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Working with the pharmaceutical industry in relation to paediatric clinical trials. A British perspective

Odile Dewit[1], Richard Tiner[2]

[1]*GlaxoSmithKline (GSK) Research and Development, Cambridge, UK*

[2]*Association of the British Pharmaceutical Industry (ABPI), London, UK*

Corresponding author

Dr O Dewit, GlaxoSmithKline (GSK) Research and Development, Clinical Pharmacology and Discovery Medicine, Clinical Unit, Cambridge CB2 2GG, UK. Email: Odile.E.Dewit@gsk.com

The implementation of the new European Paediatric Regulation, with effect from January 2007, is discussed. To provide timely compliance with regulatory requirements, the pharmaceutical industry has to consider, early in the drug development, the relevant paediatric disease, the appropriate risk/benefit assessment of engaging in paediatric therapeutic clinical trials, and the paediatric formulation. There will be an increased need to perform clinical trials in paediatric patients under regulatory standards. In the UK, infrastructure has been developed and strengthened to support the delivery of clinical and industry-sponsored research, and two examples are cited: the Medicines for Children Research Network, and the recognition of paediatric clinical pharmacology as a sub-specialty of paediatrics by the Royal College of Paediatrics and Child Health. Practical difficulties and challenges in performing drug development in paediatrics can be foreseen but the current situation is favourable to collaborative work between the pharmaceutical industry, clinical and academic investigators and scientists for the benefit of paediatric health.

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A climate for partnership for better medicines for children

A major milestone for paediatrics was reached in January 2007 in the European Union (EU) when "the Paediatric Regulation" was introduced[1,2]. The EU Paediatric Regulation governs the development and the authorisation of medicines for use in children aged 0 to 17 years. It applies to new medicinal products, existing ones still covered by a patent or supplementary protection certificate (SPC) and established ones where the patent or the SPC has expired.

The driver for the EU Paediatric Regulation was the paucity of drugs that have a licence for use in paediatrics. When there is a medical need to do so, paediatricians may prescribe, under their responsibility, medicines that are not licensed for use in paediatrics (i.e. prescription of unlicensed medicines), or medicines that are licensed but not for all age groups, for all doses or for all formulations (i.e. prescription off-label). Such prescriptions are part of daily standard clinical practice in paediatrics in Europe and elsewhere, and are reported in the literature[3-7]. They are supported by peer usage [British National Formulary for Children[8]; Medicines for Children[9]] and by some limited information from paediatric clinical trials. It was time for this situation to be addressed in the EU.

The EU Paediatric Regulation aims, therefore, to increase the availability of licensed medicines for children in the EU by increasing ethical research in children, to be conducted according to the principles of Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH)[10], and without subjecting children to unnecessary trials.

It also aims to stimulate the delivery of more appropriate paediatric formulations and better information on the safety profile, pharmacokinetics, pharmacodynamics and efficacy of medicines for children. This will contribute to decreasing the risks of adverse drug reactions or lack of efficacy, and to increasing access of paediatric patients to innovative medicines.

Where do paediatric clinical trials fit in drug development?

Depending on the indication and the type of investigational medicinal product, clinical trials in paediatric patients will frequently take place once initial safety, pharmacodynamic and/or efficacy data are available in adults. As soon as the decision is made to develop a drug for a disease in adults that may have applicability in paediatrics, the drug development team should outline their strategy for paediatrics.

The first three key questions are listed below.

- Does the disease affect children?
- Is the disease progression similar in children to that in adults?
- Is the outcome of therapy likely to be similar to that in the adult form of the disease?

When all these three conditions are met, pharmacokinetic data in children, combined with appropriate safety data in children, may be sufficient to support applications for paediatric labelling, without having to perform extensive efficacy clinical trials. If the relationship between concentration and response is anticipated to be different in children compared to adults then clinical trials of efficacy may be required.

Whenever possible, it is recommended to use a "bridging" development strategy, i.e. to plan to make the maximum use of extrapolation to children of the available adult efficacy data. Such an approach may be acceptable if there is similarity between adults and children in the indication, in the mechanism or course of the disease, and in the outcome of therapy (both beneficial and adverse). This thought process has been illustrated by Dr Dianne Murphy of the Office of Pediatric Therapeutics, Food and Drug Administration (FDA), as a Pediatric Decision Tree[11].

To plan their paediatric strategy, the drug development team should refer to the ICH guideline E11[12]. It indicates the type and timing of studies in paediatric patients depending on the medicinal product, the type of disease being treated, safety considerations and the efficacy and safety of alternative treatments. To provide timely compliance with regulatory requirements, the pharmaceutical industry will have to consider early in the drug's development what is the relevant paediatric disease, the appropriate risk/benefit assessment of engaging in paediatric therapeutic clinical trials, and the paediatric formulation.

In their planning, the paediatric drug development team should allow sufficient time to understand the disease in children (in comparison to adults) by talking with expert clinicians, academic researchers and patients. These discussions should include the biomarkers of the disease; if they are not readily available for a paediatric application, time should be given to investigate or develop them. Plenty of time should be allowed too for developing the paediatric formulation, considering all appropriate paediatric age ranges, and this should be started as soon as is reasonable.

The development strategy must encompass the preclinical aspects of drug development (preclinical safety assessment, preclinical drug metabolism and pharmacokinetics) for potential paediatric use. The standard process of drug development is to use rodent and non-rodent species to support the progression of clinical trials. These studies are designed to identify target organ toxicity and to provide appropriate margins of safety between therapeutic exposures and those that produce adversity in non-clinical studies. Although not a perfect representation of man, it is accepted that these animal models provide a robust platform for drug development. Juvenile animal studies are an extension to this paradigm in providing a comparison between adult and immature forms of the animal species. A continuing improvement in the understanding of organ development has significantly assisted decision making and risk assessment where age-related responses exist.

Finally, ample time must be allowed for planning and performing the paediatric clinical trials, as these may take longer than experience in adult trials would suggest. Advice on the design and conduct of trials necessary to demonstrate the quality, safety and efficacy of the medicine in the paediatric population can be given by the European Medicines Agency (EMEA), free of

charge, upon request prior to the submission of a paediatric investigation plan or at a later stage.

Preparing the infrastructure for paediatric clinical trials in the UK

In the UK over the last few years, a spirit of cooperation has clearly developed between academic researchers and health care professionals, the pharmaceutical industry, the political powers, and the public. They have worked together to support the development of the EU Paediatric Regulation, and of key infrastructure for clinical research in paediatric therapeutics. This has resulted in numerous significant and practical advances[13], of which the recognition of paediatric clinical pharmacology as a subspecialty of paediatrics in the UK by the Royal College of Paediatrics and Child Health in 2004 and the Specialist Training Authority is one[14]. The curriculum includes training on ethical and regulatory standards for clinical therapeutic trials, and offers the possibility for the trainees to do part of their training in the pharmaceutical industry. The Association of the British Pharmaceutical Industry (ABPI) is currently involved in partially funding two doctors in training posts (one in London, one in Aberdeen).

With the EU Paediatric Regulation, which is binding on the pharmaceutical industry, there will be an increased demand to recruit children in therapeutic clinical trials, including trials with new investigational medicinal products, to be performed under regulatory standards. It will probably be difficult to do the clinical trials in single centres because there are not enough children with the disease in single centres. In England, this has been addressed by the Department of Health who established the Medicines for Children Research Network (MCRN)[15] in 2005 as part of the UK Clinical Research Network. The objectives comprise developing and strengthening NHS infrastructure to support the delivery of clinical research, including industry-sponsored clinical trials. The pharmaceutical industry is actively involved in the process (e.g. ABPI representative on the MCRN Board; industry secondment to the collaborating centre). The MCRN is still building its capacity in order to include expertise all around the UK.

In the UK, the National Health Service (NHS) general and specialist paediatricians and nursing teams will be conducting clinical trials and as such will have to gain an understanding and training in the tight regulatory imperatives of GCP clinical trials. In addition, staff in hospital pharmacy may have to gain training in Good Manufacturing Practice (GMP) (ICH guideline Q7)[16] for some activities related to the clinical trials with investigational medicinal products.

Opportunities for collaborative work and areas of challenge

The increase in paediatric study activity following the EU Paediatric Regulation is likely to fuel innovation. The pharmaceutical industry has a good track record of collaboration in basic research and in clinical programmes worldwide doing high quality science. Going further in partnership between the pharmaceutical industry and the academic and clinical communities to translate science into medicines is key to the creation of new medicines. The Department of Health recognises this and wants the UK to become a leading country for conducting clinical research in partnership with and for industry[17]. The best alliances between academia and industry will be those with agreed goals and tangible benefit to paediatric drug development. The industry may sponsor projects across all phases of research and development.

Support from the pharmaceutical industry can take many forms, for example a grant for a strategic project, or a grant for equipment, or a grant for a temporary industry placement during science or medicine studies, or sponsored research studentships (e.g. towards a master degree, PhD or MD). Industry placement may also take place during medical training. A joint initiative of the Department of Health (Academic Subcommittee of the Modernising Medical Careers) and the ABPI is planning to establish an attachment in the pharmaceutical industry for some Foundation Year 2 junior doctors. This will provide newly-qualified doctors with an appreciation of clinical research, GCP and GMP, an appreciation of the challenges and complexities of drug discovery and development, and an insight into the rigour and governance of clinical research in the pharmaceutical industry. Such training experiences will contribute to establish the skills set of the future clinical and academic paediatric investigators.

For paediatric medicines, opportunities for collaborative research lie in the areas of basic sciences, pharmacy and clinical trials. The new EU Paediatric Regulation applies to all therapeutic areas, so all are concerned. Temporarily, the needs for research and development of medicinal products for children may be identified by the lists established in 2006 by the Paediatric Working Party of the Committee for Medicinal Products for Human Use (CHMP)[18]. In accordance with the Paediatric Regulation, the Paediatric Committee will establish an inventory of the needs for medicines intended for children and publish it

after 26 January 2009. For example, research is required in the following areas:

- basic science of paediatric diseases
- molecular targets of diseases or pathways
- biomarkers
- developmental pharmacology and its importance for drug absorption, distribution, metabolism and excretion
- drug action (pharmacodynamics)
- drug discovery
- pharmacogenetics/genomics
- pharmacokinetics, pharmacodynamics and modelling

In pharmacy, innovation and research is required to develop better paediatric formulations and to reduce dosage errors. Research in clinical trials is required in several areas:

- endpoint measurement techniques in children
- epidemiology of paediatric diseases
- ethics guidelines on consent/assent
- patients' views
- pharmacovigilance, safety and therapeutic index
- sensitive laboratory micro-assays to detect drugs in small fluid volumes
- strategy for the regulatory Paediatric Investigation Plans
- study designs that optimise recruitment and compliance

Although the pharmaceutical industry is supportive of the objectives of the EU Paediatric Regulation, difficulties in delivering timely information on new medicines for children can be foreseen. Studies in children pose multiple, unique practical and ethical challenges. For example, pharmaceutical industry and investigators will have the challenge to write age-appropriate information sheets for clinical trials with new chemical entities, and to devise a process for consent and assent that is also age appropriate: what language to use, how to make such sheets informative and not patronising. "One-size-fits-all" will not apply for paediatric studies. Industry and investigators will also have the challenge to devise study designs with study visits and investigations that suit children and family life.

The EU Paediatric Regulation aims to deliver medicines to children without subjecting children to unnecessary trials. This may create challenges in the areas of new medicines with precedented mechanism of action. The Regulation also aims to avoid delays in the authorisation of medicines for use in adults. This may be difficult as paediatric therapeutic trials often take longer to perform than adult trials.

With the implementation of the EU Clinical Trial Directive[19,20] and of the EU Paediatric Regulation, the demand for GCP-trained paediatric investigators and research teams will be considerable. GCP requires the investigators to be familiar with the investigational products. Juvenile animal data would be included in the Investigator Brochure which is the standard means of providing investigators with the preclinical background of the investigational products. Protocols would contain summarised information in the usual way. Currently, initiatives are on-going to reduce the start-up timelines for clinical trials to support the efficiency of clinical research services and to keep the UK competitive with other countries. For example, an integrated application system for regulatory and governance approvals is in development by the UK Health Departments and organisations[21,22]. This will produce benefits for academia and industry in speeding up trial initiation.

The demand for child participants in clinical therapeutic trials of new or old medicines will increase. The pharmaceutical industry in the UK will count on the MCRN to facilitate access to paediatric experts and to investigators, costing, contracting, research governance and regulatory approval, set-up of sites, conduct and delivery of paediatric clinical trials.

Conclusion

Obtaining information on the safety and the efficacy of new and old drugs in children will not be an easy task. Close and active alliances between academia, clinical teams and the pharmaceutical industry will help to provide evidence for prescribing medicines to children and better paediatric formulations, for the better health of children.

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