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From Research to the Bedside: Challenges for Pediatric Academic Researchers

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ABSTRACT

Background: Although improving, development of drugs and devices for children is still less effective than for adults. Pediatric academicians play an important role in the bench-to-bedside research process, but much remains to be done to improve their contributions.
Objective: To provide a non-comprehensive review of selected literature based on my own personal experience as a U.S. based academic researcher who has spent over 4 decades doing pediatric drug and device development.
Methods: This commentary presents a summary of a talk given at a recent pediatric drug development conference. The observations and conclusions reached were based on the author's (largely US) experience and review of past history, the role of academicians in this process, some successful models of public–private collaboration, available funding, and barriers that remain to be overcome.
Results: Pediatric-specific legislation and more available funding have increased participation from and successes of US academicians in the pediatric drug and device development process. Incentive based public–private collaborations have been particularly successful. However, academicians still face both attitude and practical barriers to success.
Conclusions: Changes are needed if academicians are to maximize their involvement in pediatric drug and device development.

Introduction

Over the past decades, awareness has increased of the need to find more ways to develop useful medicines and devices for children that are commercially nonviable. Although breakthrough therapies are being approved, such as for cystic fibrosis and other rare diseases, pediatric and (especially) neonatal drug and device development is still more limited than for adults. Although responsibility for finding better ways to develop such products is shared by all members of society, including those in government, charities/nonprofit organizations, patient/parent interest groups, for-profit industry, and academic institutions, this commentary focuses on academia.

Current Situation Overview

The critical role of academic medical research in drug and device development is well recognized. There are, however, barriers to the more effective and efficient transition of research findings from bench to bedside. This commentary offers a selective, personal view of both academic successes and some barriers that remain to be overcome for academicians to improve their contribution to this process.

The current development of pediatric drugs and devices is clearly better than it was 2 to 3 decades ago. Major improvements have been made in societal and professional attitudes about doing clinical studies in children. The attitudes of parents, patients, pediatric health care providers, and pediatric organizations such as the American Academy of Pediatrics have all moved from the position that "it is unethical to do research in children" toward, "it is unethical to not do research in children."[1] Legislators have become more active supporters of doing and funding pediatric drug and device development. The availability of the high-quality, more child-friendly regulatory, industry, and academic infrastructure required to support pediatric studies has continued to improve. There are

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increasing numbers of regulators with excellent pediatric training, experience, and focus and the methods these regulators use, especially those in the United States, have begun to move away from adult paradigms that so often are simply inappropriate for children. The attitude of industry personnel toward doing pediatric studies, as well as the methods used to design and perform pediatric trials, have all greatly improved. Most encouraging perhaps, both regulatory bodies and industry have clearly begun to successfully move from research in children to research for children.[2] The number of experienced private and academic research sites, investigators, and research support staff who are willing and capable of doing high-quality pediatric studies have also increased. Finally, academicians' attitudes toward doing pediatric clinical trials have begun to change.

These attitude, legislative, regulatory, commercial, and academic improvements and changes have been prompted both by increases in both public and patient pressure and research funding. Although there have been many more label changes for adult drugs and devices than there are new products being developed exclusively for children, there is a growing number of pediatric therapies being developed, especially for orphan and rare diseases, where not coincidentally the largest financial rewards exist. This commentary reflects my personal experiences and observations concerning academic financial realities, past successes or failures, strengths, and weaknesses, as well as barriers that remain to be overcome.

Financial and Other Realities

Academicians remain outspoken critics of the failure of industry to develop more products for children. However, efforts to promote pediatric drug development only began to accelerate after efforts were refocused on finding ways to reward for-profit development of otherwise financially untenable pediatric drugs. Examples include the carrot offered by the first Food and Drug Administration Modernization Act (FDAMA) legislation[3] as well as the prior Orphan Drug Act.[4] The success of such incentives is based on the fact that the for-profit drug industry has always been successful at developing products, including for children, when there were profits to be made. The large number of pediatric-specific therapeutic products (eg, vaccines, antibiotics, antivirals, surfactants, growth hormones, and orphan drug products) are proof that profits produce products.

In any capitalist society, product development is based on risks versus benefits. When potential benefits (ie, profits) are very likely and risks are low, there is no problem. Product development is also likely even when risks exist, if large profits are possible. Product development is unlikely when profits are low, especially when risks are great. Although risks can sometimes be reduced, especially to industry, efforts to increase what each of the many stakeholders considers benefits are also needed.

Successful attempts to promote drug and device development should be based on what motivates each stakeholder interested in promoting pediatric drug and device development. This requires understanding how each segment of society would answer the question, "What is in it for me?" Almost everyone desires better child health, but what motivates each individual stakeholder can differ. Parents, grandparents, and patient groups understandably concentrate on finding cures for their children, grandchildren, family members, or themselves. Industry employees as well as legislators, regulators, and academicians can also of course also be motivated parents, grandparents, or patients. But to survive, industry needs to generate the profits that come from successful products. Legislators need to improve their image and get votes. Regulators want to stay employed/get promoted while avoiding approving drugs or devices that are removed from the market for toxicity or lack of efficacy. Academicians are highly motivated by the search for knowledge as well as the desire to obtain promotion and tenure, reputation, and funding. Attempts to increase academic involvement in the pediatric drug and device development process should be based on what is likely to work (ie, past successes), must exploit all academic motivators, and must overcome any barriers that exist. A major reason that carrot approaches have worked is that they resulted in increased funding of academicians involved in pediatric drug and device development.

Past Successes

The initial FDAMA offered the carrot of extended marketing exclusivity in exchange for completing pediatric trials. This motivated industry and academia to perform, respectively, otherwise commercially unviable or not otherwise fundable pediatric clinical trials. These trials increased both the industry and academic infrastructure necessary to perform pediatric trials and also improved perceptions of pediatric trials in not only industry and academia but also in regulators, legislators, and the public at large. Although the clinical value of FDAMA-generated trials can be debated and there have been failures, especially with respect to promoting studies of older, off-patent, and neonatal-specific products, there is little doubt that the infrastructure necessary to do trials and opinions of what is possible were changed forever by the success of the FDAMA carrot approach. In this author's view it was successful because to took advantage of what motivates all of the various stakeholders.

The initial FDAMA legislation was replaced by the Best Pharmaceuticals for Children Act, which extended the exclusivity carrot and then the Pediatric Research Equity Act that gave the FDA a stick to demand pediatric studies. Most recently (2012), these 2 approaches were made permanent as the FDA Safety and Innovation Act. A review of the history, content, and results of these and subsequent legislation is beyond the scope of this commentary. However, it is important to note that a number of other successful approaches are based on the carrot rather than the stick approach, such as the FDA's priority voucher program created under the FDA Safety and Innovation Act and its amendments.

FDA can award exchangeable vouchers to entities that obtain marketing approval for a treatment of a commercially unviable orphan, tropical, neglected, or rare pediatric disease such as a pediatric cancer. It is important to note that parent/patient groups have played a major role in expanding this legislation (eg, 2016 Creating Hope Act). Sale of these vouchers, each of which represents the development of an important treatment, has already generated >$1 billion.[5] These sales have financially benefited both pharmaceutical companies as well as academic institutions while generating approved treatments for a range of rare, neglected, or pediatric-specific conditions. In 2014, Regeneron paid BioMarin $67.5 million for the voucher BioMarin received for developing Vimizim (BioMarin, Novato, California, United States) to treat patients with mucopolysaccharidosis type IVA. In 2015, Retrophin Inc paid $27 million (plus up to $37 million more based on sales) for the voucher Asklepion received for developing Cholbam (cholic acid) in collaboration with investigators at Cincinnati Children's Hospital to treat children with rare bile acid disorders (this voucher was later resold to Sanofi for $245 million). Also, in 2015, AbbVie Inc paid $350 million to United Therapeutics Corp for its priority review voucher that was awarded for FDA approval of Unituxin to treat pediatric neuroblastoma.

It is difficult to judge the future success or financial sustainability of such voucher legislation. As Yogi Berra is quoted as saying, "It is always difficult to make predictions, especially about the future." It is clear that voucher programs have created large financial car-

rots that motivate both private companies and public institutions to become more involved in pediatric product development.

Academic Funding and Participation

Basic science discoveries are critical to product development and are largely but not exclusively the purview of academic institutions. Industry has also contributed greatly both alone and in public–private partnerships. There are a limited number of approved pediatric-specific treatments such as cholic acid that were successfully developed by academic pediatric researchers from bench to bedside. There are many more examples of successful public–private collaborative partnerships between academia, industry, and government.

A few examples of successful, government-funded (eg, National Institutes of Health) collaborations include the pediatric and neonatal networks,[6] the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke's Drug Development Program,[7] the National Institute of Neurological Diseases and Stroke (NINDS)/FDA's collaborative Best Pharmaceuticals for Children Act off-patent drug studies program, the Clinical and Translational Science Awards Program, the Pediatric Device Consortia,[8] and the International Neonatal Consortium of the Critical Path Institute.[9] The US Department of Defense and The Walter Reed Army Institute of Research also have programs not funded by the National Institutes of Health. A review of all these programs is beyond the scope of this commentary, but they all involve funding and collaborative partnerships.[10–12]

The long-lasting (first established in 1975) epilepsy drug development program is worth using as an example of an especially productive public–private collaborative model devoted to human drug development. The program's success in my view is based on its ability to decrease the costs (ie, risks) of early drug testing. Probably the most impressive measure of the success of this government–public–private partnership is the fact that it contributed to development of 9 drugs that have come to the market since 1990 for the treatment of human epilepsy. A detailed description of the program is beyond the scope of this article.[7] Briefly, it tests, at government expense, any compound submitted to it for efficacy and toxicity while the entities that submit the compounds (called participants) retain all rights to the compound. At any stage in the testing process, the participant can take over further development of the compound. This program has tested more than 32,000 compounds submitted by more than 600 academic (~60%) and industry (~40%) participants from 38 different countries. Emulation of this model, in my view, should be considered for many pediatric diseases other than epilepsy.

There are also a number of important, privately funded collaborative programs that involve and fund academic research such as by the Wellcome Trust (UK), Gates (US), Clinton (US), Cystic Fibrosis (US), and Muscular Dystrophy Foundations US, as well as those funded by children's hospital foundations, including those in Boston, Cincinnati, Chicago (Lurie), Kansas City (Mercy), and Memphis (St Jude's). The financial rewards made possible by voucher programs such as those obtained by the successful development of cholic acid are likely to increase interest in, and foundation funding of, both these existing and new pediatric drug development programs.

One such program is the Chemical Biology & Therapeutics Initiative at St Jude's Children's Hospital. This program focuses on pediatric tumor targets, includes an industry/academic partnership, is funded by both private institutional funds and the National Cancer Institute-funded Pediatric Cancer Drug Discovery Consortia, and includes both a high throughput screening program a Good Manufacturing Practice-approved drug manufacturing facility.[13] Another is the Pediatric Drug Development Center at Lurie Children's Hospital in Chicago, which attempts to repurpose shelved oncology drugs that went through Phase I or II testing but either failed to be approved or were not submitted. These drugs are re-examined for other uses or against new targets in academic–industry partnerships.[14] Despite the promise that such programs represent, there are a number of real and perceived barriers, not all of which are openly acknowledged, which must be overcome for successful programs to be maintained or new ones to be created.

Academic Barriers

Although the situation is improving, few academicians have sufficient training in, experience in, or understanding of the development process to efficiently and effectively develop products. There are also attitude barriers that need to be overcome. One such barrier is exemplified by an academic colleague of mine who once complained that, "if the FDA wants to know how to treat children with hypertension they should just ask me." The desire for regulatory approvals to be eminence- rather than evidence-based is unfortunately, in my experience, neither uncommon nor restricted to academics. Many academicians also have clear anti-industry biases, including viewing working with or receiving money from industry as being somehow unethical. This bias is supported by the view that academics should focus on obtaining knowledge only for knowledge's sake; such work is somehow more important that simple product development as well as being free from conflicts of interest. The extremely long time (≥17 years) it takes to go from basic science discovery to actual product development[15] and the growing need for all pediatric subspecialists are additional, formidable barriers. Promotion and tenure (P&T) preferences add to these problems.

P&T committees often give disproportionate weight to publications in journals that discourage, or even refuse, submissions reporting research supported by industry. Decisions are based more on the sources, number and magnitude of grants received than on whether any useful product or therapy is produced. National Institutes of Health/National Science Foundation (US), grants, even those that failed to achieve any of their stated scientific goals, are given disproportionate weight when compared with those obtained from industry and ignore success at obtaining health care patents or developing clinically important therapies or products. This bias prompts me to paraphrase John W. Gardner, who said:

> The society which scorns excellence in plumbing because plumbing is a humble activity and tolerates shoddiness in philosophy because it is an exalted activity will have neither good plumbing nor good philosophy. Neither its pipes nor its theories will hold water.
>
> https://www.bartleby.com/73/568.html.

Academicians' interest in being involved in pediatric drug and device development are also limited by the fact that many research grant funding decisions are based more or only on the perceived promise of the ideas/concepts presented than on the possibility of producing any functional end product. Institutional funding support as well as institutional review board or ethics committee approval decisions are also usually based solely on scientific rationale and ignore any questions concerning of usefulness or quality of the data generated.

As a result of these limitations, not all academic investigator-initiated and institutional or foundation supported studies produce data of sufficient quality to support regulatory approval. As evidence of this, the initial FDAMA legislation allowed for drugs that were already being used off-label in children to be relabeled for pediatric use if their manufacturers could produce ad-

equate literature evidence of safety and efficacy. However, FDA's review of a vast amount of data from published, investigator-initiated studies was almost never of adequate quality to justify labeling. Even the recent successful approval of Cholbam would have been greatly shortened had the investigators who performed the initial studies had more experience in or appreciation for how to perform regulatory quality trials. Also, whereas the majority (up to 80%) of pediatric trials fail as a result of poor enrollment and poor study designs[16] these are not the only problems seen with investigator-initiated studies. Inadequate compliance with study protocols, sample handling, data collection, study monitoring, and even consent procedures continue to be problematic with investigator-initiated, nonindustry funded trials, especially those performed at inexperienced academic sites. Additional, poststudy problems include selective, incomplete, or biased reporting of pediatric study results, including publications that do not provide adequate description of the formulation used.[17]

Changes Proposed

Academicians should work to remove these overcome these barriers and limitations. All pediatric trials, not just those supported by industry, should be done in a way that would allow their results to be used to support regulatory approval. Clinical trial/regulatory education and certification of academicians should be increased and rewarded in the P&T process. Review boards and ethics committees should not approve pediatric clinical trials that cannot produce regulation-compliant data and should require both adequate publication and access to raw data. Medical journals should not publish incomplete clinical trial reports, including those lacking information on formulations and data monitoring methods used. Academic institutions, government agencies, and nonprofit foundations should not fund investigator-initiated trials unless they are to be performed in regulation-compliant ways and either only fund, or at least give preference to, studies that are likely to produce clinically needed but commercially nonviable products. Review boards and ethics committees should at least consider product/therapy potential when making approval decisions. Public–private partnerships and academic–industry interactions should be supported and expanded. Product development should be accepted as an academic achievement.

Additional Disruptors

The changes proposed for academic institutions would be useful but inadequate alone to rapidly improve the pediatric drug development process. Additional regulatory disruptors analogous to Apple, Uber, Amazon, and SpaceX in the commercial realm are also needed, and some have begun to appear. Examples include regulatory acceptance of alternative, nonclinical trial generated evidence of pediatric safety and efficacy and expanded use of data extrapolation. One example of the use of alternative methods is the use of opportunistic trials to gather pharmokinetic and even pharmacodynamic data from children receiving off-label drugs such as those used extensively by Benjamin's group at Duke to successfully relabel a number of off-patent drugs. An example of extrapolation was the recent FDA approval of the antiepileptic drug eslicarbazepine acetate (Aptiom, Sunovion, Marlborough, Massachusetts, United States) for use in children aged $\geq$4 years with partial-onset seizures based on efficacy and toxicity data collected in adults. These examples demonstrate the authority given to the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) 201.57(f)(9)(iv) to approve pediatric applications without actually doing any pediatric clinical trials. Expanded use of this authority could further facilitate approval of pediatric labeling and use. Also, although many adolescents, (especially older ones) are in fact physiologically adults, most nonadolescents, especially very young children, are not little adults. Therefore, the methods used to test and approve products in adults are neither appropriate nor likely to be successful in younger pediatric populations. Study designs appropriate for common adult conditions are especially inappropriate for infants, toddlers, or young children or in diseases where there are neither insufficient numbers of subjects nor pediatric appropriate outcome measures available.

Academicians should promote and increase their involvement in alternative, more pediatrics-friendly evaluation methods that regulators, especially in the United States, have actively promoted, perfected, or developed to assess the efficacy and toxicity of pediatric therapies. Efficacy examples include trial simulation, physiologic modeling, population pharmacokinetics (PK) using opportunistic trial data, microdosing, adaptive trial designs, multiple comparator trials, and surrogate efficacy/outcome measures. Alternative toxicity sources include use of disease registries, patient reported outcomes, and payer, hospital, pharmaceutical company, nonprofit foundation, and regulatory databases in addition to or instead of only Phase III or IV trials.

A number of other innovative developments have the potential to further improve pediatric drug and device development. These include the use artificial intelligence such as the Orativ program at the Mayo Clinic, and the development of siteless Contract Research Organizations (CROs) (eg, Research on Electronic Monitoring of OverActive Bladder Treatment Experience (REMOTE), Fox Trial Finder, Oregon Center for Aging & Technology (ORACATECH)). The ability of financial incentives to spur pediatric drug development has already been mentioned. The success of privately funded aerospace companies (eg SpaceX, Stratolaunch Systems, Planetary Resources, Blue Origin, Virgin Galactic, and Bigelow Aerospace) suggest that the availability of pediatric competitions such as the Impact Pediatric Health Pitch Competition, especially if greatly expanded, would also be successful. Unfortunately, given the long delay between basic science discoveries and eventual drug approval it will be years before the full effects of this approach are seen. It is useful to note that the use of vouchers was first proposed more than a decade ago[18] to create incentives for industry to develop cures for neglected tropical diseases.

The recent FDA approval of Novartis' chimeric antigen receptor T cell therapy[19] is an impressive example of the effectiveness of public–private partnerships (here among Novartis, the University of Pennsylvania, and other academic institutions). This example also demonstrates how rapid and effective regulatory prioritization can be. Orphan drug status was approved for this approach in January 2014 and final approval/access was obtained only 2.5 years later. Clearly attitudes about the time needed to obtain approval, as well as the economics, of the increasingly personalized treatment of rare (even $N = 1$) pediatric diseases need to be reassessed.

Pediatric drug and device development has improved but is still suboptimal.[20] Further improvements will require greater contributions from all stakeholders. Parent/patient groups need to continue to increase their involvement in and support of pediatric drug and device testing. Legislators need to continuously review the efficacy of current laws for possible improved or alternative approaches. Regulators must carefully and honestly evaluate, improve, and when needed even replace any review methods that are ineffective or inappropriate for children. The well-recognized, successful role of academia in making basic science discoveries is necessary but insufficient to maximize pediatric drug and device development. Changes are needed in the P&T process to remove barriers to and provide more incentives for academicians to develop new or improved therapeutic products. Expanded support for and involvement in research directed at improved or alternative study designs as well as more training, collaborative public–

private partnerships and attitude changes are also needed. Fortunately, there are a growing number of achievements that suggest that much of what previously seemed impossible may in fact not be. Some famous quotes may be appropriate to end this commentary:

"It always seems impossible until it's done." - Nelson Mandela

"It's kind of fun to do the impossible." - Walt Disney

"It is either easy or impossible." - Salvador Dali

"Impossible only means that you haven't found the solution yet." - Anonymous

Conclusions

Public-private collaboration, legislation, and increased funding have produced some successful pediatric drug development but academic pediatricians still face many barriers that limit successful pediatric drug and device development.

Acknowledgment

This material was adapted from a presentation of the same name given by the author at the 3rd Paediatric Drug Development Conference, November 14-15, 2017, Budapest, Hungary.

Conflicts of Interest

Dr Walson is an unpaid board member of the Alliance for the Prudent Use of Antibiotics at Tufts University. He is co-president of Walson Consulting, LLC, a private consulting firm registered in Seattle, Washington, through which he receives financial compensation for numerous medical consulting activities. He received travel reimbursement but no other payments from the organizers of the Budapest meeting at which he gave a presentation upon which this commentary is based. He chairs the Data Monitoring Committee that monitors pediatric studies funded by the National Institutes of Child Health and Human Development (NICHD) under the Best Pharmaceuticals for Children Act (BPCA) and a Data Safety Monitoring Committee monitoring a pediatric trial for Astellas. He is a paid member of an adjudication committee for a pediatric trial for Da Volterra and pediatric consultant to Shenox Pharmaceuticals. He serves as a paid expert witness for medical legal issues. He is editor-in-chief of both *Current Therapeutic Research* and the *Generics and Biosimilars Initiative* as well as emeritus editor-in-chief and a topic editor at large of *Clinical Therapeutics*. The author has indicated that he has no other conflicts of interest regarding the content of this article

Supplementary material

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