



Global Harmonization of Pediatric Drug Development: Critical for Progress for Developing Safe and Effective Therapeutic Agents for Children

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ABSTRACT

The article, "Questionable Industry-Sponsored Studies in Children and Adolescents in Slovenia" provides an opportunity to discuss evolving US and EU legislative measures to improve the available clinical trial-derived pediatric data and provide coherent labeling for pediatric providers in dosing of drugs for children.

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Introduction

The article, "Questionable Industry-Sponsored Studies in Children and Adolescents in Slovenia"¹ provides an opportunity to discuss evolving US and EU legislative measures to improve available clinical trial-derived pediatric data and provide coherent labeling for pediatric providers in dosing of drugs for children. As stated by the authors,¹

We investigated the medical validity of international pediatric studies with centers in Slovenia, an European Union member state, and challenge their medical utility. Methods: We analyzed international industry-sponsored pediatric studies with centers in Slovenia, listed in www.ClinicalTrials.gov, for their medical value. Results: Most pediatric studies triggered by the US Food and Drug Administration and by the European Medicines Agency were/are without medical or scientific value. They were/are formally and regulatorily justified, but lack medical sense and thus were/are unethical. Several even harm children and/or adolescents with serious diseases by exposing them to placebo or sub-standard treatment. Conclusions: Pediatric studies triggered by US and EU regulatory demands are a serious abuse of non-neonatal children and adolescents in Slovenia and worldwide. They are medically redundant at best and often deter patients from effective innovative personalized

therapy. They also exclude young patients from reasonable studies. Institutional review boards/ethics committees should be alerted, should critically review all ongoing pediatric studies, should suspend those found to be questionable, and should reject newly submitted questionable ones.

The article by Rose et al¹ discusses critical issues influencing a proper understanding of the concept of pediatric drug development and its implementation. One of the authors of this Commentary (AEM) has written extensively on this topic, including the development of a stand-alone textbook on the topic designed to act as a guidepost to multiple stakeholders involved in the development of therapeutics for children from all age cohorts.² Rose et al¹ provide a provocative position that has critical elements borne from an excellent review of the literature and recent regulatory actions in the United States and European Union from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively. They also provide a personal thesis with which we humbly and aggressively disagree: Research is bad for children and that EMA- and FDA-mandated regulations for pediatric studies can harm patients. We believe it is inevitable that some standards of care will become outdated once the studies begin, which is equally a problem for the development of therapeutic agents for adult use. An evolutionary Pediatric Investigational Plan concept could address this in the future, but was not fully vetted in this perspective article.

We are of the opinion, in contrast to Rose et al,¹ that pediatric drug development and clinical investigation is an essential activity in ensuring children have access to high-quality, age-appropriate, and reliably evaluated medicines with an accompanying evidence

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base that informs appropriate prescribing decisions. All stakeholders involved in the design, review, investigation, and approval of pediatric drug development plans have a moral obligation to ensure children have access to the same level and standards of health care as any other age group.

Drug development for pediatric patients introduces additional complexities over drug development for adult patients. The marked heterogeneity across the pediatric subgroup, from preterm babies through to adolescent patients, requires the need for careful consideration of the influence of growth and development on biological and physiological function and disease processes, which may in turn necessitate specific approaches in the design of nonclinical and clinical studies and warrant age-appropriate pharmaceutical formulations.³

In light of an established consensus on the need for age-appropriate research, it is well recognized that pediatric populations have historically been underserved with regard to medical research, resulting in considerable off-label use in children.⁴ There is extensive literature in pediatrics on the concerns of off-label use, which is defined by the administration of drugs outside of currently approved indications. Off-label prescribing refers to use that is not included in or is disclaimed in the product information approved by the regulatory body (eg, for a different indication, age group, dose, frequency, or route). Prescribing an unlicensed medicine is when a medicine or dosage form of a medicine has not been evaluated or approved by regulatory authorities for any purpose (eg, extemporaneous preparation of a formulation for pediatric use).

There are multiple reasons why providers may prescribe drugs off-label. Medications used to treat conditions experienced by pediatric patients, including many gastrointestinal illnesses, are frequently prescribed off-label. Providers may choose to prescribe off-label, such as lack of awareness that the product use is off-label, lack of approved alternatives, and to prescribe in accordance with treatment guidelines.

From the literature it is clear that studies conducted in pediatric populations under current US federal and EU laws are generating much-needed data on the safety and effectiveness of medications used in pediatric patients. Furthermore, the adjunct effect of pediatric drug development mandated by FDA and EMA is often the concomitant development of age-appropriate formulations is truly needed. Also, off-label prescribing may be necessary to provide a product in a pediatric-appropriate strength and formulation.^{4–6} On average, it takes 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric-population data.⁷ Off-label use occurs during this time period often as a necessity to treat a child with a particular disease, which is the position of Rose et al.¹

Given the breadth of potential reasons for off-label prescribing, no single approach appears likely to address all the reasons providers may choose off-label prescribing.^{5,6,8,9} In the United States, legislation designed to encourage the appropriate use of drugs in pediatric patients may decrease the frequency of adverse reactions associated with off-label use. The Pediatric Research Equity Act (PREA) (PL 108-155) and the Best Pharmaceuticals for Children Act (BPCA) (PL 107-109) provide the FDA with specific tools to promote trials of pharmaceutical products in pediatric patients.¹⁰ First, pediatric population data submitted in response to these acts must be described in labeling, regardless of whether the findings are positive, negative, or inconclusive. By including all pediatric-patient trial results in labeling, the providers and patients have access to valuable information that may decrease inappropriate off-label prescribing. For example, providers now may be able to determine whether a pediatric approval does not exist for a particular drug simply because trials in pediatric populations have not been conducted with that product, or whether

trials were done that failed to establish efficacy or revealed safety issues. That information, in turn, can inform prescribing. Second, if pediatric trials are not required because the drug would be ineffective or unsafe in a pediatric population(s) that information must go into the product's labeling.¹⁰ Third, current US legislation requires public posting of certain FDA pediatric reviews, regardless of whether the trials led to an approval.²

Currently, under the FDA Safety and Innovation Act, in the United States pharmaceutical companies are required, in most circumstances, to create pediatric drug/biologic development programs before Phase III (pivotal) adult efficacy and safety trials are underway. In 2012, the Institute of Medicine of the National Academies evaluated the influence of BPCA and PREA, concluded that “pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children”. Under BPCA and PREA, since 1998, there have been more than 460 pediatric labeling changes for medications used to treat a range of pediatric diseases.

The 460 labeling changes are valuable advances in care for pediatric patients. However, the products studied under BPCA and PREA are not necessarily the products with the most clinical significance or most commonly used off-label in pediatric health care. For example, the top therapeutic classes in pediatric health care, such as anti-infectives and anticonvulsants, are not the same as the top therapeutic classes in adults, such as cholesterol reducers and cytostatic agents. Off-label prescribing in pediatric health care tends to be higher among pediatric medicine subspecialists, and the percentage of off-label gastrointestinal medications may be as high as 80% in the pediatric outpatient setting. The issues of off-label medication use in pediatric gastroenterology has been published recently, stressing the need for approved products to treat inflammatory bowel disease, infant gastroesophageal reflux, and eosinophilic esophagitis.^{11–13} “Most patients hospitalized at tertiary care pediatric institutions receive at least medication outside the terms of the FDA product license.”¹⁴ Off-label drug use was particularly noticeable with drugs targeting the central nervous system and drugs related to fluids, nutrients, and gastrointestinal tract. High percentages of patients received off-label treatment with metoclopramide, polyethylene glycol electrolyte solution, docusate, and ondansetron. 80% of drugs used for gastrointestinal indications are used off label. Much of this off label use was associated with Miralax.^{13,14}

The goal of considering research in pediatric populations relatively early in the development process is ultimately to improve children's access to medicines that have been appropriately studied for the management of their diseases. Providers can use these public data to more clearly understand the risks and benefits involved in off-label use of a specific product for their patients.

Although pediatric trial data published in the scientific literature may be informative, those data may not present a complete picture of the benefits and risks of using a drug off-label. Only 48% of trials of products that had pediatrics-specific safety information added to the product's labeling were reported in the peer-reviewed literature and approximately half of the published articles did not emphasize the same information as did FDA labeling and drug reviews.¹⁵ Therefore, published literature alone appears insufficient to fully inform prescribing decisions, and including pediatric population trial data in labeling appears crucial. In addition, therapeutic misadventures by clinicians is frequent and at times associated with adverse drug reactions due to lack of appropriate understanding of dosing for a pediatric cohort.

Despite the potential value of FDA publically reporting pediatric trial data, simply improving that transparency appears unlikely to completely address all off-label prescribing and ensuring safety in children. For example, lansoprazole is not approved for use in

patients younger than age 1 year, and labeling describes a negative trial in that age group.¹⁶ Nonetheless, a recent analysis of outpatient prescription drug use in the United States revealed substantial off-label use for lansoprazole in infants; approximately 358,000 prescriptions were dispensed in 2010 for infants younger than age 1 year, the potential disconnect between information in labeling and prescribing practices remains a problem to consider for future intervention, including educational efforts for providers and patients.¹⁷ Based on the perspective of the authors, only clinically justified use should be used and just based on the example of inappropriate use of proton pump inhibitors in infants and young children underscores the maladaptation in the community of pediatric health care practitioners.

In the European Union, the introduction of Paediatric Regulation in 2007 inspired by the legislation in the United States has also greatly enhanced clinical research in pediatric populations through a system of obligations, rewards, and incentives. The aims of the Paediatric Regulation are to ensure that medicines for use in children are of high quality, ethically researched, and authorized appropriately, thereby improving the availability of information on the use of medicines for children. The regulation seeks to achieve this without subjecting children to unnecessary trials and therefore minimizing the burden of research.^{18,19}

The Paediatric Regulation obliges companies to agree at an early stage of a medicine's development to a Paediatric Investigation Plan (PIP) with the EMA and its Paediatric Development Committee (PDCO). All age groups from birth to adolescence are in scope of the PIP, which defines nonclinical and clinical measures (ie, studies) and measures to adapt the medicine's formulation to ensure necessary data are obtained to potentially support future authorization and on-label prescribing in children. The main role of the PDCO is to assess the content of PIPs and is composed of a chair; representatives nominated by each member state in the EU, Iceland, and Norway; members representing patients' associations; and health care professionals, which in totality represents significant expertise in the development of pediatric therapeutics and has been optimized over recent years to strengthen expertise in specific areas such as formulation aspects, pediatric-specific end points, neonatology issues, ethics, and statistics.²⁰ A recent survey²¹ highlighted that of the 38 PDCO member respondents, 7 (18%) are or were members of national ethics committees themselves, which highlights an existing link between these stakeholders. Furthermore, in more recent years, the PDCO has built interactions to exchange information with ethics committees, through workshops and guideline development, to ensure better awareness of the pediatric regulation and share expertise.²⁰

The introduction of the Paediatric Regulation has unquestionably stimulated pediatric research in the European Union since being implemented. As highlighted in the 10-year report²¹ from the European Commission, the Paediatric Regulation has resulted in a number of achievements over the period 2007 to 2016, notably that companies now consider pediatric development as an integral part of the overall development of medicinal product; more than 260 new medicines for use by children (new marketing authorizations and new indications) were authorized; more than 1000 PIPs have been written with 131 completed—which in addition to assessments of pediatric studies undertaken before the Paediatric Regulation—have helped to consolidate an already existing evidence base to complement product information with data from pediatric populations and drive the shift from off- to on-label prescribing.²¹

From a global development perspective, ongoing collaborations between the FDA and other regulatory agencies, including the EMA, facilitate these advances in product development for pediatric populations. The significant role of international regulatory personnel exchanges (short term), working groups between both

agencies, EMA Non-clinical and Formulations Working Groups, and expert meetings and workshops (including FDA representatives) and World Health Organization initiatives, are helping to facilitate critical involvement and participation. Other collaborative networks between global regulatory partners include the Paediatric Regulators Network and Essential Medicines for Children activities, Japan's Pharmaceuticals & Medical Devices Agency as observers in the FDA's and European Medicines Agency's pediatric collaboration and the FDA and NIH collaboration to develop a publicly available framework on pediatric formulations.

Rose et al¹ conclude that the “resultant updated pediatric labels have not contributed to improved child health care.” They further posit that “among the reasons that this is so difficult to grasp is the dimension of these questionable studies triggered by US and EU pediatric legislation.” We obviously offer a different perspective.

Despite the achievements that legislative changes have brought about in both the United States and European Union, a number of challenges remain; for example, there is often a lengthy delay in availability of medicines for children compared with adults. Rose et al¹ assert that “US and EU pediatric legislation need to be revised to spare children and adolescents from being recruited into unnecessary and potentially harmful studies.” It is our belief that the current legislation offers a sustainable framework for development of therapeutic agents for pediatric populations, yet equally we appreciate that its implementation must continue to evolve to address the challenges observed since its inception.

The need for further optimization of the drug development pathways for pediatric populations was discussed at a multistakeholder workshop held at the EMA in March 2018 in which the importance and commitment of all stakeholders (ie, patients, career academics, academics, health care professionals, the pharmaceutical industry, regulators, and ethics committees) in improving the implementation of the Paediatric Regulation was recognized. Central themes debated were the need for improvements in identifying medical needs of pediatric patients, better international cooperation between regulators, timely completion of PIPs, improving the handling of PIP applications, and increasing transparency around medicines aimed at pediatric populations.²¹

The established mechanisms that promote international collaboration between regulators have been described. The EMA workshop highlighted that these stakeholders, such as sponsors, investigators, and pediatrics-specific research networks, at Health Authority cluster meetings can promote greater alignment and better transparency with regard to meeting discussions. In striving for global harmony in development of therapeutic agents for pediatric populations, the pharmaceutical industry has an equally important role to play in ensuring forums for collaboration and alignment are fully utilized. For example, engaging regulators through EMA-FDA Parallel Scientific Advice offers the prospect of scientific dialogue and harmonized guidance at an early stage of a pediatric development plan (PIP). Such forums should be used more frequently to seek alignment on approaches such as extrapolation in appropriate diseases that could minimize delays in access and overcome the need for traditional comparisons with control arms in studies in pediatric populations.

The EMA workshop also highlighted opportunities for further stakeholder collaboration to optimize clinical trial design, specifically that clinical trial protocols need to be better suited to the pediatric population with the goal of improving patient recruitment to minimize delayed access and minimizing the burden of research on children. This could be accomplished through greater focus on age-appropriate outcome measures and trial designs (eg, minimal use of placebo arms) and consideration of patients' health-related quality of life. Collaboration with sponsors and ethics committees

is key, as is engagement of patients and their parents. Another suggestion at the workshop was to harmonize rules governing the work of ethics committees in their review of pediatric trials. In this respect, attention was drawn to the importance of the exchange of information and greater interactions of the PDCO with National Health Authorities/Ethics Committees in EU countries that would help promote broader alignment, because currently their scope and criteria in assessing clinical trials in pediatric populations differ. This needs to be replicated in the United States.

Rose et al.¹ state that “Studies performed in Slovenia and other centers worldwide lack(ed) medical sense. Patients are/were exposed to substandard treatment,” a claim that is substantiated with examples pediatric studies that include outdated control arms. We recognize that selecting appropriate control arms, not only in studies in pediatric populations but also in adult populations, may well have limited longevity because the current standard of care treatments due to innovative new medicines being adopted in clinical practice over time for any given therapeutic area. Changes in the way PIP applications are handled (they are typically submitted after Phase I studies are completed) could offer a solution to this issue. As presented at the EMA workshop, an alternative approach would be for PIPs to be built progressively, with staggered commitments that fit more naturally within the overall drug development process as new data come to light. Revisions to the medicine's development plan could then be informed by the availability of new data and the input of other stakeholders to ensure better study designs that take into account the latest clinical standards of treatment.

Conclusions

All stakeholders involved in the drug development process, including but not limited to academia, industry, patient and disease advocacy groups, health care professionals, regulatory agencies, and ethics committees must work collaboratively. Efforts to promote efficient, scientifically sound clinical development programs to address off-label use of drugs through the drug approval regulatory pathway should be the goal. Over the past 20 years, legislative changes have transformed pediatric research in the United States and European Union, facilitating a broader evidence base that has translated into labeling of medicines in children and allowed for informed prescribing of medicines available in age appropriate formulations. The legislative system is not perfect, yet offers a sustainable framework for development of pediatric therapeutics. There are many opportunities to further optimize the implementation of these frameworks to ensure global harmonization amongst all stakeholders in promoting studies that are indeed scientifically justified and avoid exposure of children to unnecessary trials. Further education and collaboration initiatives required to achieve this and future developments offer the promise of evolution to meet the shared goals of equitable research for pediatric populations. Addressing these issues through the International Conference on Harmonization, which has borne significant advances in pediatric drug development and global processes through collaboration and agreements seems to be a salient approach to foster.

Conflicts

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