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Editor-in-Chief's Commentary: Women and Children First

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In 2014, we will be celebrating the 50th anniversary of the creation of the DIA. Much of the impetus behind creating a nonprofit, neutral organization to increase information and communication about medical products came from the thalidomide tragedy and the resultant Kefauver-Harris Amendments to the Pure Food and Drug Act in the US in 1963. The 1938 FDA statutes also derived from a tragedy involving the deaths of children from elixir of sulfanilamide. Yet, while adverse drug effects in women and in their unborn babies and children resulted in legislation, little was actually done to improve the lot of therapeutics for these groups for years after the events.

In 2013, we can now point to huge progress that has been made in pediatric therapeutics, but perhaps somewhat less so in the treatment of reproductive age and pregnant women. There have been many challenges to studying outcomes (positive and negative) in these populations. We have struggled with ethical, legal, technological (such as measuring drug concentrations in very small blood volumes), biological (understanding the ontogeny of drug clearance and metabolism, and of drug response in children, and potential fetal effects of drugs), practical (few patients to study and need for multicenter, international studies), and financial (often high cost and low return on investment for pediatric products) challenges. Advocates for children and women's health have worked for decades in all spheres—patient groups, physicians, investigators, pediatric organizations throughout the world, NICHD (National Institute for Child Health and Human Development at the NIH), many government agencies and elected officials, pediatric investigators in industry, the international regulatory community. The fruits of those efforts are now making an impact on how we treat sick children and are hopefully providing more wisdom about safe, effective use of medicines in pregnant women.

So many efforts have contributed to the effort over the years, but a few stand out from the perspective of driving therapeutic innovation and regulatory science. Legislative efforts have been based both on the recognition of the need for high-quality, ethically conducted pediatric studies to safely and effectively administer needed medicines to children, as well as on the difficulty of doing many of the studies. Thus, "carrot" and "stick" approaches have been legislated and implemented in both the US and EU. Incentives to sponsors to undertake pediatric studies based on fulfilling defined regulatory protocols, together with mandates for pediatric studies based on specific conditions for older and newer drugs, have both been successful in driving pediatric investigation and in improving labeling of medicines for children. In the US, the Best Pharmaceuticals for Children Act (BPCA; initiated as part of the FDA Modernization Act of 1997) has been renewed for 5-year commitments with progressive improvements in the understanding of regulatory/medical needs and the practicalities of pediatric clinical investigation. In 2012, BPCA and its companion legislation the Pediatric Research Equity Act (PREA) were both renewed without time limit. Similar legislation is now in place in the EU. There remain some differences in sponsor requirements in the legislation at FDA and EMA that can be confusing to sponsors trying to do international development programs. The good news is that FDA and EMA pediatric regulators regularly discuss issues, now joined by an expanding group of regulators from Canada, Japan, Switzerland, and hopefully others. Thirteen years ago, ICH E-11 (as part of the International Conference on Harmonisation) was published, as part of a 3-region industry/regulatory agency effort including the US, EU, Japan, and observers from several other venues. It is the hope that all these efforts will evolve a truly international approach to pediatric drug development guided by the highest ethical and scientific standards, with collaboration of pediatric investigators across the globe to ensure that needed data are developed with a minimum of duplicative or unnecessary studies. Ongoing international collaboration goes to the very heart of pediatric therapeutics. It is worth pointing out, as well, that the majority of the world's children live in the "developing world" and are exposed to illnesses little seen or studied in the US or EU. We need new strategies to incentivize the investigation and development of interventions for all those conditions afflicting so many children.

In this issue of *TIRS*, we have several papers addressing innovation in clinical investigation and impact on regulatory science on behalf of pregnant women and children. The article by Dewulf, "Medicines in Pregnancy—Women and Children

First? Time for a Coalition to Address a Substantial Patient Need'' focuses on the challenges of women's health and the systematic capture of data when medicines must be used in pregnant women due to a pre-existing condition and intercurrent illness. Two papers (Thompson et al, ''Industry Survey on Current Practices in the Assessment of Palatability and Swallowability in the Development of Pediatric Oral Solid Dosage Forms,'' and Squires et al, ''A Systematic Literature Review on the Assessment of Palatability and Swallowability in the Development of Oral Dosage Forms for Pediatric Patients'') focus on pediatric formulations. Formulations designed to administer medicines in convenient, accurate, safe formats have been a major challenge, and there is a need for regulatory harmonization on ''acceptability'' of formulations and how to measure such acceptability that will fulfill requirements in all regulatory agencies. Like other areas of drug development, a strong scientific basis should guide the regulatory process, and with medicines for small numbers of pediatric patients, acceptability of formulations globally is essential. While not emphasized in these papers, there is need to consider formulations that resist high temperatures and humidity, and that are suitable for administration to children throughout the globe.

Since the inception of BPCA/PREA and other legislative and regulatory efforts, we have learned a great deal about what we do NOT know about pediatric drug development. We are now evolving novel approaches based on an increasing volume of data from pediatric clinical trials, and we need to apply that new knowledge to the drug development and regulatory processes. Thus, Marier et al (''A Modeling and Simulations Framework to Support Global Regulatory Strategies for Pediatric Drug Development Programs'') discuss modeling and simulation in global regulatory strategies, focusing on how to design the best possible programs and reach agreement among sponsors and regulators on the design, and implement the best pediatric programs.

One of the major challenges of pediatric drug development has been the issue of extrapolation of adult disease to pediatric disease. The regulatory language associated with the concept is that if the disease and likely response to intervention are ''sufficiently similar'' in adults and children, then requirements for labeling may be achieved by studies on pharmacokinetics, perhaps bridging pharmacokinetic-pharmacodynamic studies, and safety assessment. This is an important concept conceptually, and in reality it could save unnecessary studies in children. However, the challenge is in the scientific assessment of the ''similarity.'' Leil et al (''Quantitative Extrapolation: An Approach to Validation of Adult Drug Efficacy in Pediatric Subjects'') examine this issue and some of the challenges faced in drug development and regulatory process of determining similarity.

The issue of safety in children has always been paramount, and indeed safety problems in children have often led to legislative and regulatory action. In fact, while often thought of as a ''vulnerable population,'' children may be at higher, lower, or the same risk of adverse drug effects compared to adults based on the mechanism of adverse effects. For example, children generally tolerate higher doses (and internal exposure) to cancer chemotherapy drugs, and overdoses of acetaminophen. However, the very fact that children are growing and developing physically and cognitively presents a challenge to assess any adverse effects of medicines, particularly those used chronically, on these essential processes of childhood. Goldman et al (''Pediatric Pharmacovigilance: Enhancing Adverse Drug Reaction Reporting in a Tertiary Care Children's Hospital'') present a detailed look at pediatric pharmacovigilance in a large children's hospital.

Increasingly, we are looking to networks of hospitals, subspecialty organizations, and primary care practices nationally and internationally to gather data on postapproval outcomes of medical products in children. We have seen excellent examples of investigative networks, for example in cystic fibrosis, where international experts who care for these patients were primed to do outstanding investigative programs as new drugs have been developed, and who, because they continue to follow the patients, have the capacity to ensure postapproval, real-world studies of both benefit and safety. Establishing more such networks holds the promise of ''continuous-learning'' medical environments with an integrative approach to clinical care, clinical trials, and real-world assessment of interventions. The better such comprehensive approaches become, the greater the confidence of regulatory agencies to advance products into general use and the better served patients are through ongoing, systematically collected data.

In addition to the pediatric contributions, we also have articles addressing related issues—novel formulation development, simulation and innovative designs in oncology, regulatory harmonization initiatives, and patient-reported outcomes for central nervous system diseases.

A final note on the convergence of science. In the past several years, we have seen an increasing number of drugs developed for orphan conditions, based on precision targeting toward the underlying etiology of conditions. Because of the large effect sizes of many of these drugs and the selection of patients into clinical trials based on the expression of a specific target, pivotal studies have required fewer patients (often barely 200) to demonstrate efficacy. This has been the case for many new cancer drugs as well as a new drug for cystic fibrosis. The shift in paradigm and creative use linkage of diagnostics and therapeutics suggests that for many new drugs, pediatric studies will be more feasible and interpretable. The issue of ''similarity'' of diseases between children and adults becomes less relevant than the use of molecular diagnostics to tease out the etiology of an individual patient's condition and

choose targeted therapeutics based on this. "Personalized medicine" meets "pediatric drug development." Similarly, if current trends are borne out (see my previous editorial on assumptions in genetics and genomics[1]), large effect sizes and targeted entry of patients who "can" respond to a specific drug into clinical trials should remove one of the barriers to pediatric studies, ie, small patient numbers. Pediatric investigators need to broaden their perspective and take advantage of advances in drug development science per se. Small patient populations should no longer be a barrier to, and an excuse against, the feasibility of pediatric clinical studies. All of this will require much more understanding of the biology of disease in children as well as in adults. In the end, advancing science will lead the way to innovation, improved regulatory practice, and better outcomes for our patients.

—Stephen P. Spielberg, MD, PhD
Editor-in-Chief

Reference

1. Spielberg SP. Editor-in-chief's commentary: gene penetrance, therapeutic targets, and regulatory science. *Therapeutic Innovation & Regulatory Science*. 2013;47(3):289-290.

Announcement

DIA Names Barbara Lopez Kunz Global Chief Executive

Barbara Lopez Kunz has been named Global Chief Executive and will begin leading DIA on September 1, 2013. Most recently, Lopez Kunz was president, Health and Life Sciences Global Business and senior vice president and corporate officer of Battelle, the world's leading international science and technology enterprise that explores emerging areas of science, develops and commercializes technology, and manages laboratories for customers.

While at Battelle, Lopez Kunz transformed its Health and Life Sciences business through strategic investments, alliance development, and technology commercialization, delivering high rates of growth in research collaborations with industry, government, and academic sponsors. Lopez Kunz's leadership experience also includes appointments as senior vice president and general manager for Fisher Scientific International's Biosciences business, where she championed the formation and growth of the business through a series of acquisitions, and as vice president, Latin America and global vice president, Enterprise Business Group for Uniqema, one of the ICI portfolio businesses. She has also held senior roles at DuPont and PPG Industries. She started her career as a research scientist.

DIA President Minnie Baylor-Henry said, "After an extensive search, DIA is excited to have found a leader with a wealth of experience that meshes perfectly with our vision to be the global forum for knowledge exchange that fosters innovation to raise the level of health and well being worldwide. Barbara has an enormously successful track record of growing businesses that are based on innovation in science and technology and developing and implementing global strategies, and we are looking forward to her leadership and guidance."

A leader on numerous corporate and nonprofit boards, she has presided over the board of The Ohio State University Wexner Medical Center and is a trustee of both Nationwide Children's Hospital Research Institute and BioOhio, the statewide organization stimulating economic development in the bioindustry cluster. Lopez Kunz is a member of the Executive Advisory Council for the Ohio Healthcare Business Women's Association.

"I look forward to continuing the important work that DIA has spearheaded over the last 49 years. I am excited to lead this organization into its 50th anniversary celebration and set it on a course for its next half century. The foundation is in place; it is my intent to utilize my global background and my knowledge of the needs of patients and the health care community to strengthen DIA's already solid foundation of transferring knowledge across the globe. By bringing researchers, industry, academics, patient advocates, and regulators together, DIA will continue to facilitate the dissemination of vital information needed to ensure that the level of health and well being is raised around the world," said Lopez Kunz.