

Regulatory Aspects of Clinical Trials in Children

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Introduction

The paediatric population represents a spectrum of different physiologies reflecting the enormous dynamic of the development from birth to adolescence. In addition different diseases occur in the growing and maturing paediatric subgroups, which are not present in adults and therefore medicine therapy in children should be based on these specific pharmacological principles. The enormous dynamic starting with their foetal and embryonic phase throughout the birth and infancy up to their puberty and adolescence is the reason why children are very vulnerable for adverse drug reactions. Hence, safety monitoring of medicine used in children is of paramount importance and therefore, children should not be treated as “little adults”.

Up to date systematic drug development and therefore conducting clinical trials in the paediatric population were rarely performed. Consequently, children are regularly treated with medicines, which were not licensed for this age population.

Once a medicine becomes available on the market for adults, it is possible to use it in children in an off-label way as present and may be even recommended according to paediatric treatment guidance. Thus, use of un-licensed and off-label medicines for children has been a common practice for decades, which does not offer the same quality, safety and efficacy of medicines as for adults.

The lack of this information has often been responsible for a number of complications and difficulties in the paediatric population and has just been related to missing the right dose and appropriate formulation and the assessment of medicine safety in the paediatric population is regularly based on limited evidence.

Since the implementation of the EU Paediatric Regulation in January 2007, the approach for the clinical development of medicines for children has changed significantly. Further legal basis for clinical drug development has been written down for example in the GCP-Directive and EU regulation (e.g. Regulation (EC) No 726/2004, Regulation (EC) No 141/2000).

Target population

During development and organ maturation the child experiences an enormous change in many parameters, which are expected to be stable in the adult population. These parameters include important pharmacological aspects and preconditions of oral absorption, medicine distribution, medicine metabolism and medicine elimination.

These aspects need to be reflected according to the different age subpopulation to address the different pharmacological and pathophysiological specialities of the paediatric population. The internationally agreed and to some extent arbitrary classification of the paediatric population is as follows:

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16–18 years, depending on the region)

During the neonatal period the children have greatly reduced gastric acid secretion and relative achlorhydria and also show prolonged gastric emptying, which will influence the bioavailability of applied medicines dramatically. In this respect, the administration of medicines with meals needs to be tailored. In addition, medicines with a high hepatic clearance and first-pass metabolism like propranolol have a variable absorption in children

Furthermore, the much higher extracellular fluid volume, especially in premature babies as compared to full-term infants, older infants or adults is of importance for the comparison of pharmacokinetic of the drugs. On the other hand, fat content is the lowest in premature babies, higher in neonates and still higher in infants. This has to be considered when applying doses on a mg/kg body weight basis to achieve plasma concentrations similar to those of adults. Therefore, an initial loading dose may need to be included in the treatment. The dosage interval may need to be increased and the total dose decreased based on hepatic and renal function. Medicines that are cleared by the liver lead to a longer plasma half-life and thus to a longer time to reach steady state. Similarly, for medicines that are entirely eliminated through the kidney, the greater the prematurity, the less able are the kidneys to excrete and therefore the longer is the half-life. These aspects are not only important for the monitoring of the safety aspect, but need to be considered when conducting clinical trials in the paediatric population.

Clinical trial design

Medicines of major clinical importance, even essential medicines, are not readily tested in and labelled for children, especially not in the very young child. However, children have therapeutic needs, which probably cannot be met if medicines representing major therapeutic advances in adults are not tested and labelled for paediatric use. Conduct, analysis, and interpretation of clinical trials within the paediatric population may at times be constrained by the prevalence and varying degrees of the disease (e.g. neurometabolic disease). In particular, if there is little knowledge about validity of laboratory parameters and the value of diagnostic and clinical endpoints to be included in the trial design.

As established for the clinical investigations in adults, the implementation of paediatric clinical trials need to consider the inclusion of pharmacodynamic, pharmacokinetic and efficacy studies. Safety studies in the target population are requested. Such studies may be performed using different methodological approaches, which are dependent on the type of safety parameters and practical, clinical and economical circumstances. However, a major challenge in paediatric trial design is the definition of the core set of outcome measures and to develop a validated definition of improvement or for the evaluation of response to the concerned therapy.

Clinical trials enrolling several hundred patients may not be practical or possible. With regard to investigating the safety issues of the product it does mean that for most trials even common adverse reactions may not be detectable. Sample sizes in phase I and II trials are usually low and even in phase III trials sample size are nearly always based on endpoints for efficacy. That means that the sample size limits the ability to observe anything less than common reactions.

The initiation of efficacy trials in the paediatric population may be triggered by data evaluated in the drug development of adult subjects. These data and the available pharmacological evidence for the drug should be reviewed concerning its usefulness for the extrapolation into the paediatric population. For the majority of drug developments, this extrapolation may be possible at least for some paediatric subpopulation. In contrast the extrapolation of the safety data maybe, in general, very difficult as the growing and maturing organism of the children may react very different. In particular, if there is a latent period before onset or a trigger such as a change in growth, maturation or development.

Risk and benefit in the paediatric population

Paediatric pharmacovigilance assessment may be rather limited before authorization as there are often relative deficiencies in pre-authorization clinical trials of medicines for paediatric use.

The benefit-risk assessment of any kind of medicine treatment is essential. No assessment of the treatment is, however, possible without safety data and knowledge. The “trial and error” principle is not acceptable in an extremely vulnerable population. In the case of life-long treatment for chronic diseases, the total dura-

tion of treatment is longer, if started in childhood. This may expose the patient to increased risk of medicine toxicity and adverse events.

Serious adverse events are often rare and are generally not observed in the paediatric clinical trial programme, particularly if there is a lag period before onset or a trigger such as changes in growth and development. ADRs in children cannot be predicted on the basis of those observed in adults.

Given these limitations every opportunity should be taken to increase the information from ADR monitoring and to organize and communicate this information to the medical community and the public. Several methods have been used to encourage and facilitate reporting by health professionals in specific situations, like in-hospital settings or for new products or for limited time periods.

Such methods include on-line reporting of adverse events and systematic enhanced reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, the limitations of passive surveillance, especially selective reporting are well known.

Spontaneously reported ADRs remain one of the most important sources of detecting safety signals or issues in the post-authorization period. However, spontaneous ADR reporting is expected to be of only limited value in paediatric medicine safety monitoring, unless the notorious underreporting among the health professionals including the paediatrician can be overcome.

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program.

In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. In any case the elaborating surrogate parameters and indicator symptoms for adverse reactions are useful to establish case definitions for adverse reactions in children.

Defining the frequency of adverse drug reactions or the incidence associated with disease in relation with the drug, studies are needed apart from randomized controlled trials. Randomized controlled trials may be preferred from a methodological point, but are not always useful and practical in paediatrics and rare disease.

To establish a causal association of treatment and adverse drug reaction cohort, case-control studies may be considered and have been established in post-marketing safety studies.

Epidemiological studies using patient databases have been helpful for collecting information regarding the natural incidence of a specific event in the general population and may be useful for increasing the knowledge of the safety database.

Summary and Conclusion

Since introduction of the EU Paediatric Regulation in January 2007 the development and the life cycle of a drug in pre- and post-authorisation period has changed significantly. Pharmacovigilance science has traditionally been a discipline focussed on the post-marketing or post-authorisation period, with due attention directed towards pre-clinical safety data, clinical trials and adverse events.

As the biological sciences have evolved, pharmacovigilance has slowly shifted toward earlier, proactive consideration of risks and potential benefits of drugs in the pre- and post-approval stages of drug development, leading to a maturing of drug safety risk management.

The development of drugs for the paediatric population has changed the awareness that not only the safety issues need to be thoroughly investigated for a safe treatment of the children. In conjunction with the knowledge about efficacy, pharmacokinetic/pharmacodynamic and the age appropriate formulation for the concerned drug, the impact on the aim to apply safe medicines for children will steadily increase.

Therefore, a proposal for a joint effort performing clinical research and appropriate drug development and clinical trials in children needs a strong support from a number of stakeholders like Clinical Trial Network, Paediatric Society, pharmaceutical industry and authorities.

Discussion

Kleine-Tebbe: There are certain requirements from the EMEA through the working group for pediatric studies, which might also affect former studies that had been performed in adults. Could you briefly comment on that because the planning of a study, if it is done in children, also involves appropriate planning in adults? And could you also provide an internet address where you could gain some information on these subjects?

Mentzer: First of all to the internet address, EMEA has on their homepage a link that is on the right side, called “Medicines for Children” and under this link you will probably find most of the information you just asked for. With regard to the development of drugs in adults and then coming to the children, it is true that, e.g., in the PIP, all adult studies have to be included and the developments have to be mentioned. And this is not to control the development, it is more or less to control whether we are able to extrapolate from those data to the children. That is, whether we can avoid further trials in children with these data or whether we can highlight a lack of information which we do need for children. So this is of course important, especially for the understanding from a non-clinical point of view, i.e. pharmacology as well as toxicology, whether this is relevant for children or not. Of course, the adult development will have a major impact on this clinical trial in children or the request for clinical trials in children.

van Ree: To what extent do you have to do your clinical trials in the two separate groups, in adults and children, or can you pool? I mean, just as an example, if we plan a clinical trial from the age of 12 up to 45 years, can you then base your power calculation on the total group? Can you then translate that into an efficacy for children of that age and for adults, or how should I see that?

Mentzer: As far as I can see from the last years' trials, especially if you look post-pivotal, if you include the adolescent subgroup you will be able to extrapolate from mode of action and efficacy to the needs of children and you will get the indication. Maybe in some of the indications you will need specific data on safety that will be dependent on the pharmacological effects of the drug. So, to my recollection, the adolescent group is one where most likely an extrapolation is possible. There will be a request, e.g. if you have a trial with 400 subjects, that maybe 20% of the subgroup have to be included. That may be a request in the pediatric investigation plan that a certain minimum number of that subgroup will be included. But otherwise we often do the extrapolation to avoid further clinical trials in a special setting.

Sager: Some of us here in the room are in the situation that we already have long-lasting experience with our products on the market and we are right now on the way to go with them through marketing authorization processes. To what extent do you expect comparative trials and what is the ideal comparator in the situation where placebo might not be the ideal candidate with respect to ethical considerations and things like that, because you have already accumulated experience with the drug you are investigating right now?

Mentzer: With the so-called "drug of well-established use", which you may refer to, it is accepted to get an authorization with those well-established use data without doing additional trials. Those drugs where you can provide well-established use are exempted from providing a pediatric investigation plan. For this well-established use it is defined what you need. It is not, e.g., a company-initiated trial and results of that have not been published "well-established use" before. It needs to include some references as a peer-reviewed paper and it needs to have some basic evidence with relevance to pediatric health has to be provided. If you are not falling into that group and you have to do clinical trials with your drug, the question for a comparator is very difficult in children. In theory, it is seldom accepted to use a placebo-controlled trial in children. There are countries which do accept that. In Germany, we have some regulations where we can exclude those trials. Placebo can be standard treatment, e.g., so you can do sort of a treatment on top of your standard treatment within your trial. In general, to look for a comparator is very difficult. On the one hand, mainly because the comparators may also not be authorized as a treatment, so you have a problem to use it in your trial. On the other hand, if there is no controlled information about the efficacy of the comparator, you have to look into each case by itself whether there is an appropriate comparator or not. At the moment, e.g., we have the problem that a huge number of monoclonal antibodies are coming in the field of juvenile idiopathic arthritis and we currently only have maybe two drugs authorized to treat that. Now the question is whether in the future we take one of these drugs as the gold standard for treatment in children and whether this will be

the standard comparator. Or do we have to go on and look at these trials in comparison to the standard treatment, which is methotrexate and I am sure that there are no evidence-based data on that drug, but it is a standard treatment as far as I know. So it is a very difficult discussion whether you have to go for a direct comparator where you have to look at non-inferiority or whether you go for a placebo control. It needs to be a case-by-case assessment what is appropriate.