for the healthcare of children, with a higher potential for adverse and detrimental effects to the use of medicines on the health and well-being of children.

The issue of unlicensed medicines and their impact on pediatric healthcare cannot be overstated. The absence of a product license or the utilization of medications beyond their approved conditions continues to plague the medical field. Shockingly, it is believed that a staggering 50% of prescribed medications for children fall under the umbrella of being unlicensed or used off-label. This disconcerting reality largely stems from the limited availability of suitable licensed medications tailored specifically for children. Consequently, the lack of knowledge about the quality, safety, and efficacy of these unlicensed or unlabeled medications raises significant concerns. These products have not undergone the comprehensive assessments necessary to ensure their suitability for a particular use within a defined pediatric population.

The inadequate understanding surrounding the impact of unlicensed and unlabeled medications is particularly problematic when it comes to older medicines and generic products. Regrettably, extensive pediatric testing has often been overlooked or completely neglected for these medications. Consequently, there is an alarming dearth of information and knowledge regarding their effects on children. However, it is not only older medications that present challenges in terms of pediatric usage. Even recent innovative medicines may lack sufficient information beyond their approved indications, further exacerbating the issue at hand.

The widespread reliance on off-label and unlicensed medications within the European Union is unequivocally suboptimal when it comes to ensuring the well-being and health of children. By exposing them to these medications, we run the risk of potential adverse and detrimental effects on their overall health. It is imperative that we address this pressing concern and work towards enhancing the access to and availability of licensed medicines specifically designed and tested for pediatric usage. Our children's healthcare should never be compromised, and it is high time we take decisive action to rectify this deeply concerning situation.123

Prior to 2007, the situation of paediatric medicines use in the European Union (EU) was characterized by the widespread use of off-label and unlicensed medicines, and a relative lack of high-quality studies on the medicines that are used. Off-label use, which refers to the utilization of a medicine outside of its authorized product label, is considered legal in the EU. This is because the prescriber can exercise their clinical judgment to administer a medicine in a specific manner for an individual patient. However, it is important to note that off-label use poses a greater risk to the patient, as there is limited information and experience on the medicine in that particular indication or age group.

The prevalence of off-label use in paediatric medicine can be attributed to the scarcity of high-quality clinical trials conducted on children. In fact, the vast majority of medicines used in children are actually licensed only for use in adults. This lack of paediatric clinical trials and information has resulted in a perception that children are 'therapeutic orphans'. This means that they are not adequately taken care of in terms of research and the development of medicines targeted specifically for their age group.

Consequently, efforts have been made to improve the situation of paediatric medicines use in the EU. By addressing the gaps in knowledge and research, there is a growing recognition of the importance of conducting high-quality studies on the safety and efficacy of medicines for children. This increased focus on paediatric medicine is geared towards ensuring that children receive appropriate and evidence-based

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treatment. By closing the gap between the licensing of medicines for adults and their use in children, the EU aims to provide better healthcare outcomes for paediatric patients.

To further support paediatric medicine, various initiatives have been implemented. The European Medicines Agency (EMA) has been actively involved in promoting research and facilitating the development of paediatric medicines. Through the Paediatric Regulation, which came into effect in 2007, the EMA has established a framework to encourage the conduct of paediatric clinical trials and assess the use of medicines in children. This regulatory framework aims to stimulate research and the availability of licensed medicines specifically tailored for paediatric patients.

Furthermore, the EU has also introduced incentives to incentivize pharmaceutical companies to invest in paediatric research. These incentives include market exclusivity and extended patents for companies that conduct paediatric studies on their products. By providing such incentives, the EU seeks to encourage the pharmaceutical industry to prioritize the development of paediatric medicines and address the unmet medical needs of children.

In conclusion, the situation of paediatric medicines use in the EU has significantly improved since 2007. Efforts have been made to address the prevalence of off-label use and the lack of high-quality studies in paediatric medicine. Through regulatory frameworks, initiatives, and incentives, the EU is striving to ensure that children receive appropriate and evidence-based treatment. By closing the gap between adult and paediatric medicine, the EU aims to provide better healthcare outcomes for paediatric patients and eliminate the perception of children as 'therapeutic orphans'. 24

1.1. Importance of Pediatric Drugs

For a long time, there has been a critical issue regarding the treatment of medical conditions in children. Historically, medical professionals have relied heavily on extrapolating data from studies conducted on adults. This approach, unfortunately, has resulted in the under treatment of pain and illnesses in children. Moreover, it has also exposed them to potential harmful effects from drugs that have been considered safe and effective for adults but have not undergone sufficient testing in children.

The consequences of this practice have been devastating, with numerous tragic cases of adverse drug effects in children. These incidents have garnered significant attention from parents, healthcare providers, and lawmakers, highlighting the urgent need to conduct thorough drug testing specifically in pediatric populations. By doing so, researchers can determine appropriate dosages and assess any potential toxicity, ultimately improving the safety and efficacy of medications for children.

EMU's Pediatric Regulation, along with closely linked legislations in the United States, has been a significant step towards addressing this issue. Nonetheless, the global problem of limited development of pediatric drugs persists. There is still a lack of medications that have been specifically formulated, tested, approved, and authorized for use in children. However, with the Pediatric Regulation now fully enforced, there are several incentives for pharmaceutical companies to engage in pediatric development.

As a result, there is a growing interest and heightened activity among companies in both the United States and the European Union related to pediatric medicinal development. This positive trend is promising, as it signifies a shift towards prioritizing the healthcare needs of children. To further support these companies, this paper aims to outline the pediatric regulatory procedure from the perspective of pharmaceutical companies. It will also emphasize the importance of global planning and integration when approaching pediatric drug development.

2. Objectives

i. To explore ethical considerations: Explore the ethical considerations and challenges associated with conducting clinical trials involving pediatric populations in the EU and the US.
ii. To Analyse the safety and efficacy of pediatric drugs: Research the safety and efficacy of US-marketed and EU, EU-approved pediatric drugs, including postmarketing surveillance and drug performance measures.
iii. To Suggest regulatory strategies: Develop evidence-based regulatory strategies and recommendations to

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improve the regulatory framework for pediatric medicines in the EU and the US.

iv. To Identify Regulatory Challenges: Investigate and document the key regulatory challenges that pharmaceutical companies encounter when developing pediatric drugs in the EU and the US.

3. Methods

1. Regulatory Challenges

The Food and Drug Administration (FDA), a regulatory authority in the United States, released a comprehensive report in 2002 providing a detailed analysis of pediatric trials. This pivotal report shed light on a concerning fact: a staggering 50% of the pharmaceutical products utilized for treating children had not undergone testing in pediatric populations. Consequently, children were frequently subjected to medications that had solely been examined on adults. The underlying assumption was that the effects of these drugs would be identical in both adults and children. Unfortunately, this assumption proved to be flawed.

In numerous cases, due to the lack of pediatric-specific testing, parents found themselves administering medications to their children in an "off-label" manner. This term describes the usage of pharmaceutical drugs in ways that deviate from the FDA's approved guidelines. It encompasses scenarios where prescribed medications are repurposed for treating different illnesses or populations, as well as instances where different dosages or age groups are targeted. Shockingly, it is estimated that approximately 80% of drugs prescribed or administered to children fall under this "off-label" category. While it is true that this practice has historical roots and certain drugs have demonstrated safety and efficacy in pediatric use, there have been unfortunate instances where adverse effects occurred. In some cases, the off-label administration hindered the child's recovery or even caused more harm than good.

Recognizing the significance of pediatric drug research, the FDA experienced a notable shift in its approach. An industry survey conducted among 159 pharmaceutical companies revealed a doubling in the number of requests for pediatric use studies from the FDA. The percentage of requested studies surged from 15% in 1998 to an impressive 30% in 2000. This change indicates a growing awareness of the necessity to produce solid scientific evidence specifically tailored to pediatric populations.

Within the realm of medical research, the concept of informed consent serves as a fundamental cornerstone. Informed consent ensures that participants in clinical trials fully comprehend the nature and specifics of the study, enabling them to make voluntary decisions based on a complete understanding of the facts. In the context of pediatric drugs, it is not the child but rather the parent or legal guardian who provides consent for the child's participation in a clinical trial. This intricate issue is further complicated by differing opinions on what constitutes informed consent across various age groups of children. Additionally, potential conflicts of interest arise when considering the financial incentives that parents may have for their involvement in the trial, potentially overshadowing the best interests of the child.

Acknowledging the complexities surrounding informed consent in pediatric trials, the European Union (EU) enacted a directive in 2006 known as 2006/204/EC. This directive mandates member states to implement measures aimed at establishing a robust system of ethics committees. Furthermore, it emphasizes the importance of giving due weight to the opinions of the child when assessing the acceptability of a clinical trial. The EU's initiative demonstrates a commitment to ensuring that ethical considerations are at the forefront of all pediatric research endeavors.[678]

1.1. Lack of Clinical Trials

The lack of appropriate clinical trials is a frequent public misconception, mainly from the assumption that all paediatric patient groups are 'therapeutic orphans', that is they have no effective treatment and therefore should receive experimental therapy. In truth, this only applies to a small number of paediatric conditions. In many cases, drugs used to treat adults or older children have never been tested in the relevant paediatric population. Often these drugs are used 'off label' where the dose or formulation is adjusted in the absence of specific scientific data, increasing the risk of adverse drug reactions or therapeutic failure. In such cases, pharmaceutical companies are required to perform paediatric clinical trials under the US Paediatric Research Equity Act (PREA) 2003 and the EU paediatric regulation 2007. Failure to agree a paediatric investigation plan (PIP) can lead to deferral, partial or

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full waiver under a decision of the EMA, and non-compliance can lead to the imposition of financial penalties. Although the article by Mentzer et al. was specific to oncology, it provides a good example of the problem where in the US various paediatric-based legislation was passed but the percentage of children enrolled into the trials for new drugs remained small and the form of the trials significantly diverged from the adultequivalent.

As a result, there was no significant increase in the number of new drugs approved for use in children and in some cases even led to drugs being withdrawn from use in children due to lack of proven effectiveness or evidence of harm. If these regulations are to be successful, it is essential that there is high-quality safety and efficacy data for the relevant drugs and that a matched adult/paediatric trial clearly defines the differing needs in terms of dosage, formulation, safety, and effectiveness. Without such clarification, there is the risk that the drug may no longer be used for the treatment of the child's condition but may still be administered off label or in the incorrect formulation. Failure to agree a waiver has also raised the prospect of companies halting sales of specific drugs in European countries to avoid penalties, risking a shortage of a particular treatment for a disease.[9]

It is crucial to address these challenges and ensure that paediatric patients receive appropriate treatment options. By conducting thorough clinical trials and adhering to regulations such as the US Paediatric Research Equity Act and the EU paediatric regulation, we can gather necessary data on the safety and efficacy of drugs specifically for paediatric populations. This will not only protect children from potential harm caused by off-label use but also increase the number of approved drugs available for paediatric use. Additionally, it is vital for these trials to accurately represent the paediatric population and account for their unique needs in terms of dosage, formulation, safety, and effectiveness.

The Mentzer et al. article highlights the problem in the field of oncology, where paediatric-based legislation in the US did not significantly increase the enrollment of children in trials for new drugs. Furthermore, the design of these trials differed significantly from those conducted in adults. This disparity in research and approval processes can hinder the development of effective treatments for children and even lead to the withdrawal of certain drugs due to their lack of proven effectiveness or potential harm.[10]

To prevent such consequences and ensure the availability of appropriate treatments for paediatric patients, clear regulations and guidelines must be established. By requiring high-quality safety and efficacy data for paediatric drug use and implementing comprehensive adult/paediatric trials, we can bridge the gap between adult and paediatric medicine. This approach will enable us to determine the optimal dosage, formulation, and safety measures for paediatric patients, ultimately improving their outcomes and protecting them from potential harm caused by inappropriate drug use.

However, it is not enough to simply establish regulations; it is equally important to ensure compliance and cooperation from pharmaceutical companies. Failure to comply with paediatric investigation plans (PIPs) can result in deferral, waivers, or financial penalties. This incentivizes companies to prioritize the development of safe and effective drugs for children and align their research processes with the specific needs of paediatric patients. With proper enforcement, these regulations can lead to increased access to suitable treatments for paediatric conditions and reduce the reliance on off-label use or incorrect formulations.

In the European context, the failure to agree on waivers has raised concerns about potential drug shortages. To avoid penalties, companies may choose to halt the sales of specific drugs in European countries, depriving patients of vital treatments. We must address this issue to ensure the continuous availability of necessary medications and prevent disruptions in the healthcare system. By finding a balance between regulatory requirements and industry cooperation, we can safeguard against shortages and maintain a stable supply of treatments for paediatric diseases.[11]

In conclusion, addressing the lack of appropriate clinical trials is crucial for paediatric patients. By complying with regulations and conducting comprehensive studies tailored to the needs of this population, we can improve the safety, efficacy, and availability of treatments for children. It is essential that pharmaceutical companies take responsibility for conducting paediatric clinical trials and gathering high-quality data to support the approval of drugs for paediatric use. Additionally,

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regulatory bodies must enforce compliance to avoid deferrals, waivers, and financial penalties. Through concerted efforts and a focus on the unique needs of paediatric patients, we can ensure that children receive the necessary treatments while minimizing the risks associated with off-label use or incorrect formulations.[12]

2.2. Ethical Considerations

As has been previously noted, it is important to acknowledge that a significant portion of severe illnesses experienced during childhood, as well as many critical treatment options, occur within the palliative care realm of life-restricting disorders. It is crucial to recognize that children, for the most part, lack the ability to make autonomous decisions in these circumstances, ultimately requiring their parents or legal guardians to act in their best interest. However, it is imperative to consider that there are certain situations in which the perspectives of parents may be influenced by sociocultural or religious factors, which can potentially lead to decisions being based on communal norms that may not align with the optimal course for the child's well-being.

As human beings, we are inevitably shaped by the prevailing cultural attitudes of our time. Consequently, it is plausible to assume that these attitudes have impacted the clinical evaluation of pharmaceutical drugs, specifically those that have lost their patent protections but still possess the potential to significantly contribute to the overall improvement of global child health. It is essential to acknowledge the complex nature of globalization and the ongoing outsourcing of the pharmaceutical industry to third-world countries, as these practices introduce a unique set of challenges and considerations that have not been fully explored and addressed within the context of pediatric trials.[13,14,15,16]

Different perspectives of the ethical issues that arise often reflect the state of the prevailing philosophical outlook of the time. In the classical tragic era, the Stoic overriding attitude of duty to the state or even to a higher authority often meant that individual patients were simply viewed as a means to an end. In the Christian era that followed, there was usually a compassionate individual concern for the sufferer but tempered by the overriding consideration of the afterlife. Nowadays, the prevailing view in the West is Humanist, placing the most emphasis on personal autonomy and the right of individuals to determine for themselves.[17]

2.3. Regulatory Hurdles

Regulatory hurdles are defined as steps in the creation, development, and licensing of pediatric medications that have become a significant barrier in itself to the creation of safe and efficacious drugs for children. This is a pervasive and complex issue that encompasses a multitude of daunting obstacles, many of which have already been extensively explored in the vast body of literature concerning pediatric clinical trials and the notion of on-label drug use. A comprehensive and meticulous analysis of the intricate context surrounding regulatory hurdles has been thoroughly documented by the esteemed Commission on Therapeutics of the American Academy of Pediatrics (AAP), and these invaluable concepts have been widely employed to explicitly and precisely define the multifaceted complexities and intricacies intrinsic to regulatory hurdles in the realm of pediatric medicine.

The wide array of regulatory hurdles faced in the creation, development, and licensing of pediatric medications presents a formidable challenge that cannot be overstated. These hurdles, which serve as substantial impediments, hinder the timely and efficient production of safe and effective drugs specifically tailored for children. Within this complex issue, numerous obstacles of great magnitude must be addressed, and indeed, they have been exhaustively explored in the substantial body of literature dedicated to the examination of pediatric clinical trials and the concept of on-label drug utilization. Through the diligent efforts of the highly regarded Commission on Therapeutics of the American Academy of Pediatrics (AAP), a comprehensive and meticulous analysis has shed light on the intricate context in which regulatory hurdles exist. By leveraging these invaluable insights, the multifaceted complexities, and intricacies inherent to regulatory hurdles in the realm of pediatric medicine can be explicitly and precisely defined.[18,19,20]

As cancer (Shah and others, 2014) and HIV/AIDS (FDA, 2016) become chronic conditions in children, drug therapies to treat these and other diseases are a growing need. However, this growth is slow compared to adult medicine due to the small population size and the biological differences due to growth and development. As the prevalence of pediatric illness increases in the developed world, an effort to create more pediatric drug therapy options is necessary. Initial pediatric clinical

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trials are extremely important to determine the safety and efficacy of a drug. Success in these trials leads to FDA and EMA approval, granting a license to a drug company to market a drug to children. Unfortunately, trial success is limited in pediatric oncology (Adamson and others, 2010) and pediatrics in general (Perry and others, 2011), leading to "off-label" drug use, which is associated with a higher risk of adverse effects and often lower medication effectiveness due to the use of adult formulations (Ward and Schultz, 2014).[21]

3. EU Regulatory Framework

Under the EU and US pediatric regulations, the key driving force/pressure is to facilitate availability of good quality labeling information on the effects of medicinal products in the pediatric population. This stems from the high incidence of off-label and unlicensed prescribing of medication in children due to the lack of evidence-based or child-specific advice and a widespread reluctance of prescribers to use available drugs in the absence of such information. Because of the intrinsic vulnerability of the pediatric population and its dependence upon its guardians, the regulatory legal framework must be such that it ensures that the necessary development is carried out in all areas where therapeutics for children are needed. Although the EU and US pediatric regulations differ slightly, they are jointly committed to reaching the aforementioned goal. This has been most recently addressed in the EU with the revision of the EU pharmaceutical Acquis, and in the US, with the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA).[22,23]

3.1. Pediatric Regulation

In 2007, the EU paediatric regulation was introduced, which applies to all member states of the EU as well as Iceland and Norway. This regulation sets out to improve the health of children by facilitating high-quality research and the development of medicines for use in children, and by increasing the availability of authorized medicines. The regulation requires that a paediatric investigation plan be carried out and agreed upon either through an agreed decision, or a deferral or a waiver must be obtained. The paediatric regulation applies to all medicines containing a substance which was not authorized prior to 2007, which includes off-patent and generic medicines as well as new medicines. The PIP will detail the measures and the timetable proposed to investigate the medicine in children and must be agreed upon before any testing of the medicine in children. As mentioned in the Hunt et al. article, for a product for which the indication does not contain a relevant use in the paediatric population, it is often difficult to determine the point at which a paediatric license would be necessary.

The PIP agreed upon may also be varied to reflect changes in knowledge or changes in the marketing authorization, and the decision to vary must also be agreed upon. A waiver or a deferral of the obligation to investigate the medicine in children can be obtained on several grounds, some of which still require the submission of data, development of a specific formulation or indication for use in children, documentation of the medicine's ineffectiveness or a public health issue. This can be complex because the vast majority of paediatric formulations are developed from off-patent medicines and generic medicines. These medicines, which are commonly used by children, form the highest number of medicines available to them. Therefore, ensuring their safety, efficacy, and appropriateness for paediatric use becomes paramount in order to address the unique needs of this population. Meeting these requirements may involve conducting additional studies, clinical trials, and research to ensure the optimal dosing, administration, and therapeutic benefits of these medicines for children. Moreover, it is essential to evaluate and monitor any potential adverse effects or interactions that may occur in the paediatric population. By doing so, healthcare providers can make informed decisions and recommendations regarding the use of medicines in children, ultimately improving their health outcomes and overall well-being.

Overall, the EU paediatric regulation plays a crucial role in promoting the development and availability of medicines specifically designed for children. It recognizes the importance of addressing the unique healthcare needs of this vulnerable population and emphasizes the significance of conducting thorough investigations and research in paediatric medicine. By implementing this regulation, the EU, and its member states, along with Iceland and Norway, aim to ensure the safety, efficacy, and appropriateness of medicines used in children, thereby fostering better health outcomes and quality of life for paediatric patients across Europe.[24,25]

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3.2. Paediatric Investigation Plans (PIPs)

A Pediatric Investigation Plan (PIP) is a comprehensive development plan that is specifically designed to ensure that an adequate amount of data is acquired to support the authorization of a medicine for children. This plan is formed through mutual agreement between the pharmaceutical company responsible for the medicine and the Paediatric Committee of the European Medicines Agency (EMA). Within this PIP, there is an inclusive and thorough list of studies that are to be conducted, each encompassing their own specific objectives, designated timing, predetermined measures of success, and even a comprehensive discussion regarding any potential waivers or deferrals that the company believes may be applicable.

It is crucial to note that the agreed-upon PIP is subject to periodic reviews until the point in time when all of the outlined measures are deemed as satisfactorily complete. The decision to request a waiver or defer certain aspects of the development plan constitutes a pivotal and transformative moment for the company, as it carries considerable legal and financial implications. In the event that a waiver is granted, it signifies that the specific drug under scrutiny is exempt from the obligation of being developed for pediatric use. This exemption may arise due to the sole occurrence of the intended indication in adults or due to the absence of the disease or condition in children, consequently rendering the product unsuitable for pediatric treatment. In such circumstances, the waiver will be swiftly and automatically granted, as it acts as an essential mechanism for adaptability and efficiency.

Conversely, a decision to decline the waiver constitutes a significant event, as it would result in the company receiving a non-renewal and non-reissue able qualified one-year extension of the Marketing Authorization. This extension serves as a time frame during which the company is required to initiate and carry out the necessary studies, as outlined and detailed in the previously agreed PIP. It is essential to emphasize that any request for a waiver must be founded upon scientific grounds and will subsequently be subject to the discernment and decision of the EMA. The refusal of a waiver exemplifies the necessity for the company to actively pursue the approved studies within the designated time frame, as failure to comply with these requirements could have far-reaching consequences.

Thus, the Pediatric Investigation Plan plays a critical role in ensuring that medicines intended for use in children undergo a meticulous and comprehensive development process. It is an essential framework that establishes clear objectives, measures of success, and study timelines, while also providing a structured pathway for the consideration of waivers or deferrals when warranted. Through this strategic plan, the goal of providing safe and effective medication options specifically tailored for children is pursued with great commitment and dedication.[26]

3.3. Incentives for Pediatric Research

This section of the essay will begin with establishing the importance of paediatric drug research and development and set the scene of what is required to tackle the next challenge of stimulating paediatric research on off-patent medicines. This is designed to demystify paediatric research for industry and provide confidence that future trials will be well designed and conducted and that the agreed public health benefits will be delivered. This should significantly impact child healthcare by increasing the availability of information on the safe and effective use of medicines for children. From 2007, a new rule will oblige all applications for human drug marketing authorization to include the results of studies as to whether a medicinal product is authorized, recommended or on the market can be used in children. This can be for new or off-patent products. This is anticipated to have a major impact in the future, but it is well recognized that certain medicinal products must be researched in the adult population before it is known if they are used for a child. At present, this is referred to as the deferral system and will be one of the main challenges in implementing the PIP legislation. To provide significant incentive for conducting trials in children on previously authorized products, the regulation has outlined a system of rewards and penalties in the form of a reward for conducting studies as well as disincentives for the failure to do so. High rewards will be granted for the conduct of a PIP agreed to be up to twice the basic reward, i.e. ten years. A well conducted PIP may lead to a paediatric-use extension of up to two years. Step-by-step rewards will be given for partial completion and 60% of each reward will be paid only

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where the results of the studies are favorable to children. A system of scientific opinion has also been touted to offer guidance to industry as to whether a product is likely to be developed for use in children and the need for specific studies.[1,27]

4. US Regulatory Framework

After the thalidomide disaster, the United States Food and Drug Administration expressed the need for a separate pediatric rule, and the result of this was the FDA Modernization Act 1997. This act did provide some major improvements in pediatric labeling of medications and labeling of products that are not tested in pediatrics, but still, this act did not provide any incentives to the industry for better testing their products in pediatrics. The next major milestone in this field came with the Pediatric Research Equity Act (PREA) 2003. PREA makes it mandatory for companies to perform pediatric studies for new products by providing a 6-month extension to all current patents. This act applies to all new products where the indication is for adults with an added subset for pediatric indication.

In a study done by the FDA, it was found that more than 50% of drugs, although approved for use in children, still did not have enough data to determine the right dosing, safety, and efficacy of these drugs in children (which can include over-the-counter, prescription drugs, or biologics). The Best Pharmaceuticals for Children Act (BPCA) 2002 provides a new method for testing these products that are already on the market. The first step is to identify the current use of the medication in children. Then the FDA compiles a priority list of the most needed studies to determine safety and efficacy, and finally, the company agrees or disagrees to perform these studies in exchange for a Written Request Report from the FDA. BPCA also offers an incentive to companies for on-patent and OTC products, where providing data will earn an additional 6-month exclusivity, and on-patent products will be granted deferred submission of any ANDA, or 505(b)(2) application made by any other party.[27,12,5]

4.1. Pediatric Research Equity Act (PREA)

The Pediatric Research Equity Act (PREA) was initially introduced in the United States in the year 2003, as a direct response to the FDA Modernization Act (FDAMA) of 1997. The FDAMA had provided sponsors with an incentive of six additional months of exclusivity for conducting studies on patented drugs specifically in children. However, this incentive proved to be ineffective in generating substantial and adequate pediatric studies, and it failed to significantly increase the availability of labeled drugs for children, particularly in therapeutic areas where information regarding the effects of drugs in this population was urgently required.

To address these shortcomings, PREA was designed with stronger enforcement mechanisms and health incentives, aiming to facilitate the initiation of pediatric studies for both on-patent and generic drugs. According to the Act, pharmaceutical companies intending to submit a new drug application are now required to conduct pediatric studies for that particular drug, as requested by the FDA. These studies must incorporate the specific formulations used in children, starting from infants. Nevertheless, the Act also acknowledges that certain waivers or deferrals may be granted based on specific reasons.

Undoubtedly, this marks a significant stride toward promoting therapeutic advancements tailored to the needs of pediatric patients. The intention is to provide patients and physicians with comprehensive information about the utilization of drugs in the pediatric population and to augment the labeling of drugs specifically approved for pediatric use. To reinforce compliance with the Act, the FDA possesses measures such as restricting a drug's indication solely to the adult population or initiating procedures to withdraw non-compliant drugs from the market.

As anticipated, the widespread implementation of this Act is expected to yield positive outcomes for children's health. The amplified labeling of drugs approved for pediatric use will enable the pediatric population to access a wider range of treatment options, akin to those available to the adult population. It is important to note that PREA exclusively focuses on pediatric therapeutics, and any newly established regulations or rules will only become effective upon completion of an internal review by the FDA commissioner. Furthermore, it is mandated that these changes are vetted to ensure they unequivocally "benefit the public health."[28]

4.2. Best Pharmaceuticals for Children Act (BPCA)

The Best Pharmaceuticals for Children Act (BPCA) is a legislation enacted in the United States in 2002 with the

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aim of providing support and necessary medications to pediatric patients. It was specifically created to ensure that children have a healthy start in life and to prevent the inappropriate off-label usage of medicines. According to this regulation, any new drug application must include data on the usage of the drug in the pediatric population, which encompasses individuals from birth to 16 years of age.

In cases where no studies have been conducted on the pediatric population, pharmaceutical companies have the option to submit a deferred data request. If this request is granted, the New Drug Application (NDA) will be revised to defer the submission of some or all pediatric assessments until the completion of the necessary studies or for a designated period. The ultimate goal of the Best Pharmaceuticals for Children Act is to increase the potential for the most commonly used drugs among children to be effective, safe, and appropriately dosed.

Furthermore, if a drug is widely used among the pediatric population, the pharmaceutical company may receive a Written Request from the Food and Drug Administration (FDA) to conduct a study. Pediatric study plans, initiated through a written request, culminate in the submission of a report known as the Pediatric Study Plan Decision. There are three potential outcomes for this submission, one of which may impact the drug's labeling.

The first outcome is a submission that includes either a full or partial waiver. The second outcome entails a report that explains why one or more of the Pediatric Assessments have been deferred. Lastly, the third outcome consists of a report that includes the assessments of the Pediatric Studies once they have been completed. Any of these outcomes can be expected for studies initiated through a Written Request.

Based on data collected from the Pediatric studies, or in comparison to stagnant data from adult studies, the labeling of the drug may be modified to reflect recommendations for clinical use, useful comparisons with other drugs, and other pertinent information. In some cases, the labeling may directly incorporate the data from adult studies. The Best Pharmaceuticals for Children Act includes provisions for labeling changes when clinical trials or studies provide new data that impact the clinical use, comparability with other drugs, safety, and effectiveness of the product in the pediatric population.

However, it is crucial to consider the timing of these labeling changes. Changes suggested as recommendations are proposed to the FDA when the expert panel or FDA requests the company to present a change at a meeting. If approved, the changes will be implemented. On the other hand, changes mandated by the FDA must be implemented within the timeframe required for the continued approval of the New Drug Application, or within a specified period of time.[29]

4.3. Pediatric Exclusivity

Pediatric exclusivity was first introduced in January of 2002 and is an amendment to section 505A of the Federal Food, Drug, and Cosmetic Act. It is a voluntary agreement between the FDA and the pharmaceutical company and is a six-month extension on the company's existing patent or exclusivity rights. This act was meant to counteract the incentives created by the Price Competition and Patent Term Restoration Act. By allowing manufacturers to extend their patents by testing the safety and efficacy in children, this act has resulted in a dramatic increase in pediatric research. In the first two years following the implementation of pediatric exclusivity, studies showed that there was a 15% increase in labeling changes and a 10% increase in new drugs tested in or on children.[12730]

Pediatric exclusivity was created to provide an incentive for pharmaceutical companies to increase efforts in studying their products for use in children. Before the Best Pharmaceuticals for Children Act (BPCA) and pediatric exclusivity, there was little regulatory obligation for companies to conduct testing for the pediatric population. With the fear of label restrictions, costly clinical trials, and the potential that a drug was more toxic rather than beneficial to children, companies were often hesitant to conduct pediatric studies. Unfortunately, due to the lack of testing, many drugs were still being used in the pediatric population without adequate information regarding safety, dosing, and efficacy. On multiple occasions, drugs were even being used off label because it was widely believed that the potential benefits outweighed the cost of an uncertain risk. In 1994, the FDA implemented a new regulation requiring "pediatric labeling" for new drugs, biologics, and medical devices. Since adults typically have a different disease progression and differing responses to treatment, this regulation was more of an inconvenience

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for companies rather than an initiative to initiate pediatric studies.[31]

5. Harmonization Efforts

The initiative to harmonize regulatory requirements for drug development was formally launched in 2001, following the FDA's initiation of a provision in the Food and Drug Administration Modernization Act (1997). This provision stated that the US and the EU agreed to confer on scientific and technical issues surrounding the development of pharmaceuticals. The ICH brings together the regulatory authorities and pharmaceutical industry of the three key regions - EU, Japan, and US - to address the scientific and technical aspects of drug registration. To date, the ICH has produced a total of 44 guidelines, of which 19 are concerned with the quality of drug products, 10 deal with safety, 5 cover efficacy, and a further 10 are general guidelines. Commissioning of the ICH has led to some regulations being abolished or revised. For example, the duration of carcinogenicity studies in both rats and mice, which was previously 6 months to 1 year, was altered to 6 months based on the recognition that this time period was sufficient to detect potential carcinogens. This change has led to a reduction in the number of animals used and the associated cost of testing. The establishment of the ICH and its subsequent guidelines enhance the possibility of global development of pharmaceuticals by alleviating concerns about fulfilling differing regulatory requirements in different regions. It also serves to encourage harmonization in areas outside of the ICH topics by acting as a model for regulatory discussion of other issues. Moving towards an increased use of ICH guidelines is a reasonable and practical step for companies developing pediatric drugs, even those primarily targeting the EU or US. However, it should be noted that most ICH guidelines are not legally binding, and regulatory agencies must be consulted regarding the use of non-ICH compliant methods.[27,28,29]

5.1. International Council for Harmonization (ICH)

One of the major recent developments is the progress made by the International Council for Harmonization (ICH). The ICH brings together the regulatory authorities of Europe, Japan, and the United States, along with distinguished experts from the pharmaceutical industry in these three regions, to collaborate and engage in in-depth discussions on the scientific and technical nuances surrounding the process of pharmaceutical product registration. The primary objective of these enlightening discussions is to foster and promote a greater degree of scientific and technical harmonization across the globe. By doing so, the ICH strives to create a universal framework that ensures the efficient development and registration of safe, effective, and high-quality medicines.

Central to achieving this ambitious goal is the standardization of regulatory requirements and the formulation of comprehensive guidelines. In this vital aspect, the ICH has triumphed remarkably, as its guidelines have not only become the unparalleled gold standard within the ICH regions but have also gained worldwide recognition and adoption. A significant accomplishment of the ICH is the creation of guidelines that possess a generic nature, rendering them readily applicable and adaptable in all regions. This crucial facet eliminates the need for redundant efforts and greatly facilitates the seamless movement of pharmaceutical products across international borders.

The impact of the ICH has been nothing short of extraordinary, ushering in rapid and substantial transformations in both the European Union (EU) and the United States' regulatory landscapes. While a comprehensive exploration of these profound changes is beyond the scope of the present article, it is pertinent to note that many of them will be thoroughly discussed in the subsequent sections. For instance, the implementation of ICH guidelines has had a considerable influence on numerous domains, including the creation of common technical documents for applications seeking market approval for new drugs, the establishment of meticulous quality, safety, and efficacy testing protocols throughout the various stages of drug development, and a more rational and evidence-based approach in utilizing pharmacology and toxicology data. Furthermore, the ICH has played a pivotal role in the progressive shift from certain clinical studies to the analysis of pharmacovigilance and epidemiological data, thereby effectively enhancing the monitoring of drug safety and the evaluation of potential risks.

Through its unwavering dedication and unmatched achievements, the International Council for Harmonization has undeniably emerged as a transformative force in the global pharmaceutical

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landscape. Its resolute pursuit of scientific and technical harmonization has not only improved the efficiency of drug development and registration but has also fostered an environment conducive to the creation of innovative and life-saving medications. As we delve further into the subsequent sections, we will explore in greater depth the multifaceted impact and tangible benefits bestowed by the ICH upon the pharmaceutical industry and beyond.[32,33]

5.2. Collaboration between EU and US Regulatory Agencies

Europe and the United States, both of which possess the largest markets for pediatric drug development, play a crucial role in advancing this field. It is of paramount importance for these two regions to collaborate and coordinate their efforts, with the primary goal of minimizing redundancy in clinical trials, reducing unnecessary studies, and alleviating the burden on patients and their families. By doing so, they can ensure the availability of safe and effective medicines for the treatment of children.

To enhance their cooperation, the US Food and Drug Administration (FDA) and the European Commission signed the "US-EU Agreement on Bilateral Cooperation in the Area of Pediatric Medicines" in 2007. This historic agreement aims to promote public health within the EU and the US by focusing on the improvement of children's health. It facilitates increased discussions and the sharing of valuable scientific and regulatory information pertaining to the development of pediatric medicines.

The very essence of this agreement lies in the identification and implementation of approaches that expedite the efficient development of safe and effective medicines specifically designed for children. These approaches are carefully devised to minimize the need for additional studies. In order to assess the progress made in implementing the 2007 agreement, the FDA, and the European Medicines Agency (EMA) convened their inaugural annual bilateral meeting in July 2012. During this meeting, various subjects were discussed, including the newly introduced EU Pediatric Legislation and the incentives granted to companies partaking in pediatric studies.

The invaluable information shared during these collaborative meetings plays a pivotal role in equipping both regulatory agencies with the necessary tools and capabilities to effectively deal with pediatric medicines. By keeping each other informed and engaged through these annual forums, the FDA and the EMA can closely monitor and evaluate the activities and progress of their counterparts. This exchange of knowledge and expertise serves as the foundation for their shared vision of authorizing medicines for use in children based on studies conducted specifically in the pediatric population or extrapolated from adult studies.

The aim of this ongoing collaboration is to minimize any superfluous studies that solely seek to gather information about the effects of a product in the pediatric population. By working hand in hand, Europe and the US move closer to the ideal scenario where medicines can be approved for use in children with assurance, derived from studies tailored for this specific age group. Consequently, the joint efforts of these regions will pave the way for a brighter and healthier future for pediatric healthcare worldwide.[34,35]

5.3. Challenges in Harmonization

In this section, a comprehensive and in-depth analysis of the challenges and obstacles faced during the process of harmonization is conducted. It is strongly argued that these difficulties primarily stem from the contrasting business cultures prevalent in the European Union (EU) and the United States (US), wherein the EU tends to adopt a more cautious and conservative approach towards drug regulation and the US leans towards a more permissive and liberal approach. To address and shed light on these discrepancies, the Institute of Medicine (IOM) released a comprehensive assessment of the European Medicines Agency (EMA) in 2005, alongside a Vision paper containing recommendations on how to enhance and refine the functioning of the European regulatory body. Concurrently, the US embarked on its own journey of modernizing and enhancing its regulatory agencies. Consequently, it became increasingly evident that the simultaneous implementation of International Council for Harmonization (ICH) guidelines in both the EU and the US did not yield genuine harmonization of standards for pediatric medicines, particularly in relation to the development and regulation of drugs for children.

Recognizing the pressing need for a more concerted and structured approach, joint conferences between the EMA and the Food and Drug Administration (FDA) were

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convened to meticulously identify the discrepancies and variations in regulations that impeded the simultaneous development of drugs for children in both the US and Europe. Notably, a crucial aspect of this collaborative effort was the study and examination of successful instances and remarkable achievements in the field of pediatric drug development. The “Bridging the Gap" conferences marked a significant milestone in this regard, as they not only shed light on several success stories but also presented detailed and comprehensive case studies that have been recently published. Finding inspiration in these encouraging instances, a further progressive step was taken with the creation of a specific ICH topic, namely E11, which specifically revolves around the utilization of pharmaceuticals in children. This critical addition aimed to facilitate and streamline global drug development for children, alongside improving the labeling and prescribing information for medicines designed for pediatric use.

Amidst these remarkable advancements and notable progress in recent years, it remains inherently challenging to evaluate and quantify the true success and impact of the E11 guideline. Thus, the third phase of the Pharmacotherapy and Regimen Optimization in European Pediatric Medicine (PRIME) initiative is primarily dedicated to meticulously assessing and gauging the effectiveness and efficacy of the E11 guideline in promoting and advancing pediatric drug development. Emphasizing the importance of continuous improvement and growth, this initiative strives to identify any areas that may necessitate further attention and enhancement, ultimately ensuring the utmost safety, efficacy, and well-being of children in relation to pharmaceutical treatments.[27,32,33]

6. Strategies for Pediatric Drug Development

Initial pediatric planning involves a written request that the FDA voluntarily agrees on its own accord to develop a specific medicinal product for a rare disease or condition affecting pediatric patients.6 In agreeing to the pediatric development of a specific product, the FDA will consider the complexity of the product and its potential benefit for pediatric patients, the seriousness of the disease or condition, the availability of other treatments, and the impact that an FDA action would have on the healthcare of children.6 In cases where the risk to pediatric patients may be too great to study the drug in children, the FDA and sponsors can also request a deferral, in which the FDA delays pediatric studies until further information is available to evaluate the safety and effectiveness of the product in adults. The written request will lay out the studies that must be conducted, including the formulation studies, pharmacokinetic studies, and safety and efficacy studies, necessary for the FDA to determine whether the drug would represent a meaningful therapeutic benefit for pediatric patients and would be approved for use in pediatric patients. To increase the efficiency of pediatric trials, sponsors are encouraged to include pharmacokinetic studies or studies using an appropriate surrogate endpoint that could predict a clinical benefit, rather than the most costly and time-consuming studies in proving efficacy of a product. This may be an area in which European and American trials differ, as data from adult studies and bridging studies using the extrapolation approach can often support pharmacokinetic and pharmacodynamic evaluation using modeling and simulation to support a dosing and regimen for pediatric trials.3 The acceptance of additional types of data and use of modeling and simulation can greatly reduce the number of trials that must be done in children and the duplicate similar study designs completed in the US and EU.

In the pursuit of pediatric planning, it is imperative to commence the process by presenting a written request to the FDA. Through this voluntarily agreed agreement, the FDA undertakes the development of a distinct medicinal product exclusively curated to address a rare affliction or condition specifically impacting pediatric patients. When endorsing the pediatric development of a distinct product, the FDA meticulously evaluates the intricacy of the product and its potential benefits for pediatric patients, the gravity of the disease or condition at hand, the availability of alternative treatments, and the consequential impact of FDA actions on children's healthcare. In instances where the well-being of pediatric patients may be jeopardized by conducting drug studies, the FDA, in conjunction with the sponsors, maintains the ability to prevail upon a deferral. This deferral would delay pediatric studies until the collection of substantial evidence that would sufficiently evaluate the safety and effectiveness of the product in adult patients.6 The written request delineates the indispensable studies that must be conducted, encompassing formulation studies, pharmacokinetic studies, as well as safety and efficacy

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studies. The thorough execution of these trials is undoubtedly pivotal in enabling the FDA to discern the potential of the drug as a viable therapeutic option for pediatric patients, ultimately warranting its approval for use in this demographic. In order to optimize the efficacy of pediatric trials, sponsors are actively encouraged to incorporate pharmacokinetic studies or studies employing an appropriate surrogate endpoint. By doing so, they can effectively predict the clinical benefits of the product, essentially obviating the need for arduous and expensive studies aimed solely at proving its efficacy. This is an area in which European and American trials may potentially manifest discrepancies. European trials commonly utilize data derived from adult studies and bridging studies, employing the extrapolation approach to reliably support pharmacokinetic and pharmacodynamic evaluations. This often entails the utilization of comprehensive modeling and simulation techniques to establish appropriate dosing and regimens for pediatric trials.3 Cohesively, the acceptance of a more diversified range of data as well as the integration of modeling and simulation methodologies have the potential to significantly diminish the number of mandatory trials conducted on children. Moreover, this approach eliminates the need to replicate similar study designs within both the US and EU jurisdictions.[252712831]

6.1. Early Pediatric Planning

The objectives of the kick-off meeting are to ensure that the study(ies) will result in the robust data required that will fulfill the regulatory requirements, to conclude on any additional measures that may increase the safety of the study and/or the tested medicinal product and that the developmental and formulation changes that may occur over the period of study, will be taken into consideration. It may also be used as an opportunity to make a protocol assistance application. This allowed for an earlier scientific opinion from the CHMP on the specifics of the study protocol, providing confirmation and security for the company on the acceptability of the study. In cases of relative rarity or a specific subpopulation of a disease, it may be difficult to design a study that will result in the required data, one option available is to ask for a 'waivable agreement' from the competent authorities. A specific agreement in writing that if the conduct of a study is implausible using present medical knowledge, less data can be accepted, and the study may be substituted with the conduct of a pharmacovigilance/post-authorization safety study.

Expanding upon the objectives as mentioned earlier, it is of utmost importance for the kick-off meeting to meticulously address and ensure that the upcoming study(ies) yield a comprehensive and extensive compilation of data that not only satisfies the rigid regulatory prerequisites but also fulfills the critical need for in-depth understanding. With an overarching aim of acquiring accurate and reliable outcomes, additional measures may be identified or established during this collaborative session, potentially augmenting the safety aspects associated with both the study and the experimental medicinal product. Furthermore, it is necessary to actively acknowledge and incorporate any potential developmental or formulation alterations that may transpire over the course of the study. By doing so, a holistic approach can be adopted, ensuring that the ever-evolving nature of the study is adequately taken into account and effectively addressed.

Moreover, the kick-off meeting presents a remarkable opportunity for interested parties to submit a protocol assistance application. This unique avenue allows the concerned company to receive a prompt scientific opinion from the CHMP, thus facilitating the smooth progression of the study. By obtaining a preliminary evaluation of the study protocol, the company gains invaluable confirmation and heightened confidence regarding the acceptability and viability of the proposed study. Such valuable insights enable the company to proceed with a sense of reassurance, knowing that their study conforms to the relevant standards and is aligned with the overall objectives of the regulatory authority

In cases characterized by the relative rarity of a disease or when targeting a specific subpopulation, the design and implementation of a study that generates the required data may pose significant challenges. In such instances, an alternative approach may be pursued, involving the acquisition of a 'waiver able agreement' from the competent authorities. This distinctive arrangement, expressed in written form, offers a pathway where, if the practical execution of the study is deemed implausible based on the prevailing medical knowledge, a reduced amount of data may be deemed acceptable. Thus, the study can be substituted with the conduct of a pharmacovigilance or post-authorization safety study,

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providing an alternative means to gather and assess the necessary information in a manner that is both scientifically rigorous and ethically sound.[323334]

Following successful discussions and agreement on a PIP, all subsequent discussions relevant to a specific pediatric investigation can be recorded and tracked within the agreed upon PIP. Usually in a kick-off meeting, involving the relevant functions of the company and the rapporteur and co-rapporteur of the relevant CHMP Scientific Advice working party, all aspects of the study(ies) should be discussed and agreed upon. Confirmation of adherence to the decisions made should be included in the following study protocol submitted in an application for a deferral/waiver.

6.2. Innovative Trial Designs

Various innovative trial designs have been advocated, and there is no one-size-fits-all solution, with the most suitable design depending on the specific research question and characteristics of the disease and therapy being studied. Model-based approaches such as pharmacokinetic and pharmacodynamic modeling can be used to predict the best dose and assess likely efficacy and safety of a given therapy but are complex and unfamiliar to many clinicians and require relatively high-quality existing data to build the model. Decision platform designs allow for a degree of adaptation in the trial based on interim results and can be an attractive compromise between the conventional separate trials and full adaptive trials. However, full adaptive trials are potentially the most efficient way of obtaining evidence about the best treatment for a given disease, and current regulations in both the US and Europe provide scope for these trials in the pediatric population. An adaptive trial is one that allows a degree of learning as the trial is conducted and uses preplanned decision rules to make modifications to the trial without undermining the validity and integrity of the trial. This learning may take the form of dropping certain treatment arms, sample size re-estimation, or changes to the randomization ratio. This approach is particularly suitable for trials in which there are various unknowns about the best treatment (dose, duration, type of therapy) for a given disease. It has been argued that trials in pediatric populations represent an ideal opportunity to implement adaptive designs, as there are relatively few established therapies and the best treatment for many diseases is unknown. However, concerns have been raised that there are too few statisticians with the necessary skills and knowledge of regulatory requirements to implement these complex designs.[3536]

The progression from efficacy studies to reformulation and testing at different doses requires flexibility and innovation in trial design. Conventional trials designed to evaluate safety and efficacy of one drug in one trial are frequently an inefficient way to answer important clinical questions through the three age ranges, as they involve testing a given therapy in a sequential fashion at different ages. For example, the REACH trials comparing the efficacy of simvastatin in reducing cholesterol levels involved three separate placebo-controlled trials in children aged 8-21 years with familial hypercholesterolemia, using a similar protocol to a trial in adults with the same condition. Each of these trials took several years to recruit and required the reformulation of the drug, which was not available in suitable doses for children. This approach is time-consuming and resource-intensive with high opportunity costs, as separate trials for each age group mean exposure to placebo for longer and a longer delay before the drug becomes available for all children with the condition concerned. When one considers that the regulatory authorities require evidence of safety and efficacy at all doses likely to be used in the target population, a further common reason for conducting separate trials in different age groups, this method is often duplicated. An efficient trial design would aim to answer all important clinical questions in the smallest number of patients and taking the least possible time.[3738]

6.3. Adaptive Pathways and Real-World Evidence

An additional benefit of the recent AP proposal by Eichler et al. is the provision of early scientific advice. This would be of great assistance to pediatric drug development under the new regulations given the necessity of increased collaboration between various groups involved in pediatric development in order to facilitate best practice and avoid repetition in the trials of different age groups. [39]

AP is clearly a major means of enhancing R&D of drugs for use in better understanding the diseases they are seeking to ameliorate. Although it is not solely focused on pediatric medicine, it has considerable potential in facilitating pediatric development by investigation of

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safety and efficacy more specifically in defined subgroups of adult patients and directly in pediatric patients. This would be conducted under the provisions of the proposed regulation for a single PIP, where investigation can be conducted and changes to the development can be facilitated to fulfill requirements of a marketing authorization and complete knowledge of the drug's properties.[39]

The concept of adaptive pathways (AP) involves a stepwise developmental methodology for a drug, starting with early authorization in a restricted patient population to enable timely access to patients. Significantly, the type of development initiated under AP is not an alternative to the traditional pathway; it primarily involves real-world evidence. It has been proposed that products authorized through AP be subject to managed entry (or an entry/exit scheme) to facilitate access for the appropriate patients. Managed entry involves the collection of data on effectiveness and safety in a specific patient population. This is tied to the pricing and reimbursement (P&R) of a product and allows for revisions to the criteria for use in different subgroups or termination of funding if the product does not meet its expected value.[40]

7. Safety and Efficacy Assessment

One of the most significant FDA initiatives in pediatric therapeutics is the implementation of the Pediatric Rule, passed by the US Congress in 1998 and in effect as of April 2000. It requires that all new drug applications for a molecular entity containing a new active ingredient that is submitted after this date, whether an on-patent or off-patent product, contains a pediatric assessment in the form of a plan that is reviewed by the Pediatric Advisory Committee prior to the submission of the application. The resulting studies extrapolate from adult data or elucidate the drug's effects on children. The creation of this rule was in response to concern that many drugs prescribed to children had not been tested for safety and efficacy in this population, and sometimes physicians were using licensed products but in an unapproved way.

In the EU, there are similar initiatives without the force of law but having a significant impact on pediatric research. A 2007 regulation allows the Paediatric Committee of the European Medicines Agency to request a product-specific opinion to receive a marketing authorization that specifies the studies needed for a medicine. If overlooked, the EMEA can issue an agreement deferral or refusal, granting issuing of its own. The result is more research on drugs tested on children, now also with pharmacist's assistance, allowing a better understanding of dosing and administration. These regulatory changes have led to a subsequent increase in pediatric clinical trials.[4142]

7.1. Ethical Considerations in Pediatric Trials

All these advances in pediatric clinical pharmacology and the changes in legislation are positive steps, but the future for pediatric clinical trials is still uncertain. With global economic recession, there is a risk that industry may conduct trials in a few select countries with lower costs. There is also the increasing complexity of multinational trials requiring simultaneous regulatory and ethical approval in several countries. This is still a difficult process, with many differences in local regulations and ethical requirements for pediatric research. In order to be competitive in the global market, industry may pressure regulators to accept data extrapolated from adult studies or undertaken in developing countries where the disease burden is high. Pediatric clinical pharmacologists and those working in pediatric regulatory affairs need to be vigilant in working to ensure that all trials are of high quality and are conducted in the best interests of children.[43]

The role of the pediatric clinical pharmacologist is evolving and there is an increasing awareness of the importance of their involvement in pediatric drug development. Their input into industry is principally as an external expert to advise drug companies, or to be directly involved in pediatric clinical trials within academia. However, the academic pediatric clinical pharmacologist must interact with the industry at the early stages of drug development, as this can optimize pediatric trial strategies and increase the likelihood of successful efficacy and safety testing of a new drug in children. This may involve complex study designs using innovative pharmacometrics (concentration vs effect) methods, or an extrapolation of adult data to define the dose and dosing regimen for children. Industry also needs to produce more child-friendly formulations of new and existing drugs. This remains an area of unmet need, as many adult formulations are unsuitable for children. Finally, there is also a growing need for pediatric clinical pharmacologists to work in regulatory affairs. The recent changes in legislation and the

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development of specific pediatric regulations in the EU have generated a demand from the industry for experts who understand the science of pediatric clinical trials and the practicalities of developing medicines for children.[4445]

Poor children receive minimal, if any, attention in the research and development of drugs. The reasons for this are multiple and complex. First, it is only recently that legislation and regulations in the US and EU have forced drug companies to consider carrying out pediatric trials. Second, because of this, there is little expertise in pediatric clinical trials. Furthermore, these trials are time consuming, expensive, and require a specific skill set. Many drug companies are not willing to invest in this. Third, there is still a misperception that children are small adults and drugs can be tested on adults and then extrapolated down to children. This is a fallacy, as children's physiology is often different from adults and varies greatly in the different age bands, which affects the pharmacokinetics of the drug.[45]

7.2. Age and Weight-Based Dosing

Dosing in children is a very complex matter and often becomes a topic of much debate among clinicians, regulators, and the pharmaceutical industry. One school of thought is to use a dosing regimen based on body weight, which is backed by several lines of reasoning. Firstly, it is well known that many drugs follow linear pharmacokinetics, i.e. drug clearance and volume of distribution are proportional to the patient's size. In these cases, it is sensible to give a larger person a larger dose. Secondly, it is commonly assumed that the risk of adverse events is similar in larger and smaller children and therefore it would be preferable to give a larger child a proportionally larger dose. This dosing method has been historically used in the US and is favored by the FDA. However, there are many unresolved issues with weight-based dosing.

Firstly, several studies have found that clinicians often misuse this method and are either under or overdosing children, sometimes with serious consequences. This is due to many drugs being formulated and/or packaged for adult use, calculated doses often being difficult to administer using the available formulations, and differing opinions on whether to use mg/kg or body surface area to calculate a dose. A major problem is that there is a lack of data on the pharmacokinetics and pharmacodynamics of drugs in children, and few drugs are licensed for use in pediatric patients. This means that dosing is often extrapolated from adult data, which can be dangerous if children metabolize the drug differently or have an increased susceptibility to its side effects.

Weight-based dosing also does not consider the wide variation in drug metabolism, and clearance rates may be up to 10 times higher in an infant than in an adolescent. Additionally, there is a growing recognition of the importance of considering other factors such as the maturation of organs involved in drug metabolism and the presence of comorbidities or concomitant medications. These factors can greatly impact how a drug is processed and cleared from a child's system.

As more research is conducted and more information becomes available, there is a need to reconsider and reevaluate the current dosing practices in pediatric patients. This includes exploring alternative dosing methods that may better reflect the unique pharmacokinetic and pharmacodynamic profiles of children. It also calls for improved communication and education among healthcare professionals to ensure accurate and safe dosing practices.

In conclusion, while weight-based dosing has been a widely used approach in pediatrics, it is not without its limitations and risks. The complexity of dosing in children necessitates a more comprehensive and individualized approach that takes into account multiple factors beyond just body weight. Only through continued research, collaboration, and education can we hope to improve the safety and efficacy of drug dosing in pediatric patients.[46]

7.3. Long-Term Safety Monitoring

What is of utmost importance in long-term studies is that they should involve the pediatric population and not just assess any changes in the use of the drug through epidemiological data. There should also be consultation with the relevant authorities of Member States to determine the best method of assessing long-term safety, and it should be proven that the benefit-risk profile of the medicine is continuously reassessed. It is likely that this will pose a significant financial burden in some cases, but in following up the disasters of medicines in the past, it is something that has become a necessity.[4748]

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In the European Union, the specific provisions stipulate that long-term safety trials should be meticulously conducted, employing the most advanced and reliable methods of clinical practice. These studies ought to be comprehensively pre-planned and intricately designed, with the primary goal of addressing specific safety hypotheses and diligently identifying any potential toxic effects. It is crucial to take into consideration the recent notable improvements that have been made to the European Union clinical trials directive while strategizing and organizing the indispensable specifics of a long-term safety trial. These positive changes ensure that the trials adhere to the highest standards of safety and efficacy, thus promoting the well-being of patients and the advancement of medical science.47

Once a pediatric drug has been licensed and used within the general population, it is not always followed up to evaluate its safety over a long period of time. In many cases, this has resulted in catastrophic outcomes, as seen with Chloramphenicol, which is now contraindicated in children following reports of fatal aplastic anemia. In light of the disaster seen with thalidomide, strong provisions were made in requiring companies to provide long-term safety data for their products. This is mirrored in both the US and EU clinical developments of this era. Even so, there is no specific guidance in the US with regard to long-term safety monitoring, and as of 2002, indications were that most post-marketing studies that were being carried out were based upon previous adverse reactions to drugs, rather than an evaluation of the safety of a specific product. In recent times, an ad hoc method of monitoring safety has been to assess drugs being given license extensions, as seen with the COX-2 inhibitors.49

8. Labeling and Information for Healthcare Professionals

Many of the specific issues regarding labeling and product information for pediatric drugs relate to the difficulties in obtaining data and marketing authorizations for specific age subgroups. The pharmaceutical companies may seek to avoid costs in achieving pediatric labeling aiming towards a broader indication.

Enforcement of the pediatric labeling requirements may result in certain adult products having labeling such as "use in children is not recommended" or "use in children is contraindicated". Both EMEA and FDA have specific requirements for labeling content and format. These will add to the complexity in obtaining labeling for pediatric medicines. It may be difficult to demonstrate that certain data is not available due to ethical considerations. Duplication of labeling may also occur if a specific product being developed for children is based on an existing product with insufficient pediatric data. This may be viewed as preventing therapeutic innovation and is to be avoided. EU authorities plan to revise the current note for guidance on the clinical investigation of medicinal products in the pediatric population. This will explain the procedure for obtaining a pediatric indication and should provide advice on how to demonstrate that the product has been developed specifically for children. Any such changes should be reflected in new guidance from the Committee on Proprietary Medicinal Products (CPMP/ICH) on developing pediatric medicines.50

8.1. Pediatric-Specific Information

Traditionally, obtaining labels for pediatric use has always been a challenging and demanding area of focus within the pharmaceutical industry. However, in recent times, there have been positive developments that have made this process slightly easier. One notable improvement is the mandatory requirement for companies to develop a comprehensive pediatric investigation plan (PIP) for new drugs. This requirement is enforced by the European Medicines Agency (EMA) and must be fulfilled in order to receive marketing authorization for the product.

The PIP serves as a pivotal tool that outlines the necessary studies to be conducted in order to demonstrate the effects of the drug in the pediatric population. These studies are carefully reviewed and agreed upon by a pediatric committee convened at the EMA. It is important to note that PIP also has a profound impact on the type of license granted to the drug. In cases where all the studies are conducted exclusively with the pediatric population, the drug may be granted a product-specific license. This signifies that data from the adult population cannot be extrapolated to determine the drug's effects in children.

On the other hand, if the pediatric studies are not given the due attention they deserve, it is possible for companies to request a deferral of these studies until sufficient data becomes available from the adult population. Nonetheless, it is crucial to recognize that this deferral is only permissible if it is proven that

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conducting pediatric studies at that particular juncture is not feasible or clinically rational.

In certain situations, based on a thorough evaluation by the committee, companies can also apply for a waiver. This waiver the necessity of conducting pediatric studies when it is generally agreed that the drug is not suitable for the pediatric population. This provision offers a sensible approach to ensure that children are not exposed to medications that may be harmful or ineffective for their specific needs.

In the United States, the process of pediatric labeling changes and the submission of relevant information is less rigid compared to the European framework. Companies can submit pertinent information at any time, and this information is scrutinized by the pediatric subcommittee every six months. As new knowledge emerges, and substantial advancements are made in pediatric drug research, necessary changes and improvements are implemented within both the European and US frameworks.

It is essential to emphasize that all the aforementioned information should be regarded as dynamic and subject to continuous updates with new findings and advancements. As research progresses and more pediatric drugs are thoroughly studied, it is highly likely that further changes and improvements will be integrated into the existing frameworks of both the European Union and the United States.[5051]

8.2. Risk-Benefit Assessment

The concept of risk, noting the distinction between risk and risk perception, has long been a complex and challenging matter in the realm of pediatric drug treatment. It is widely acknowledged that the public, as well as the broader healthcare community, does not readily embrace the notion of risk when it comes to treating children. This prevailing sentiment has resulted in a systematic under-treatment of pain and other conditions in children, despite the fact that their symptoms and impairments may be disproportionately severe compared to those experienced by adults.

This risk-averse culture within pediatric healthcare has led to a prevalent reliance on off-label and unlicensed medications for children. It is important to recognize that these alternative treatments inherently carry a greater degree of uncertainty and potential risk when compared to licensed alternatives. Countless studies have demonstrated that the perceived risk associated with a particular treatment significantly influences the decision to proceed with it, regardless of the objective risk posed by the disease itself.

Misconceptions often surround the interpretation of specific diseases and their progression in children, creating an environment where the risk-benefit ratio of various treatment options remains obscure. Ideally, this situation would necessitate a comprehensive analysis of the existing treatments as well as those currently being explored, followed by a comparison with the relative severity and natural course of the disease. In practice, however, the assessment of risk-benefit is often conducted in a casual and subjective manner, influenced by the misconceptions as mentioned earlier and the personal views of individual physicians.

While a systematic methodology for risk-benefit assessment exists in the form of decision analysis, its implementation within pediatric medicine has been limited. Some argue that decision analysis may not be applicable in the realm of pediatric medicine due to the inherent uncertainties associated with this field. Nevertheless, this perspective is misguided; it is precisely in circumstances marked by uncertainty that decision analysis proves most valuable in determining the optimal course of action.[52]

8.3. Educational Resources

Educational resources for healthcare professionals may also be significantly enhanced by the legislation. Advocates of children's health have stressed the importance of proper training in pediatric therapeutics for all students in health-related disciplines, and for postgraduates and practicing professionals. To support these goals, Article 46 of Regulation EC 1901/2006 calls for the European Commission to issue a report on the possibility of establishing a European network of independent research centers and academic institutions with expertise in pediatrics. These centers would be responsible for conducting or coordinating studies in the pediatric population to generate data needed for marketing authorization, determining off-patent formulations, and assessing the comparative effectiveness of different treatments in pediatric populations. The existence of these centers, though not guaranteed, could facilitate pediatric research on

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medicinal products and provide a valuable resource for the healthcare community.

In the US, the situation is more straightforward. The BPCA required the establishment of a Best Pharmaceuticals for Children Act Pediatric Formulations Initiative, a public-private partnership to conduct research on the needs of pediatric patients and to prioritize compounds for further study; and a Written Request Fund to enable the FDA to request pediatric studies on specific products. These mechanisms should ensure a steady flow of information on pediatric drugs through various healthcare professional channels, which will be useful to those who wish to keep pace with this rapidly evolving field.[5354]

9. Post-Marketing Surveillance

The purpose of pharmacovigilance is to monitor the safety of medicinal products in order to detect any change to their risk-benefit balance. This is particularly important in children where many medicines may only be tested in adults yet have the potential to cause harm to the pediatric population. Both the EU and the US have recognized the need for specific monitoring of drugs used in children and have introduced legislation to make this happen. In 2002, the pediatric regulation in the EU aimed to increase the availability of specifically authorized medicines for children and improve the information on medicines, through research and specifically designed trials in children. It states that safety monitoring should be carried out in the same way as for medicines used in adults, with the adverse events having similar criteria for submission. Efficacy or harm arising from the lack of efficacy of the authorized medicinal product shall be monitored and compared to existing treatments. All data generated in compliance with an agreed pediatric investigation plan and all data obtained on an authorized medicinal product labeling the use in children should be included in the EU system of collection of adverse event reports. The US has introduced a similar but less formal requirement to provide pediatric labeling with safety and efficacy data. The prescribing information shall include a statement on whether or not there have been adequate studies to demonstrate that the medicinal product is safe and effective in children, or whether studies have been conducted and failed to demonstrate the safety or effectiveness of such product. This will result in a substantial amount of pediatric post-authorization safety data, which can only be properly monitored through access to adequate databases.[5556]

9.1. Pharmacovigilance in Pediatric Population

Post marketing surveillance is critical in understanding the safety of medicines used in children. However, no specific plans for pediatric post-marketing surveillance currently exist in the EU. Nonetheless, plans for mandatory Pediatric Investigation Plans (PIP) are likely to require specific post-marketing plans for certain products. In the US, all new drugs are required to have a risk management plan which includes a pharmacovigilance plan. In cases where the drug represents a major therapeutic advance or there is a considerable increase in safety in treating the condition, the drug may be approved with the requirement for post-marketing studies to establish safety and efficacy. Economic incentives to bring off-patent medicines up to standard or to develop new medicines may still result in off-label prescribing of the new (or newly tested) medicine in preference to existing treatments. Studies comparing on and off-patent drugs are needed to ensure that there is a prompt switch to on-patent use, deferring these studies may result in a lost opportunity to gather comparative safety data, whilst off-label use continues. EU post-marketing observational research will require specific methodological approaches set out by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance and further guidelines are expected on conducting observational research on medicines. High-quality observational data is also needed in the US to monitor off-label drug use and compare the safety and efficacy of drugs which have not been directly tested against each other, however funding and logistical limitations may result in it being easier to fulfill such requirements in the EU. New surveillance techniques such as the use of registries and data-linkage will enhance the ability to conduct post-marketing observational research in assessing the safety and effectiveness of medicines in children.[5758]

9.2. Reporting Adverse Events

In the US, adverse events can be reported to the FDA's Office of Surveillance and Epidemiology using the FDA Adverse Event Reporting System (FAERS) - a system that functions similarly to Surveillance. Any post-marketing studies or clinical trials are then subject to the

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same adverse event reporting requirements as they would be where the pediatric drug is still in the investigational phase. It is important to note that failure to monitor and report adverse events can result in serious legal consequences for the sponsor and a loss of public trust. In order to enhance pediatric participation in post-marketing surveillance, the FDA has developed a program in which patient families can report adverse events directly to the FDA and also receive pediatric-specific safety information on drugs.[5]

In the EU, sponsors must report any serious adverse events (occurrences which result in death, are life-threatening, require hospitalization or prolongation of hospitalization, result in disability or incapacity, or a congenital anomaly) to the Surveillance database within 15 days. Non-serious events should be reported within 90 days. As of July 2012, all reports involving patients under 18 years of age must be submitted using the electronic form provided by the European Medicinal Agency. This initiative is intended to make the reporting of adverse events more child-specific and to increase the overall volume and quality of reports involving pediatric patients.[59]

In both the EU and US, once a pediatric drug has been approved for use, its sponsor is legally required to report any adverse events that come to their attention. An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. This means that anything from a life-threatening reaction to a congenital abnormality diagnosed in a child whose mother took the drug during pregnancy should be reported.[60]

9.3. Pediatric Registry

The FDA Amendments Act of 2007 demanded pediatric studies for new drugs, and the European Union is considering new laws to require proof of a waiver before examinations are not started (or completed). If obstacles to pediatric studies are not removed, the only alternative will be to have children participate in adult phase IV trials. This would be unethical, whereas some adult data are extrapolatable and there would be little interest in drug use or its effects on children. Therefore, the USA and EU efforts are leading to pediatric investigations during the life cycle of a new drug.

While this is a positive move for children's health, the studies must be of high quality and ethical and are only necessary studies. The last 50 years have seen many examples of children being subjected to research that may not have been in their best interests. Therefore, if the research is necessary, the most information must be gained from the smallest number of children. This is achieved through good study design and conduct, and having the right tools to be able to identify the research that is not needed or produces negative outcomes (i.e. a registry of all pediatric studies). Step 1 is to have the FDA and EMEA publish lists of accepted pediatric studies and decline requests with an explanation. This will enable all those involved in pediatric research to learn from the experiences of others and gain an understanding of what studies the agencies will accept. Steps 2 and 3 involve the setting up of a database to hold all raw data from completed pediatric examinations, and a registry of all pediatric medicines.[24]

4. Conclusion

"We embarked on writing this paper with a view towards figuring out how drugs for pediatric patients could be more effectively and safely regulated, and in a way that would stimulate innovation and access. In doing so, it soon became apparent that the regulatory climate is complex. On the one hand, we recognize the incredible importance of enacting safeguards to ensure medicinal products for minors are well-tested for safety and efficacy. As demonstrated by Heubner's law and the disaster of chloramphenicol, drugs for children have often been untested and frequently found to be harmful. The response to this has been more legislation and regulation. Through orphan drug laws, and now pediatric legislation, legislators have tried to create incentives for industry to perform the necessary testing, and sometimes they have even outlawed the use of certain products in children. On the other hand, though, there are ethical problems associated with child drug testing, and it is impossible to eliminate all risks. A company can successfully perform a licensing trial that includes a few incidents of harm, even if the incidence is less than in the general population, and still be unable to market the product to the children affected. This was the case with enalapril, which was banned for use in treating hypertension, one of the principal side-effect prone uses of ACE inhibitors, despite evidence that it was the most effective drug. Increased legislation and safeguards

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preventively annul potential beneficial treatment options. ACE inhibitors are not as severe in the effects of legislation and safeguards on limiting the availability of medicines are often difficult to assess, and they are rarely checked against what would have been the alternative. Given that using placebo controls in areas of known effective therapy is unethical, it is often the case in pediatric trials that new medications under question are being compared to the standard adult treatment which is frequently not appropriate to the disease being treated. This has much potential to improve safety and neglect it. New medications may still be used in treating children off-license. Now that it is illegal to use an unlicensed medication unless there is no suitable licensed alternative, it is doubtful whether they will be tested at all. This situation looks similar to the study also comparing enalapril to the standard treatment (furosemide) for the treatment of heart failure in children, which carries higher risk and is unsuccessful. Despite it and similar studies, a new pediatric formulation of enalapril was completed and the testing of it with a placebo proved too dangerous to be continued. This case saw no benefit for the children involved, enalapril was simply given a black box warning, and it is again unlikely that the compared medications would be tested."

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