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Improving pediatric drug development: challenges, opportunities and lessons learned

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A book review on
Addressing the barriers to pediatric drug development: workshop summary

by Cori Vanchieri, Adrienne Stith Butler and Andrea Knutsen.
Institute of Medicine., Forum on Drug Discovery, Development and Translation, National Academies Press, Washington, DC, USA, 2008

Pediatric drug development concepts and applications

by Andrew E. Mulberg, Steven A. Silber and John N. van den Anker.
Wiley-Blackwell., Hoboken, NJ, USA, 2009

Pediatric drug development has been challenging for more than 5 decades. Two recent books; one a workshop report and the other a volume prepared from the perspective of the pharmaceutical industry offer modest hope that clinical therapeutics within this vulnerable population is beginning to be addressed. Both unfortunately focus predominantly on pediatric drug development within the US, however, parallel activity within the World Health Organization (WHO) offers hope that pediatric drug development will improve in both developed and developing countries (see the WHO website for more information http://www.who.int/mediacentre/factsheets/fs341/en/index.html, accessed 25 August 2010).

The Institute of Medicine's (IOM) Forum on Drug Discovery, Development and Translation held a workshop in 2006 to explore issues in pediatric drug development. Topics addressed included; regulatory framework, challenges in developing and prescribing drugs, models for enhancing pediatric drug development and challenges and opportunities for the future. Several legislative activities have stimulated pediatric drug development in the United States beginning with the Food and Drug Administration Modernization Act, Best Pharmaceuticals for Children Act and Pediatric Research Equity Act. Despite the recent legislative, regulatory and research activity in the US and Europe, barriers to pediatric drug development are substantial, and the workshop identified many of them. See the following web sites for current information:

US NIH: http://bpca.nichd.nih.gov/

FDA: http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm

EMEA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea

DG Research: http://imi.europa.eu/index_en.html

Published after the IOM report is a volume with potential solutions to some of the challenges identified by the IOM Forum. While pediatric pharmacology began in earnest in the late 1960s, the struggle to place drug development for infants, children, and youth on the same footing as adult drug development remains far from satisfactory. The editors of *Pediatric Drug Development* have created a volume which reviews earlier work in pediatric pharmacology while providing a resource for learning about pediatric drug development from a pharmaceutical industry perspective. They summarize the history of pediatric drug development, explore ethical aspects, describe regulatory environments, and then consider the traditional steps in drug development: preclinical evaluation, clinical studies across the diverse ages and developmental stages. The two final sections focus on manufacturing and case studies.

PAST, PRESENT, AND FUTURE OF PEDIATRIC DRUG DEVELOPMENT

There is a substantial burden of childhood diseases for which there are no approved drugs, representing an opportunity for drug development. However, this burden of unmet healthcare is often at odds with the low priority of children for health care resources. The consequence of the low priority of children is that globally about 3/4ths of drugs do not carry regulatory approval for use in infants, children or youth; 2/3 of medications used in children in the US are used off label, in Europe about half and in Japan less than 20% of package inserts have sufficient information for treating infants, children, or youth.

ETHICAL UNDERPINNINGS

While US legislation encourages pediatric drug development, there are differences between NIH and FDA guidelines for excluding infants, children, and youth from clinical trials. The ethical complexity grows as the age of the child decreases, and unfortunately most clinical trials in neonates have insufficient numbers of subjects for adequate evaluation of the therapy under consideration.

Within pediatric clinical trials, the issues surrounding use of placebo and equipoise deserves special attention. Further challenges include the complexity of parental permission and parental understanding of the clinical study in which their child is participating. Globally, the issue of ethics becomes more challenging, however, this is

a critical component of drug development because most pediatric clinical trials occur in an international context, in multiple countries with many different ethics systems.

REGULATORY GUIDELINES FOR PEDIATRIC DRUG DEVELOPMENT: STIMULATION OF PEDIATRIC DRUG RESEARCH BY REGULATORY AUTHORITIES

While there are many similarities between US and EU regulatory guidelines, there remain important and critical differences. European legislation involves both country and EU specific guidelines. Within Japan the off-license or unlabeled use of drugs in children is as common as in the US and EU, however, there is no pediatric legislation, although there are efforts to develop such legislation.

PRECLINICAL SAFETY ASSESSMENT

Preclinical assessment, for both efficacy and safety, is a critical area as is clear from the missteps in assuming pediatric safety can be extrapolated from adult studies. Industry and regulatory bodies are currently working to define preclinical safety methodology, but much remains to be done.

PHARMACOLOGICAL PRINCIPLES IN PEDIATRIC DRUG DEVELOPMENT

One domain in which pediatric pharmacology has been successful, is alerting industry and regulatory bodies to developmental differences in absorption, distribution, metabolism, and elimination. This knowledge is well summarized in sections dealing with hepatic pharmacology, pharmacogenomics, and population pharmacokinetics and sparse sampling.

CLINICAL TRIAL OPERATIONS DIFFERENCES BETWEEN PEDIATRIC AND ADULT STUDY SUBJECTS – DEVELOPMENT ISSUES RELATED TO ORGAN DEVELOPMENT AND ENDPOINT CHOICES

The essential component of childhood is growth and development, understanding its stages and vulnerabilities is crucial for pediatric drug development. Among all organ systems, most attention has been given to the consequences of drugs on the developing central nervous system and brain. Of special interest is the broad period of vulnerability – beginning in utero and extending into late adolescence or early adulthood. This broad window of vulnerability makes it difficult to collect human data on safety and efficacy, implying the need for drug development and regulatory activity to rely on animal models, *in vitro* data and computational approaches.

Consideration of the cardiovascular system points out gaps in routine pediatric data; for example what are normal blood pressures and how should they be measured? Similarly, data collected by the pediatric ECG needs validation; lead placement and sampling frequency are important, automated ECG algorithms developed in adults may have little utility in children.

The kidney plays important roles in determining elimination and reabsorption of drugs as well as being a target for drug action. However, much remains to be done to understand developmental stage changes in glomerular filtration, tubular secretion, and reabsorption.

CLINICAL TRIAL OPERATIONS AND GOOD CLINICAL TRIALS

Emerging discussions on ethics in pediatric trials is the informed consent process for conduct of pediatric trials. Parents can provide informed permission, but are both parents required to provide informed permission? In addition to parental permission the assent of the child must be sought, dependent on age or developmental state of the child. Long term studies, necessary to fully understand efficacy and safety may require consent/assent/permission at multiple time points. Part and parcel with consent are the processes for recruitment and retention, with special attention to the potential for coercion, especially where families have limited health care resources.

CLINICAL EFFICACY AND SAFETY ENDPOINTS

Across the course of development the endpoints used to assess safety and efficacy can differ, as noted above in the discussion of the CNS, cardiovascular and renal systems. An additional constraint in pediatric studies are the volumes of blood or other media removed for these analyses. Use of innovative non-invasive approaches is encouraged, as are surrogate endpoints and patient reported outcomes.

FORMULATION, CHEMISTRY, AND MANUFACTURING CONTROLS

Pediatric friendly formulations remains a vexing issue for drug development. Interestingly the European pediatric drug legislation may offer a pathway to enhance pediatric formulations by providing 8 years of data protection and 10 years of marketing protection.

CASE STUDIES SUCCESSES FOR CHILDREN

The book ends with several case studies.

SUMMARY

Over the past 5 decades there have been advances in pediatric drug development; understanding of pk and pd have improved, attention to regulatory and ethical issues has advanced so that more pediatric trials have been conducted. Despite this progress much remains to do, and part of the path forward is outlined in these two books. Those interested in pediatric drug development from the perspective of the pharmaceutical industry should review both volumes as they will find them useful resources for teaching, research and all other relevant aspects of pediatric drug development.

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