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Better medicines for children – where are we now, and where do we want to be?

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Traditionally, drug development in children was performed where the targeted disease was frequent and where a high medical need was perceived. Examples are medicines against epilepsy or asthma, antibiotics, or vaccines. For most other drugs no systematic safety and efficacy data were generated in children, and their use in children was and is off-label. This gap is more pronounced in neonates and very young children [1].

Society has an interest that all drugs to be used in children are also properly tested. But the number of children is small in comparison with adults, and the child population is fragmented into age groups that often require separate investigations. Pharmaceutical companies live by the rules of the market, i.e. they assign limited resources to profitable products. As these rules per se are not sufficient to create a demand in paediatric research, there is a need for societal intervention. This has been addressed by paediatricians since the 1960s [2], but has reached government interest only in the 1990s in the USA and in the new millennium in Europe. Different models are imaginable: academic research, public funding of private research such as US paediatric exclusivity, philanthropic programmes, e.g. the Bill & Melinda Gates Foundation, governmental legislation, or combinations of the above.

All in all, there is a broadening agreement that children should benefit more from the considerable progress pharmaceutical development has achieved over the last decades. Furthermore, the weakening of traditional barriers, more vocalized patient interests and global communication through modern information technology contribute to a vision of further pushing the boundaries

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of medical research for the benefit of adults and children.

The debate concerning the consultation on a paediatric legislation draft published by the EU Commission in March 2004 [3] has contributed to more clarity about the timing of child research in general drug development. Undoubtedly, it would be an appealing vision to have paediatric use of new medications registered at the same time as adult registration. However, as pointed out in the ICH E 11 guideline [4] on drug development in children, a careful balance is required between the potential therapeutic benefit of a new drug in children, between the therapeutic alternatives available, and the risks of exposing children to a new chemical or biological entity. Modern drug development is a complex process that involves much more than clinical trials. Accelerated development in children would require toxicology studies to be started much earlier as well as an earlier development of paediatric formulations, usually a liquid. But most early projects are abandoned at a later development stage, mostly for safety issues, and the investments into toxicology and paediatric formulations are lost if the respective project is terminated. Accelerated development for paediatrics will therefore be an exception reserved for promising therapeutic breakthrough in life threatening diseases. The routine procedure will be a deferral, i.e. agreement between the health authority and the company, to perform paediatric development once more safety and efficacy data are available in adults. Where the targeted disease does not exist in children at all, a waiver will be granted.

The introduction of 'paediatric thinking' into the drug development process is a considerable investment for each company. Paediatric assessment of new compounds at several stages of development requires knowledge of the epidemiology of the targeted disease, of age dependence and outcome of the targeted disease, and of the mechanism of the disease in various paediatric age groups as opposed to adults. In later development stages pharmacodynamic endpoints in children need to be defined, extrinsic and intrinsic factors that influence PK in children need to be investigated, and data on absorption, distribution, metabolism and excretion need to be generated. A paediatric assessment of each new chemical/biological entity at early development stages has a profound impact on the general drug development process. Accelerated development for children needs to be assessed for every single compound, although the decision to do so will be rather the exception.

The US Pediatric Research Equity Act (PREA) [5] was signed December 2003 and asks for routine paediatric assessment at submission of the NDA application. The EU paediatric regulation published as a formal draft by the EU commission in September 2004 [6] will probably take some years until it comes to force. Large companies with a presence in the US market have to adhere to the US legislation today. They have to build up paediatric expertise by establishing their own paediatric departments, by establishing cross-functional expert groups, or by using external competence of paediatric consultancy. These core expert groups need to train the various development departments and subgroups within the relevant aspects of paediatric drug development, have to keep track of changing regulations, as well as keeping paediatric issues on the radar screen of senior management. Also, European companies will be advised to start with building up paediatric competence over the coming years.

It is the hope of the pharmaceutical industry that the EU Health Authorities will respect the commitments once these have been agreed upon between the FDA and the developing company, respectively, as soon as a European legislation is in force. It is a concern of pharmaceutical industry that the drug development process is burdened with a multitude of requests for development in children at premature stages. We need to bear in mind that it is always the developing company that bears the risk of drug development. The health authorities that request additional paediatric investigations do not carry the financial risk and do not directly pay for the additional costs they create by formulating these requests.

Modern drugs tend to be less and less soluble in liquids, but liquid paediatric formulations have been increasingly requested by the FDA in its Written Requests for Pediatric Exclusivity. There is little doubt that technical development will accelerate in this area. Modelling to extrapolate dosing from adults to older children, and from older to younger children, has developed over the last few years and will continue to develop even further. Virtual trial simulation is possible to a degree that was unimaginable few years ago. More research in neonates and preterm newborns will certainly be performed. Drug companies need to acquaint themselves with these modern technologies and methodologies, and use them as often as possible to prevent unnecessary exposure of children to multiple blood sampling and other invasive examinations. However, all modern methodologies would be useless if the health authorities should decide not to acknowledge the result and insist on the use of older, more established methods. Both sides, industry and regulatory authorities, need to stay up-to-date and need continuously to exchange information about new knowledge acquired.

In contrast to the incentives of the Pediatric Exclusiv-

ity, where the size of the adult market is known today and can at least be reasonably estimated for the lifetime of the patent until expiry, the worth of an incentive of 6 months patent extension at the end of patent life is almost impossible to estimate today. New chemical entities that will be registered in, for example, 2006 will lose their patent protection between 2016 and 2020, while the costs for additional investigations for children are generated before or only a few years after adult registration.

As health authorities are insisting on being involved in drug development for children, it cannot be emphasized enough that this is a development which assigns new roles to both sides: a shared responsibility in the development of better medicines for children. We think that these new roles should also be reflected in the composition of the Pediatric Board (PB) which is planned to be established in Europe. At present, only representatives from the European Health Authority EMEA and representatives from each member state are planned. As the paediatric drug development will be performed and planned by the pharmaceutical industry, industry should be invited to participate in the PB. Details should be taken up with the European representation of the research-based pharmaceutical industry, EFPIA [7].

While paediatricians are quite aware of the gaps in pharmaceutical treatment in children, this is probably much less true for the general population in Europe. Hopefully, a broad public debate will be initiated by the submission of the draft paediatric regulation to the European parliament. Several key stake holders have until now not participated in the public debate, for example, nurses' organizations, medical doctors responsible for school health, other professionals involved in child health care and, most importantly, parents' organizations.

The EFGCP, a European think tank, has established a Children's Medicines Working Party to promote this dialogue in Europe [8]. At present, Europeans are more used to being governed by the authorities than are, for example, US citizens. Here Europeans can learn from their American counterparts. It will probably take some time until we have powerful patient organizations in the new member states that will help to convince their respective national governments how important further research is for their children.

In the coming years we will observe more preclinical and clinical research in children in the USA and in Europe. A comparable debate has also started in Japan. In order to be a main player in this development, Europe needs a solid regulatory framework for paediatric drug development, a strong academic infrastructure for clinical research, and a strong pharmaceutical industry. An open and trustful dialogue between the key stakeholders for paediatric health care needs to be established and maintained for the good of our children.

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References

1 Choonara I, Nunn AJ, Kearns G, eds. Introduction to Paediatric and Perinatal Drug Therapy. Nottingham: Nottingham University Press 2003, ISBN 1897676379.

2 Choonara I, Mclntyre J, Conroy S. Paediatric Medicines: Global Development and Clinical Investigations. University of Nottingham, Derbyshire Children's Hospital, PJB Publications Ltd 2000.

3 http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/mar/Paediatric%20consultation%20document%20final%208%20March%2004.pdf.

4 http://www.ich.org/MediaServer.jser?@_ID=487&@_MODE=GLB.

5 http://www.fda.gov/cder/pediatric/index.htm.

6 http://pharmacos.eudra.org/F2/Paediatrics/does/Paeds%20reg%20adopted%2029%20September%202004%20English.pdf.

7 http://www.efpia.org.

8 http://www.efgcp.org.