More Than Baby Steps: Perspectives on Pediatric Translational Research

Edward Connor,* Donald Lombardi, and John van den Anker

Although children represent 25% of the U.S. population and nearly 40% of the world’s population, pediatric product development typically lags behind that targeted at adults. Here the authors describe the challenges and opportunities of pediatric product development and the unique issues that surround pediatric research. Assuring advancement in pediatric health through clinical and translational medicine is a high priority and an investment in the future.

Children make up 25% of the U.S. population and nearly 40% of the world’s population. Although it is clear that our investment in biomedical research over the past several decades is paying off, it is unclear how much of this will be translated into products that benefit children. The challenges of product development in general and the unique issues that pertain to pediatric research represent both obstacles and opportunities for the translation of scientific knowledge into advancements in pediatric clinical medicine. Although researchers have made progress, the question remains whether the scientific community has the collective will and focus to convert the iterative advancement in pediatric research to date into a national/global health priority for the future. Given that data suggest that adult diseases such as diabetes and cardiovascular disorders can begin in childhood, an advancement in pediatric health through clinical and translational medicine represents not only a measure of our commitment to the world’s children but is also an investment in the future health of the adult population.

The development of innovative new products (drugs, biologics, devices, diagnostics, and behavioral interventions) is the cornerstone of advancing medical practice. Exemplified by drug development, this process is in crisis, given its high cost (~$2 billion), high risk (<20% success rate), delayed gratification (~10 years), and declining productivity—despite increasing investment. The erosion of public trust in the drug development process and the decreasing pool of skilled clinical research investigators also have had a substantial impact on the translational research enterprise. The public and private sectors have recognized the need to retool our approach, organizing around the issues of team science, translational research, and personalized medicine, and promoting new public/private partnerships to commercialize products.

Pediatric product development typically lags behind that targeted at adults and has a number of unique issues. Historically, only limited (if any) data have been collected on the pediatric use of medical products, leaving pediatricians to improvise when treating children. Over the past 30 years, advances in regulatory and public policy (Table 1) have iteratively altered this practice. At the turn of the century, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) stimulated pediatric studies (through collaboration with the U.S. Food and Drug Administration (FDA) and the National Institute for Child Health and Development (NICHD)) of patented and off-patent drugs, and hundreds of pediatric labeling changes have been made as a result.

In 2007, the Food and Drug Administration Amendments Act and the European Union Pediatric Regulation moved children from an afterthought to a required forethought for sponsors of drug, biologic, and device product development. The European regulation mandates the submission of a pediatric investigation plan for drugs in the regulatory pipeline. This attention to issues surrounding the inclusion of children in product development research by regulators and government policy-makers is much needed and has been long in coming. However, deliberation has been complex, given the need to balance the protection of children as vulnerable research subjects and the obligation to assess the use of new products for the maintenance of health and treatment of disease in children.

Economic considerations represent another critical reality in pediatric translational research. Pediatric products are generally of two types: (i) those developed exclusively in children and for which children represent the primary marketplace; and (ii) those developed in adults and used for treating children, and for which sponsors view the return on investment as insufficient to justify full development and approval specifically for children (the vast majority of biomedical products on the market). Lack of attention and inertia related to pediatric product development by pharmaceutical companies has resulted in glaring deficiencies in the number of pediatric-specific products and the knowledge base to guide pediatric use of products developed for adults. Regulatory and policy reform alone is not sufficient to rectify the situation. Also required is an understanding and management of the business as well as scientific factors at play in product development, given the need to use all of these elements to motivate the development of products specifically for children.

Success in product commercialization is dependent on the presence of several critical elements, namely: (i) a defined unmet need; (ii) a sense of urgency/priority to fill the need; (iii) an available candidate solution that appears to fit the need; (iv) a feasible plan for evaluation, with a path to regulatory approval; (v) a rational business plan to make the product available (market, acceptability, cost-effectiveness, manufacturing, reimbursement, and distribution); and (vi) a capable business partner. If any of these elements is missing, efficient product commercialization simply does not happen. Attention to each of these elements accelerates the product commercialization process, results in resource efficiencies, and avoids blind alleys.

For pediatric products, the last three elements often represent a substantial challenge and result in many promising opportunities languishing or dying off. It is the responsibility of the pediatric research community to participate actively in the process of understanding and validating these “business” aspects of product commercialization. It cannot be left to industry alone, as the de novo motivation and the primary expertise may not reside there. Expertise in pediatric academic entrepreneurship is necessary as a bridge between nonprofit academia and for-profit industry. These partnerships are...
a necessary (albeit controversial) part of product development, given, for example, that typically neither academics nor the government manufactures and distributes products. However, academic-industry collaborations should (i) respect the various motivations and priorities of different stakeholders (such as the public and private sectors, profit and nonprofit organizations, and biomedical science and the community); (ii) be transparent and minimize and manage inevitable conflicts of interest; and (iii) embrace accountability to the public trust. To be effective, collaborations require a high level of maintenance and value-added by each contributor. Academic entrepreneurship encompasses the skills needed to establish both the scientific and innovation development aspects of product development. These skills include scientific and clinical expertise and mastery of knowledge related to regulatory strategy, intellectual property, clinical trial design, reimbursement issues, health policy, and business development.

Understanding the need and market for pediatric products is not just a matter of involvement in the “push” of product development (applying discoveries to pediatric needs) but also the “pull”: complete characterization of the need and market at the start and the deciphering of solutions through scientific discovery (Fig. 1). The latter approach (the “pull”) is exemplified by the work of the Institute for Pediatric Innovation (IPI), a nonprofit organization that uses a new paradigm for pediatric product commercialization. IPI and its partner pediatric academic centers work with front-line practitioners to characterize product needs specific to pediatrics, assess their feasibility (similar to the elements above), and then create and articulate the marketplace to potential investors to facilitate their involvement. This process is already yielding results. For example, through work with neonatal intensive care units, an adhesive is being developed that allows physicians to secure monitoring or treatment devices without causing trauma to premature infants’ skin when the devices are removed. Also, work with the World Health Organization has begun to facilitate the development of pediatric-appropriate formulations for drugs used in the management of tuberculosis.

The conducting of clinical trials in children is more complex than the trial process in adults. Obtaining relevant preclinical data, addressing developmental differences, informed consent, ethical considerations, and patient recruitment are some of the specific challenges. In addition, because of the limited numbers of patients at any one center, multicenter trials are often necessary even at the early stages of development. The U.S. National Institutes of Health (NIH) Modernization Act of 2006 not only established the mechanism and funding for the development of a clinical and translation science centers consortium [through the Clinical and Translational Science Awards (CTSAs)], but also required the preservation of infrastructure and funding for pediatric centers. This new infrastructure is designed to catalyze the interface between basic and clinical sciences. It encourages innovative relationships with nontraditional research partners, recognizes the concepts of product development, and identifies public/private collaboration with industry as a priority. The CTSA Consortium Child Health Oversight Committee has organized around a number of important issues, including operations, metrics, pediatric drugs and devices, translation of clinical studies into practice, pediatric-adult life span, research ethics, and rare diseases. The dialogue of the CTSA Consortium is a move in the right direction and can serve as the infrastructure and agent for changes in pediatric product development. Key will be the level of efficiency and accountability for increased productivity.

The development of pediatric products is also dependent on a knowledgeable child-focused workforce. Specific programs designed to ensure the availability of product development and academic entrepreneurial skills are critical to the effort. This involves the maintenance of specialized pediatric talent and the providing of incentives for new and nontraditional talent. NIH-funded training opportunities in pediatric clinical research are essential, including innovative programs through the CTSA and programs such as the NICHD-funded Pediatric Pharmacology Research Units. This need goes beyond medicine to biotechnology, nursing, engineering, health economics, business, policy, health care finance, community engagement, and law. Support for these academic entrepreneurial aspects of product development is also needed.

A significant portion of pediatric development involves “orphan” diseases; that is, conditions for which there is little financial incentive to discover and develop therapies and that thus have not been “adopted” by the pharmaceutical industry. Even with federal assistance, product development here has been slow. For example, while promising approaches to the treatment of muscular dystrophy (for example, exon skipping) recently have been identified, the movement of these discoveries into clinical trials has been problematic (6). A number of issues have contributed to this problem of moving from preclinical to robust clinical studies of oligonucleotide antisense treatment for muscular dystrophy, including (i) the uncertainties of the regulatory path to approval of so-called designer or personalized medicine
products; (ii) the lack of comprehensive and effective public/private partnerships to motivate development; and (iii) the challenges of ensuring commercial feasibility. Another example is in the field of pediatric oncology, in which, despite reform of the development process for cancer therapeutics and their enhanced priority, rarely are drugs specifically approved for children, and rarely do the therapies have pediatric labeling (7, 8).

This is an important time in pediatric product development. Although there is still a lot of work to do, progress in being made. Regulatory policy is supportive, infrastructure is being institutionalized, and new models to catalyze success are being implemented. There is also increasing recognition that the need goes beyond drugs, to devices, diagnostics, and behavior interventions. These are all important steps, in fact, more than baby steps. Indeed, transformational change is now possible. We can ensure this transformation in two ways. First, critical to the effort is the development of a true pediatric national/global translational research agenda. Second, the research community can strengthen the motivation to advance innovation development for children by providing avenues for professional advancement based on product innovation and impact on pediatric health.

### Table 1. Key milestones in pediatric product development.

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<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>1979</td>
<td>FDA Rule: Pediatric Use Section established in package labels.</td>
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<td>1983</td>
<td>Orphan Drug Act signed, which provided federal assistance in the development of products for the diagnosis, treatment, and prevention of rare diseases/conditions. Health and Human Services (HHS) Final Rule incorporated protection of children as research subjects in HHS research.</td>
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<td>1994</td>
<td>Modification of the FDA rule related to Pediatric Use and extrapolation of adult data: Required that a statement be included in the drug labels of agents for which there is not sufficient evidence that products are appropriate for pediatric use.</td>
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<td>1997</td>
<td>Food and Drug Administration Modernization Act (FDAMA): 6 months of extended patent protection is given for sponsors who provide certain pediatric data in compliance with the FDA.</td>
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<td>2000</td>
<td>Children’s Health Act required research on FDA-regulated pediatric products to comply with HHS subpart D and a review of subpart D by the secretary of HHS.</td>
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<td>2001</td>
<td>International Conference on Harmonisation (Clinical Investigation of Medicinal Products in the Pediatric Population) came into operation.</td>
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<td>2002</td>
<td>Pediatric Rule was enjoined as a result of a legal challenge. BPCA: Renewed pediatric exclusivity provisions and provided for testing of on- and off-patent drugs in children; a Priority List was developed by FDA in collaboration with NICHD.</td>
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<td>2003</td>
<td>PREA: Required the study of drugs and biologics in children with only specific exceptions; established the Pediatric Advisory Committee.</td>
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<td>2006</td>
<td>NIH Modernization Act: Established the CTSA consortium in the United States and preserved infrastructure and funding for pediatric centers.</td>
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<td>2007</td>
<td>The Food and Drug Administration Amendments Act (FDAAA): Reauthorized BPCA and PREA and included the Pediatric Medical Device Safety and Improvement Act. European Union Pediatric Regulation: Comprehensive regulation that required that pediatric data be available at the time of drug approval based on a pediatric investigation plan.</td>
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References

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