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Clinical Research in Children – A Pharmaceutical Industry View

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Abstract

From the point of view of a pharmaceutical company, developing a product for use in children presents both opportunities and problems. Such a development may lead to new market use and extension of patent life in the USA. However, there are obstacles and these include not just the obvious ones of new clinical trials, but also other more complex ones such as the development of new formulations. Thus, while there will be an expansion of clinical development programmes in children, the enthusiasm for them needs to be tempered with some reality as to the complexities involved.

Key words: Children – Medicines – Trials

Introduction

While some pharmaceutical products, such as antibiotics and drugs for epilepsy, have traditionally been developed for use in children, in general there has been reluctance by pharmaceutical companies to explore paediatric use. The reasons for this are complex, but include the difficulties of recruitment, uncertainty about clinical measurements, concerns about liability and relative size of the market. There have also been concerns about clinical trials in children shown by some ethics committees.

This has presented the practising paediatrician with a dearth of products with approved uses in children from which to prescribe. In a recent paper[1] it was found that 46% of medicines prescribed for children in hospitals in a number of European countries were either not licensed for use in children or were being used off label.

This situation is changing rapidly with greater public awareness of the problem, prompting the US government, through the FDA Modernization Act[2], to introduce incentives for companies to include paediatric studies in their development programmes. In addition, the International Conference on the Harmonization of Medicinal Products for Human Use (ICH)[3] is developing a guideline, which will have global application. Also, the initiation of an Orphan Drug Directive within the European Union will have some benefits for paediatric development[4].

This paper describes some of the issues, both beneficial and problematic, that face pharmaceutical companies when they determine whether or not to carry out a paediatric development programme. It is important to recognise that this involves more than just doing some clinical trials, which may be the easiest part of the programme.

Why do Companies Develop Products for use in Children?

The most obvious reason why a company should undertake such a development is that there is a market for the product in that population and that market is unsatisfied and will accept the new product.

There are some clear markets where the needs of children are well established. These include anti-infectives, epilepsy, asthma, diabetes and growth hormone deficiency. Companies will usually start clinical trials in appropriate age groups after they have acquired a 'reasonable' amount of data in the adult population. The problem is in defining what is 'reasonable'. Most companies would not start enrolling children into studies before at least 500 adults have been exposed to the product, without the appearance of serious adverse events. There are a few conditions that occur only in children,

and so studies in the target population would start much earlier, even in the absence of exposure in adults, except for normal volunteer studies.

Other conditions where there is a clear need for medicines in children are cancer, anaesthesia and various dermatological problems. A review of the ABPI Data Sheet Compendium[5] shows that there is great variability in the amount of data that is available for the use of products in these children, with clear recommendations on dose in different age groups for some and a complete dearth of information on others.

With the enactment of the FDA Modernization Act, there is an added incentive for companies to carry out a paediatric clinical development programme. If the FDA issues a written request for the company to carry out such a programme and the company complies with that request, an extra six months of patent life will be added to the product[3]. This extension is for the product, not just the added indication for use in children. This requirement can be for products that are already on the market or those still in development. The European regulatory authorities have offered no such incentive; they have taken the stick, rather than the carrot, approach and have stated that they require to see paediatric data, where appropriate.

Disincentives to Developing Products in the Paediatric Population

There are a number of reasons why a company may not develop a new medicine in children or why it may try to extend the use of a current one into this population. These reasons may be either financial or due to practical difficulties.

The business reasons are those of balancing investment versus reward. If the market is very small, the investment needed far exceeds the extra potential revenues. This was one of the factors that persuaded the US Congress to allow the extension to the patent life for those who complied with requests to provide paediatric data. Examples of such markets are hypertension, cardiac failure, peptic ulcer and various psychiatric disorders.

The costs involved in a development programme are not simply those of the clinical trials. They include:

- Formulation development
- Stability testing
- Preclinical safety testing (toxicology)
- Clinical trial programme
- Manufacturing
- Regulatory
- Long-term follow-up

Formulation Development

Unless the product is normally given by injection, it is unlikely that the formulation that has been developed for adult use will be suitable for children, at least those in the lower age groups. Thus, at least one, and possibly several, new formulations and concentrations will need to be developed. The reason for a number of formulations is that children do not comprise a homogeneous population. The ICH guidelines have divided the population into five categories (Table 1).

Table 1. Age classification of paediatric patients

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

Thus it can be seen that it may be necessary to have drops for the youngest age group, syrups or suspensions for the next, and it is only when one gets to the older age group that it will be possible to give the adult product.

Practical problems involved in developing a formulation include the chemical form, whether it lends itself to the required formulation, the solubility of the bulk chemical, the taste, the restrictions on the use of various colours, the use of additives such as sugar, and the problem of storage of bulky bottles rather than small blister-packed tablets.

Stability Testing

All product formulations that are to be tested in clinical trials need to be tested for their stability over a range of conditions that include exposure to different temperatures, degrees of humidity and intensity of light. Before studies can start these tests need to last for three months. However, before a company can make an application for a product to go onto the market, the stability programme is much more extensive. It normally requires that three batches of each formulation and strength be tested for one year. It may be possible to 'bracket' some of the studies, and if there are three strengths of one formulation, it may be possible to study only one batch of the middle strength. But even with this possibility, this is a major and expensive undertaking.

Preclinical Safety Testing (Toxicology)

One of the burdens being placed on companies who wish to start a paediatric development programme is

the requirement that is being set down by the FDA and alluded to in the proposed ICH guideline – the need for neonatal/juvenile animal toxicology studies. These seem to be a fairly routine requirement in the USA and, while the proposed ICH guideline only talks in terms of 'The need for juvenile animal studies should be considered on a case by case basis, and based on developmental toxicology concerns', such language will inevitably be interpreted as meaning a general requirement. There are a small number of toxicology laboratories capable of performing such studies. They tend to be expensive – upwards of $500 000 per study. There is no suggestion that by undertaking such studies there might be a compensatory reduction in the need for standard adult animal toxicology studies, and so this seems to be an added burden, both in terms of costs and animals sacrificed at a time when there is a general desire to reduce the numbers of animal used in experiments.

Clinical Trial Programme

In principle, undertaking clinical trials of an appropriate design should be no more difficult than undertaking studies in adults. There are a number of practical and procedural issues that need to be addressed, as well as the usual ones of designing a good protocol and case report form. However, these are not an excuse for not doing high quality research in children, as children are entitled to have medicines made available to them based on good evidence of efficacy and safety, as are adults. Also, although undertaking the studies may be difficult, the number of studies required will be lower than for the initial adult indications.

It must also be born in mind that the term *children* covers the five populations already described, and it should be the plan to study all five unless there are clear reasons not to. Indeed, for some products it will be more important to get data on the very young children than the older groups, as certain conditions may be relatively more common in the early postnatal period than in later years.

Some of the practical problems that need to be considered are:

- Population available – how easy will it be to get the numbers required by the protocol?[6]
- Investigators – are there a number of suitable investigators available? Do they have enough experience in GCP quality studies? Do they have the time, motivation and resources to carry out the protocol?
- Ethics committees – are they used to reviewing protocols involving children, or are they so naïve in this area that they will regard any study in children as unethical? Would they even consider the possibility of placebo, or would they reject any such suggestion, no matter how irrational such a decision was? How will they feel about extra invasive procedures, such as taking extra blood for blood-concentration levels?
- Consent – parents are possibly apprehensive if they hear the word *research* mentioned. Naturally they want the best available treatment for their children when they are ill[7]. Where the child is able to, their assent should be sought in addition to the parents' consent. Consent will often be more difficult if the trial includes a placebo arm and also needs the taking of blood samples that would not be needed for investigational or treatment purposes.

Manufacturing

The ideal product from a manufacturing point of view is a single strength, a single formulation and a single pack size. This allows for maximum manufacturing efficiency. Medicines for children are often the opposite of this ideal scenario. Different age groups may need different formulations, strengths and presentations. Thus, for the very young a drops presentation might be needed, and for children a suspension, while adolescents may be able to cope with the adult presentation. In addition to presentation, various concentrations may be needed if there is a wide dose-response curve, or slightly different indications require different amounts of drug, e.g. different infections requiring different doses, depending on severity. Liquid formulations tend to need bulkier packaging and, therefore, storage space. These factors add to the manufacturing and warehouse costs, driving up the end price of the product.

Regulatory

Putting together a regulatory submission is not simply a question of sending the clinical trial data to the appropriate authorities. It involves all the data associated with the application. If the product is already on the market for adults, then cross-reference can be made to the original when applying for a paediatric indication. Nonetheless, there will be a lot of data that needs to be assembled, in the prescribed format and including expert opinions, before an application can be made. The costs of this exercise can be significant and may be too much for a small company, who will probably have to subcontract the work, and for whom the potential sales are going to be minimal.

Long-term Follow-up

This is also, perhaps, the prospect that worries pharmaceutical companies the most. The FDA has started to talk about the possibility of following up children who have received specific medications for an, as yet undefined, length of time. Whether this means until adulthood and will only apply to medications that might present a higher than usual risk, is not clear. It also seems odd that this should be required for products that have been subject to formal clinical evaluation and regulatory scrutiny, and would not apply to those used in an *ad hoc* uncontrolled way. The argument for such a requirement may be quite reasonable for products used to treat cancers, severe immunologically based diseases and diseases where new technologies are being introduced, such as gene therapy. It is probable that their physicians would follow up these patients anyway and any specific requirements to follow the possible delayed adverse events associated with a new drug could be built into that programme. However, to require the same commitment for a new antibiotic of a known chemical class that is being used in community-based infections, seems to be an unnecessary burden that would deter any company from developing such a product.

Conclusion

It can be seen from the foregoing that there are a number of reasons why a company might wish to develop a pharmaceutical product for use in children. The recent incentives introduced in the United States will ensure that more companies will undertake such programmes. However, some of the new requirements that are being suggested may well counterbalance the incentives and result in no change from the traditional picture where the therapeutic needs of children are not catered for.

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