

Editor-in-Chief's Commentary: DIA, *TIRS*, and ICH

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DIA serves as an impartial organization to bring together individuals, organizations, and knowledge to advance the efficient and effective conversion of science into products that improve the health and well-being of people throughout the globe. We connect people with knowledge. *TIRS* serves as the peer-reviewed journal for DIA, attracting and publishing impactful original articles and commentaries as part of a knowledge continuum that begins with meetings and training sessions and continues through our evolving electronic formats for timely communication. ICH, the International Conference on Harmonisation, has been bringing together industry and the regulatory community from the United States, Europe, and Japan to align approaches to medical product discovery, development, and evaluation since 1990. The goals of each of these organizations, DIA and ICH, are thus remarkably aligned.

Thirteen years ago, I had the privilege of representing the US pharmaceutical industry to work on the development of an international agreement of pediatric drug development, and served as the rapporteur for "ICH E-11, Clinical Investigation of Medicinal Products in the Pediatric Population."¹ There is discussion at the moment of providing some updates to E-11 as it enters its "adolescence," and now is a good time to review some the challenges in using scientific knowledge in "real time" to develop guidelines. In turn, this can help illuminate some of the challenges and opportunities that we face at DIA and in *TIRS*.

At the time that E-11 was being considered as a topic for ICH, patient advocacy and legislative and regulatory initiatives, then in the US but now truly global, had led to a huge increase in pediatric investigative activity. Thinking back to that time, we were all excited about new requirements for pediatric studies as well as the potential of "incentives" to industry to drive investment in pediatric drug development, initiated as part of the Food and Drug Administration Modernization Act (FDAMA)² in 1997 in the US. However, there was concern about the state of the scientific and regulatory basis of pediatric clinical trials and the clinical trial infrastructure available, as well as ethical issues of doing studies in subjects not able to consent to participation. Concerns were

raised about assuring the highest ethical and safety standards in undertaking pediatric studies; the small numbers of patients available for trials and the likely need for international studies was also considered.

Looking back on the document, it has stood the test of time well, and has helped facilitate much-needed new knowledge about the safe, effective use of medicines in children. We, of course, recognized at the time that much of what we wrote would need updating, that many of the concepts we set forth would change as new knowledge of developmental science, the pathogenesis of disease, clinical trial methods, and ethical considerations all would evolve. The rapidity of those changes has been more remarkable than any of us could have predicted. I have remarked on this in prior editorials in *TIRS*, and how even a journal has the need to develop new approaches to communication.

Very shortly after completing E-11, the Institute of Medicine undertook a project updating ethical issues in pediatric research, at the request of the US Congress in 2002 as part of the Best Pharmaceuticals for Children Act.³ As pediatric clinical investigation and drug development have expanded over the years, additional areas requiring clarification have also been defined. The need for information on the safe, effective use of medicines in children requires studies in children; our approach to protection of subjects (and their families) in research remains ever a priority. We need more and better scientific understanding of developing cognitive and ethical abilities of children, of complex changes occurring during adolescence, and further dialogue of the roles children play in the context of their families around the globe. We have learned a great deal from patients and patient advocacy groups about such issues as patient-centered outcomes and patients' understanding of benefit and risk. Much less has been explored in this realm for children of different ages. We still struggle with validated outcomes and what matters to pediatric patients and parents. What matters to a premature infant, pre-school child, school-age children, adolescents *and* to their families, and how to assess outcomes are important subjects for future research. Ethics and knowledge will continue to advance, and

continue to be intertwined. DIA, TIRS, and ICH all have roles in this endeavor.

The overlap in ethics and study design was highlighted in the concept of “extrapolation” of efficacy that the FDA had been developing at the time of the original ICH effort. An underlying ethical principle of pediatric studies was, and is, to minimize the burden of investigation, in other words to avoid unnecessary studies beyond those needed to acquire data to make decisions about safety and efficacy. The practical aspect of this was the small numbers of patients available for study and the limited investigative sites to carry out pediatric clinical research. Thus, FDA and ICH argued that pediatric labeling could be accomplished with information on proper dosing and safety if “the condition being treated and likely outcome of the therapeutic intervention were likely to be sufficiently similar” in adults and children. The concept was valid and appropriate from a regulatory point of view; the difficulty lay in how to establish “sufficient similarity.” In the intervening years, we have learned a huge amount about the molecular basis of “conditions,” and we are in an era of redefining disease based more on specific etiology. Recognizing that the things we categorize by signs and symptoms may be due to different causes, we are entering a time of more targeted therapeutics. We are also recognizing that things we name similarly in pediatrics and adult medicine, or even among patients of similar demographics may, in fact, be quite different. Given the paradigms of contemporary target ascertainment and candidate drug development, the concept of extrapolation needs to be re-examined from a “personalized” targeting point of view. Furthermore, we now have far more experience with modeling and simulation, which can help design much tighter, smaller, and informative clinical trials (see Marier et al⁴ and Leil et al⁵ from previous issues). Thus, scientific advances at the molecular and clinical pharmacology/simulation/statistical study design levels can help in regulatory decision making about the extent and type of clinical trials that will be needed for pediatric labeling. It will also inform and help ethical decision processes to ensure both

protection of patients in clinical trials and assurance that data are generated to maximize safe, effective therapeutics. The ICH process can then help further establish harmonized guidelines so that international clinical trials can meet the scientific, clinical trial, and ethical requirements across the globe.

Our knowledge of ontogenic processes of drug disposition and effects will change. Our knowledge of the etiology of conditions in children and adults will expand. The volumes of data will explode and challenge us how to collate and interpret new information. The need, however, to have forums where all participants in the process—investigators, regulators, patients—can struggle together with evolving science will remain. DIA, TIRS, and ICH will all have critical roles in defining this shifting scientific landscape as we move forward.

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Publications Editor-in-Chief, DIA

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