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Pediatric exclusivity and other contemporary regulatory initiatives: aligning financial incentives with the needs of our patients

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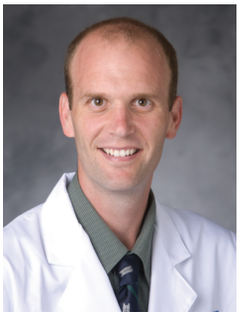

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Children have historically been under-represented in drug trials with dosing, safety and efficacy extrapolated from clinical trial data in adults. This practice is largely inappropriate as children have unique differences in developmental drug pharmacokinetics and disease pathophysiology when compared with adults. Failure to account for these differences risks safety events or suboptimal efficacy. These concerns have long been recognized by regulatory authorities in the USA and the European Union and, over the past 15 years, important initiatives have created incentives and mandates to improve drug study in children. While successful, these initiatives have been costly. Looking forward, it will be important to refine incentive structures in order to optimize the cost-benefit relationship in pediatric drug development.

Pediatric drug labeling

An important metric in evaluating quality of drug study in children is the inclusion of pediatric information or a pediatric indication on the US FDA drug label [1]. The FDA has strict approval standards, typically requiring a minimum of two well-controlled clinical trials that follow trial design, dosing, enrollment and outcomes criteria specified in an FDA issued 'written request.' Once completed, the trial data are reviewed by an expert panel before pediatric-specific information can be approved for inclusion on the drug label [2].

Prescribed drugs without a pediatric indication are considered 'off-label' [1]. Because these drugs typically lack adequate data evaluating safety, efficacy and dosing in children, off-label drugs pose a greater risk of safety events and/or suboptimal efficacy. In a recent analysis evaluating off-label pediatric drugs that were studied in response to an FDA-issued written request, serious safety concerns were identified for 33/137 (24%) products [3]. Historically off-label drug use has been necessary for most drugs prescribed to children due to a lack of adequate clinical trial data; in the late 1990s, three of every four drugs used in children were used 'off-label' [4–6].

History of regulatory initiatives

Lack of clinical trial data in children has long been recognized as a major concern. In the 1970s, the American Academy of Pediatrics argued that failure to conduct drug trials in children was unethical [7]. In 1979, the FDA responded by requiring that drugs marketed to children include pediatric information on the drug label [8]. However, this could be in the form of a 'disclaimer' stating that safety and efficacy had not been established in children. Most industry sponsors chose to simply include the disclaimer to avoid the costs associated with pediatric drug trials. Therefore, in 1994, the FDA issued the 'Pediatric Rule' allowing labeling of drugs for pediatric use based on extrapolation of efficacy from adults and additional pharmacokinetic, pharmacodynamic and safety studies to pediatric populations [8]. The objective was to ease labeling standards and encourage pharmaceutical companies to assemble pediatric data. However, the Pediatric Rule did not accomplish this objective as there

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was little financial incentive for industry to conduct pediatric drug studies.

To remedy this, in 1997 the US Congress passed the FDA Modernization Act (FDAMA) including section 505A, known as the Pediatric Exclusivity provision [9]. The exclusivity provision granted an additional 6 months of patent protection to pharmaceutical companies in exchange for conducting pediatric trials in response to an FDA-issued written request. The potential financial gains associated with extended patent protection stimulated a large number of pediatric trials of newer drugs. However, FDAMA did not provide a process for older, off-patent drugs. In 2002, the Best Pharmaceuticals for Children Act (BPCA) extended the patent protection for new drugs, and established a program to study off-patent drugs in children [10]. In 2003 further progress was made as Congress passed the Pediatric Research Equity Act (PREA) requiring that, for all applications submitted to the FDA for new drugs (including new indications or dosage forms), sponsors must include data that assess safety, effectiveness and dosing of the product in pediatric subpopulations [11]. Collectively, FDAMA, BPCA and PREA have established incentives and/or mandates for study of three broad classifications of pediatric therapeutic agents: drugs that are still on patent, drugs that are off patent and drugs not yet approved for marketing. In 2007 the FDA Amendments Act reauthorized BPCA and PREA stipulating improved FDA and applicant accountability for the agreed-upon pediatric studies. In 2012 the FDA Safety and Innovation Act (FDASIA) permanently re-authorized PREA and BPCA [12]. In Europe similar initiatives have been implemented by the EMA, also designed to encourage pediatric drug study.

Progress in pediatric drug labeling

These regulatory initiatives have had a tremendous positive impact on pediatric drug study. Since 1998, the FDA has approved more than 500 pediatric-specific labeling changes as a result of studies conducted under FDAMA, BPCA or required by PREA. These labeling changes have resulted from an unprecedented industry commitment to the study of pediatric drugs. Over a 6-year period before passage of the pediatric exclusivity provision (1991–1996), drug sponsors promised to complete 71 postmarketing studies, but only 11 were actually completed [13]. In the first 2 years after passage of Pediatric Exclusivity (1998–2000), sponsors completed 58 pediatric studies that resulted in 25 grants of Pediatric Exclusivity [13]. This trend has continued, and since the 2007 renewal of the Pediatric Exclusivity program, >450 studies have been conducted in children under the auspices of PREA and BPCA, enrolling >175,000 study subjects [14]. Significant additional benefits have included improvements in pediatric trial infrastructure as well as important advances in understanding of the study of drugs in children – as an example, in this issue of *Clinical Investigation,* we highlight pediatric trial designs employed in pediatric antihypertensive drug trials and describe unique pediatric factors contributing to success or failure of these trials.

Room for improvement

Although there have been substantial gains as a result of the Pediatric Exclusivity provision, the financial commitment has been significant and incentives have not always aligned with pediatric need. The incentive structure encourages study of blockbuster on-patent drugs with a greater potential financial return from patent extension. In a 2007 cost analysis that accounted for economic returns from patent extension, the net benefit to the industry sponsor for study of a blockbuster drug in children was estimated to range from US$119.1 to $507.9 million depending on the drug [15].

Industry sponsors initiate >80% of studies conducted for pediatric exclusivity and are principally motivated by financial return. Therefore, they have focused their efforts on the highest yield drugs. As an example, we analyzed all pediatric cardiovascular trials registered on ClinicalTrials.gov. Industry-sponsored pediatric cardiovascular trials have focused on blockbuster adult drug classes such as antihypertensives and lipid-lowering drugs while drug study for other diseases and conditions (e.g., congenital heart diseases, heart failure) are markedly under-represented [16]. Indeed, out of 27 pediatric cardiovascular drugs that have been labeled for pediatric use under BPCA or PREA, 23 (85%) represent either pediatric anti-hypertensive drugs (including five different angiotensin converting enzyme inhibitors and five different angiotensin receptor blockers) or cholesterol-lowering drugs (including seven different statins) [17]. Hypertension and hypercholesterolemia represent important areas requiring drug study; however, they do not represent 85% of the pediatric cardiovascular disease burden and there is no specific need for pediatric labeling of so many different drugs within the same drug class.

The fact that economic factors are driving pediatric drug trials is part of the reason for the tremendous successes of pediatric exclusivity. However, pediatric financial resources remain limited and therefore need to align better with needs. This is particularly true for rare diseases and conditions where economic returns have traditionally been lower. These concerns have been recognized and several provisions were incorporated

into the 2012 FDASIA initiatives in an attempt to encourage study of rarer diseases and conditions [12]. These include the Expanding and Promoting Expertise in Review of Rare Treatments Act, designed to expand cooperation between FDA and outside rare disease experts and patient advocates, and expansion of a priority review voucher program to include pediatric rare diseases [12]. These represent positive steps but it is unlikely that these provisions will be sufficient to appropriately align industry incentives and pediatric need.

Importantly FDASIA also permanently re-authorized Pediatric Exclusivity, which previously required every 5-year review and re-authorization. While broadly a victory for child health, a downside to permanent re-authorization is that there will now be fewer opportunities to refine regulatory provisions. Without the review process, the pediatric community will need to assume greater responsibility for aligning child health needs with the financial incentives that drive industry commitment. As a community it is critical that we ensure that every pediatric study results in improved healthcare for children. Indeed too many previous pediatric studies have been negative (e.g., failed to show efficacy) and it remains unclear whether this reflects that these drugs do not work in children; or that they do work, but the study failed to demonstrate this due to inappropriate trial design or drug dosing [18]. As we continue to gain important insight into the unique complexities of pediatric clinical trials, we must work to influence trial design and conduct so that the trials optimally meet the needs of our patients and not just the financial needs of our industry partners.

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