Guide to Paediatric Drug Development and Clinical Research

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Children in the developed world have never enjoyed better medical care. Life expectancy is increasing, and child mortality is improving in most countries. However, the more we can do, the more we also see what could be done better. Every week five new genetically based rare diseases are described – for most of them there is no effective treatment and children with these diseases die early. Cancer in children is no longer untreatable. With the use of chemotherapy, radiation and surgery around 75% of the children survive. However, there are still several cancers in children where treatment is unsatisfactory, and the quality of life of many surviving children is seriously affected. The survival of children with cancer is one of the greatest success stories of medical research in the 20th century. It was not achieved by revolutionary break-through medication, but by combining the chemotherapeutic agents that reached the market in the 1940s and 1950s in new ways and new doses. From 1970 on, with each decade of diagnosis the survival of children with, e.g., acute lymphatic leukemia increased by 10–15% and is today around 90%. But in hindsight, many lives could have been saved earlier had we known how to use the existing medication. This gap was closed by systemic testing and is probably the best argument to show the value of clinical research in and with children. There are other success stories, including the advances in vaccines, surgery, nutrition, and many more.

The rapid advancement of scientific understanding of even more details of the human body combined with the availability of a large group of new genetically engineered medications has increased the desire to make these new treatment options available to children as soon as possible. This is the aim of the EU Paediatric Regulation, in force since January 2007, that has resulted in the formation of the Paediatric Committee, the strengthening of the paediatric department in the European Medicines Agency, and the submission of hundreds of Paediatric Investigation Plans by the pharmaceutical industry.

On the other hand, there are the children in developing countries that are exposed to diseases that in the majority of cases could be easily treated using existing medicines. In the days of modern communication technology, the visibility of these children and the theoretical possibility to help them with access to existing medication have increased the expectations that these children should receive more attention in general and specifically should receive better health care.

The public discussion about medicines for children and the health of children in the developed as well as in the developing world has in the past years reached an unprecedented intensity. One main driver has been the introduction of the EU paediatric regulation, in force now since January 2007, which has exposed pharmaceutical industry to an unprecedented need to include
children into the drug development process. An additional driver has been the launch of the WHO campaign 'make medicines child size', which is drawing increased attention to the health of children in the developing world. Further drivers are the increased collaboration between the regulatory authorities of the USA, EU, Japan and other countries and regions in their effort to bundle forces to promote better medicines for children.

On a different level, and less visible for the general public, there have been multiple developments at the clinical, scientific, academic and educational levels. Paediatric clinical pharmacology has established itself as an academic discipline in its own right, represented by the two large international organizations PPAG and ESDP. But what is paediatric clinical pharmacology?

Firstly, paediatric clinical pharmacology is the work of clinical pharmacologists in hospital pharmacies. They advise paediatricians and people in other medical disciplines that take care of ill children on the appropriate dosing of a given medication. They provide the appropriate, mostly extemporaneously prepared, formulation of medications where a child-friendly and age-appropriate formulation is not provided by the manufacturer.

Secondly, paediatric clinical pharmacology is the research undertaken by academic clinical pharmacologists that measure the absorption, distribution, metabolism, and excretion of medicines in children. It was due to their work that a common understanding evolved on how all body functions of the child mature at a different pace. This paediatric clinical pharmacology has, among others, elucidated that a much higher variability in ADME exists in children and that the degree of this high variability further increases if the child or infant has additional issues such as fever, stress, malnutrition or obesity, or is receiving multiple medications.

Thirdly, clinical pharmacology is the discipline in the pharmaceutical industry that tries to predict the dose of a given new medication when administered to children for the first time. Part of this work is modeling and simulation (M&S). M&S allows estimating the first dose of a given medication in a child. This assumed first dose has to be verified against the predicted serum concentration of the medication. If necessary, the prescribed dose has to be adapted based on the observed factual serum concentrations, and, in consequence, the underlying M&S assumptions have to be corrected. It would be unethical to expose children to a drug where basic safety and efficacy data have not yet been established in adults. Consequently, phase 1 clinical trials in healthy volunteers that are routine in adult drug development are not allowed in children. Therefore, clinical pharmacology data in children can only be generated in a setting where a child should benefit from the therapeutic potential of the drug in discussion. As a consequence, paediatric clinical pharmacology in the drug development process can by definition only happen in the framework of phase 2 or phase 3 clinical trials.

Clinical pharmacology is also the discipline in pharmaceutical industry that is part of the multi-disciplinary development team that brings a drug through the development process from initial discovery through preclinical and clinical testing to the registration as a medicine. The roles of the clinical pharmacologists in this process include advising on the doses to choose for clinical trials, time point of first exposure of a given drug in adult healthy volunteers, advice on the appropriate time point of a first paediatric exposure, advice on dose adaption in case of renal, hepatic or other impairments, and many more.

The two first types of clinical pharmacology concern drugs that are already existing. Modern drugs have evolved with industrialization and the ability of chemical engineering. Increasingly, biological engineering plays an important role in drug development. When we talk about off-label use of drugs in children we should not forget that modern labels have only evolved since the Kefauver-Harris acts in the USA in 1962 and that drugs in the modern sense of the word only exist for just over 100
years. On the background of this evolution, paediatric clinical pharmacology has been a logical consequence of this development. As always, it only seems to be a logical consequence in hindsight. If we look at the time axis, we see that paediatric clinical pharmacology is only at its early stages.

The level of clinical pharmacology service in hospitals and the level of collaboration with the discipline of paediatrics varies considerably. 'Advanced' hospitals have an own department of paediatric clinical pharmacology. 'Less advanced' hospitals just have a department of clinical pharmacology which may or may not include one paediatric clinical pharmacist who talks with the paediatricians. And let us not forget those hospitals in less-developed countries that may have only one pharmacist for the entire hospital. How paediatricians and clinical pharmacologists interact varies from country to country and from hospital to hospital. The collaboration is driven partially by science and partially by tradition.

Research in children is less developed than research in adults. Not all publications on research in children have the methodological scrutiny that has become standard in adult publications. That there is room for improvement is perceived by the most advanced representatives of the professional learned societies of paediatrics, pharmacology, clinical pharmacology and paediatric clinical pharmacology. On the other hand, most paediatricians are rather conservative. They have learned their profession, are proud of their profession, and are not very exposed to paediatric research in their daily clinical work. Speaking of better medicines for children must take into account the different levels of awareness that exists. Conferences on clinical pharmacology and paediatric clinical pharmacology have in recent years had sessions that were specifically dedicated to the new paediatric legislation in the USA and EU as well as to the WHO campaign 'make medicines child size'. Interestingly, the interest of paediatric practitioners has been rather limited. The call for better medicines for children is a movement that is represented and driven forward by a relatively small group within the professional bodies of paediatric pharmacology and clinical pharmacology. It is a movement that still is not strongly represented in the mindset of practicing paediatricians.

Key organizations to promote academic paediatric clinical pharmacology are the IUPHAR and the ESDP. Their key representatives have, together with key representatives from the International Pediatric Association (IPA), established a movement that culminated in the foundation of the IA: International Alliance for Better Medicines for Children. The journal *Pediatric Drugs* is now the official journal of this alliance.

The ethics of research in children is another area. Several issues are at its core. Basic dilemmas are the interest of the child, its inability in young years to represent its interests on its own, and the need of parents to decide in the best interest of their children, in short, their legal status. All involved institutions must balance the potential benefit of a new medication with the potential risk it may carry. But risks are not fully predictable. In consequence, the degree to which potential risks are accepted varies considerably over time depending of tragedies that happen, serious threats like a pandemic that has the potential to change the perception of need risk taking, and many, many more factors.

Ethics committees/IRBs have the institutional obligation to systematically evaluate paediatric research projects. Ethics committees need paediatric expertise. With the number of paediatric research projects increasing, the number of ethics committees that are exposed to paediatric research is increasing as well. The debate of ethics in paediatric research has therefore several elements. One is the question of right and wrong. Another one is the operational organization of decision processes by ethics committees. The literature on ethics in paediatric research is immense and growing. Dilemmas in daily clinical work exist and can by definition not be resolved. They must be handled operationally.
On the other side, the forced exposure of pharmaceutical and medical device industry to paediatric research and an increased academic discussion about paediatric research will also open new dimensions of ethical challenges. Large companies have own departments of quality assurance and are used to scrutiny by the public. Smaller companies have to now deal with paediatric development as well – and they do not have a dedicated paediatric infrastructure. They will be the tempted to find quick solutions. Hopefully this will just remain a temptation. We all know that human nature is immune to temptations. Another temptation will be academicians without proper background and experience who will nevertheless try to get research funds for paediatric projects. For an ethics committee, it is easier to reject a research project from a pharmaceutical company than from a fellow academic. We will over the next years and decades see a lot of movement.

Drug development in general is multidisciplinary. Paediatric drug development reflects as a microcosm the complexity of drug development, narrowed to the specific focus of children. The main disciplines that come in, apart from paediatricians, clinical pharmacologists, ethics, ethics committees and parents and patients, are the departments dedicated to the development of paediatric formulations; the departments that have to run the preclinical pharmacology, safety and toxicology in vitro and in vivo with animals; the clinical development departments, and the departments that are responsible for trial methodology.

This planet is not a perfect place. There is no planet’s government. There is war, and there is peace, there are regions with some order and other regions with a lot of corruption. Even in the richest countries children’s pharmaceutical and medical treatment was not as perfect as professionals thought long time it was. Diseases that were believed to be near extinction have re-emerged, there are new diseases and new health challenges, and a lot of more challenges. Different institutions address different dimensions. The WHO is focusing on frequent diseases in low income countries, predominantly tuberculosis, malaria and HIV/AIDS. There are other areas that are less visible to the general public. We have included one chapter on paediatric oncology in Europe, and a second one on paediatric oncology in Africa. For any child in Europe the diagnosis of leukemia was a death sentence 60 years ago. It is no longer today. But also a child in Africa has better survival chances today than decades ago. European and US paediatric oncologists support their African colleagues. Paediatricians from rich countries try to support their counterparts in less-rich countries. Where should funds be allocated? Who should allocate them? The development of new drugs for neglected diseases is today done more by private public partnerships than by the pharmaceutical industry. The funding often comes from philanthropic organizations such as the Gates or the Clinton foundation. It is almost impossible to keep an overview over the multitude of initiatives currently going on.

In this edition, we have tried to find suitable representatives of the various disciplines, voices and positions involved. Some key stakeholders are heavily involved in operational activities such as the regulatory authorities. Others have a more strategic role, e.g. the World Medical Association. The processes are complex and the different partners are sometimes on different sides. Although we have tried to keep the chapters to a high level, the final composition of this book’s faculty can by definition not be perfect. However, we have tried to elucidate the multitude of facets this movement has. The content of this book should give anybody with an interest in paediatric clinical trials and drug development sufficient material to see how complex the matter is and how many completely different disciplines have to work together. We simply tried our best. Many, many thanks to all the authors that have contributed. We hope that you will enjoy the reading.

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Klaus Rose
Dr. Klaus Rose was born in Heidelberg, Germany. He qualified in medicine in Berlin after initial studies in Romance languages and psychology leading to an MS in psychology. He completed his post-graduate clinical training in General Medicine in Germany and England before joining the pharmaceutical industry in 1991. Since then, he has held various positions in clinical development of progressively increasing responsibility culminating in 2002 in the position of Global Head Paediatrics, Novartis, Basel, Switzerland. In 2005, he joined Roche as Global Head Paediatrics and established a focus for excellence in paediatric drug development. Since 2010, he is Principal Consultant at Granzer Regulatory Consulting in Munich, Germany.

Dr. Rose is a frequent speaker on national and international conferences on paediatric drug development including academic conferences, the EFGCP (European Forum for Good Clinical Practice), the DIA (Drug Information Association), the ECPM (European Course of Pharmaceutical Medicines) and others. He was chairman of the IFPMA paediatric task force from 2008 to 2009 and is chairman of the EFGCP children’s medicines working party since its foundation in 2003.

He is married with two daughters. His private interests include Mediterranean-style cooking, good wine, gardening, Latin languages, and classical guitar.
Prof. Dr. John van den Anker was born in the Netherlands. He qualified in medicine in Rotterdam in 1983 and completed his post-graduate clinical training in General Paediatrics and Neonatal-Perinatal Medicine in 1991. In 1995, he successfully defended his PhD thesis in Clinical Pharmacology and in 1997 he became the Division Chief of Neonatology at Erasmus MC-Sophia Children's Hospital in Rotterdam. In 2001, he moved to the USA to direct one of the 13 NIH-funded Pediatric Pharmacology Research Units but stayed strongly connected with Erasmus MC-Sophia Children's Hospital. Currently, he is Vice Chair of Paediatrics for Experimental Therapeutics at Children's National Medical Center in Washington, D.C. and holds the Evan and Cindy Jones Chair in Paediatric Clinical Pharmacology. In addition, he is Professor of Paediatrics, Pharmacology and Physiology at the George Washington University.

Prof. Dr. van den Anker is currently 100% funded by the NIH for his clinical and translational research and is a frequently invited speaker on national and international conferences on paediatric clinical pharmacology. He was the President of the European Society for Developmental, Perinatal and Paediatric Pharmacology from 2006 to 2008 and a member of the Board of Directors of the American Society for Clinical Pharmacology and Therapeutics from 2005 to 2008. In 2008, he received the Distinguished Investigator Award from the American College of Clinical Pharmacology and is a member of the editorial board of the major clinical pharmacology journals. Finally, he has been a longstanding member of the Paediatric Working Party of the EMA representing the Netherlands.
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