Improvement of Pediatric Drug Development: Regulatory and Practical Frameworks

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ABSTRACT

Purpose: A dearth in pediatric drug development often leaves pediatricians with no alternative but to prescribe unlicensed or off-label drugs with a resultant increased risk of adverse events. We present the current status of pediatric drug development and, based on our data analysis, clarify the problems in this area. Further action is proposed to improve the drug development that has pediatric therapeutic orphan status.

Methods: We analyzed all Phase II/III and Phase III trials in ClinicalTrials.gov that only included pediatric participants (<18 years old) between 2006 and 2014. Performance index, an indicator of pediatric drug development, was calculated by dividing the annual number of pediatric clinical trials by million pediatric populations acquired from Census.gov. Effects of the 2 Japanese premiums introduced in 2010, for the enhancement of pediatric drug development, were analyzed by comparing mean performance index prepremiums (2006-2009) and postpremiums (2010-2014) among Japan, the European Union, and the United States. The European Union Clinical Trials Register and published reports from the European Medicines Agency were also surveyed to investigate the Paediatric Committee effect on pediatric clinical trials in the European Union.

Findings: Mean difference of the performance index in prepremiums and postpremiums between Japan and the European Union were 0.296 ($P < 0.001$) and 0.066 ($P = 0.498$), respectively. Those between Japan and the United States were 0.560 ($P < 0.001$) and 0.281 ($P = 0.002$), indicating that pediatric drug development in Japan was more active after the introduction of these premiums, even reaching the level of the European Union. The Pediatric Regulation and the Paediatric Committee promoted pediatric drug development in the European Union. The registered number of clinical trials that includes at least 1 participants <18 years old in the European Union Clinical Trials Register increased by 247 trials (from 672) in the 1000 days after regulation. The ratio of pediatric clinical trials with an approved Paediatric Investigation Plan increased to >15% after 2008.

Implications: Recruitment and ethical obstacles make conducting pediatric clinical trials challenging. An improved operational framework for conducting clinical trials should mirror the ever-improving regulatory framework that incentivizes investment in pediatric clinical trials. Technological approaches, enhancements in electronic medical record systems, and community approaches that actively incorporate input from physicians, researchers, and patients could offer a sustainable solution to recruitment of pediatric study participants. The key therefore is to improve pediatric pharmacotherapy collaboration among industry, government, academia, and community. Expanding the regulatory steps taken in the European Union, United States, and Japan and using innovative clinical trial tools can move pediatric pharmacotherapy out of its current therapeutic orphan state. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮)

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INTRODUCTION

Marketability and profitability, as well as attractiveness of a drug target, largely influence the go/no-go decision making of many drugs developed by pharmaceutical companies. Pediatric drugs and drugs for rare diseases share a segment of the drug market, known as therapeutic orphans.[1] Although drug development in rare disease areas is increasing, easy drug targets have been exhausted. Additional challenges of conducting pediatric clinical trials, such as ethical and legal aspects; evaluation of tolerability and efficacy; incomplete etiology and methods, including formulation; and low profitability, have resulted in low activity in the field of pediatric drug development.[2] Moreover, the negative attitude adopted by many pharmaceutical companies toward pediatric drug development has serious, real-life consequences. Therefore, pediatricians are often left with no alternative but to prescribe unlicensed or off-label drugs. The risk associated with these prescriptions is often compounded by the lack of reliable information on dosage and administration routes in children. The unlicensed or off-label use of drugs results in an increased risk for both developing adverse events or undesired effects and underdosing or not finding therapeutic drug concentrations.[3,4] The seriousness of this dearth in pediatric drug development has been acknowledged internationally and must be addressed promptly.[5]

Numerous regulatory actions have been implemented with the aim of improving pediatric drug development worldwide. In the United States, the Food and Drug Administration (FDA) Modernization Act was enacted in 1997 and included a financial incentive, exclusivity for 6 months, if the pharmaceutical company conducted clinical trials to expand the indications of their drugs to children.[6] This act was reauthorized and modified as the Best Pharmaceuticals for Children Act in 2002, which expanded the provision to off-patent drugs.[7] Moreover, this regulatory framework was complemented by the Pediatric Research Equity Act in 2003 in which the FDA required mandatory pediatric clinical trials or assessment for all New Drug Applications and Biologic License Applications except orphan drugs.[8] This regulatory framework was reauthorized in the FDA Amendments Act (2007) and the FDA Safety and Innovation Act (2012).[9,10]

In the European Union, the Paediatric Regulation (European Commission No. 1901/2006) was enacted in 2007, requiring pharmaceutical companies to provide a mandatory Paediatric Investigation Plan (PIP) at the end of adult pharmacokinetic trials. PIP is evaluated by the Paediatric Committee (PDCO) at the European Medicines Agency (EMA).[11] If a pharmaceutical company conducts pediatric clinical trials, a 6-month marketing exclusivity incentive is built into their EMA approval. In other words, regulatory actions for pediatric drug development in the United States and the European Union are legal frameworks that promote pediatric clinical trials, with the combination of regulatory powers or provisions and rewards to pharmaceutical companies.

Japan, in contrast, has used a different type of framework to improve pediatric drug development. In Japan, the Ministry of Health, Labour, and Welfare (MHLW) uses the unique national health insurance system to determine and control drug prices, which principally go down every 2 years. Therefore, the MHLW provides premiums to pharmaceutical companies as rewards for developing pediatric drugs by not reducing the prices of those drugs. These steps were fully implemented in 2000 with the introduction of the Extension of the Drug Re-examination Period and were further extended in 2006 with the premium for pediatric use.[12,13] In 2010, both the premium to expand drug indications to include pediatric use and the premium to promote the development of new drugs and eliminate off-label use were introduced to promote pediatric drug development in Japan.[14] The companies that agreed to develop drugs requested by the Evaluation Committee on Unlicensed and Off-label Drugs received this "premium to promote the development of new drugs and to eliminate off-label use" on their new drugs rather than the requested drugs. This 2010 policy change resulted in the development of hundreds of important unlicensed or off-labeled drugs in Japan. In this study, we analyzed relevant data to present the status of pediatric drug development, clarify the problems in pediatric drug development, and propose further actions to