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CHILDREN'S MEDICINES

All medicines undergo clinical trials to assess their safety, quality and effectiveness. Most tests use adults; fewer than 50% of children's medicines have actually been tested in children. A new European regulation that aims to increase the development and testing of medicines specifically for use in children will become law in the UK by the end of 2006. This note examines current and future regulation of research into, and clinical trials of, children's medicines and discusses the issues raised.

Background

Many medicines prescribed for children have not been specifically licensed for use by them. Rather they have been tested and formulated for adults. This varies according to the setting in which the medicines are prescribed. Whereas only 10-20% of medicines prescribed for children by general practitioners have not been licensed for use in children, this number rises to about 45% of medicines used in general paediatric wards and over 90% of those used in neonatal intensive care[1,2].

Doctors prescribing such medicines for children have to take responsibility for this unlicensed (off-label) use. They may prescribe adult formulations, or use licensed medicines in an unlicensed way (for example crushed in drinks to enable children to take them). Because a child's body does not behave like that of a small adult, it is not possible to make a simple extrapolation from the adult data. For some medicines, this lack of information or appropriate formulations may expose children to side effects, over-dosing or under-dosing (lack of efficacy). These issues are discussed further on page 4.

Why are so few medicines specifically licensed for use in children? Until 10-15 years ago there was widespread reluctance to conduct studies of medicines on children due to ethical reasons. However, there has been a significant shift in opinion in recent years, such that the lack of trials and the dearth of information, is now seen as the chief ethical concern. There are also practical difficulties that may make clinical studies on children more complex and expensive than those on adults. Finally, the pharmaceutical industry chooses what medicines to develop, test and market. The potential return often is not sufficient to justify investment in R&D of medicines specifically for children.

Concerns over children's medicines surfaced in the UK in the late 1990s. In 2000 the Council of Health Ministers decided that the European Commission would address this issue. The resulting new EU Regulation on Medicinal Products for Paediatric Use[3] should enter into force in the UK before the end of 2006.

Regulation

UK medicines, including those licensed for use in children, are regulated under European law by the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMEA) (see Box 1).

Box 1 Licensing medicines

Medicines are approved under Directive 2001/83/EC relating to medicinal products for human use[4]. The medicine itself must have a licence called a 'marketing authorisation'. In addition, the companies involved in all stages of the manufacture and distribution of the product need to have licences (manufacturers' and wholesale dealers' licences).

Medicines must either receive marketing authorisation approval through the centralised EMEA procedure or under the "mutual recognition" procedure. Here approval of a product application by one Member State's competent authority (in the UK this is the MHRA) should allow that product to be marketed in all Member States. New medicines have to demonstrate their quality, safety and efficacy through clinical trials data. In the UK, clinical trials are regulated by the Clinical Trials Regulations 2004 which implement the EU Clinical Trials Directive. This takes into account some specific concerns on performing clinical trials on children, and in particular it lays down criteria for their protection in clinical trials.

New regulation

The European Parliament approved the final agreement on a new regulation on paediatric medicines in its second reading on 1 June 2006; it should enter into force by the year end. The Regulation aims to increase the development and testing of medicines specifically for use in children. It will establish a legal framework based on a system of requirements and incentives (see Box 2). The incentives, such as a six month extension of patent protection, are designed to increase the amount of money companies can make from a particular medicine. A new expert body, the Paediatric Committee (PC), will oversee the Regulation. All new marketing authorisation applications must include the results from a Paediatric Investigation Plan (PiP), agreed by the PC. The PiP sets out the studies to be conducted to assess the use of the medicine in children. The PC may grant a waiver on the grounds that the medicine is unlikely to benefit children.

Details of trials carried out under PiPs will be entered by the EMEA on the European Clinical Trials Database established under the Clinical Trials Directive. The EMEA will co-ordinate the establishment of a European Paediatric Clinical Trials Network to encourage communication and collaboration between existing European networks. In addition, the Regulation makes provision for funding research into children's medicines through the European Research Framework programmes.

Box 2 EU Regulation - requirements and incentives

The Regulation will introduce the following requirements and incentives:-

- **New and patent-protected products**: companies are obliged to submit a PiP before marketing authorisation can be granted. Information about how the product can be used (or not) in children arising from a completed PiP will be rewarded with a 6 month extension of patent protection.
- **Products no longer covered by patent protection (sometimes known as generic products)**: companies can apply for a new category of marketing authorisation called the paediatric use marketing authorisation (PUMA) for a product that will be used solely in children. This will be rewarded with a ten year period of data protection and exclusivity.
- **Orphan medicinal products**: these are products that target rare diseases that affect small numbers of people. Information arising from a completed PiP will be rewarded with two years of market exclusivity beyond the ten years to which orphan medicinal products are entitled under existing EU legislation.

Issues

Developing and licensing medicines for use in children raises a number of issues. In general these fall into two main categories: regulatory issues and research issues.

Regulatory issues

The new EU Regulation aims to increase the availability of medicines specifically adapted and licensed for use in children. The House of Lords European Union Select Committee recently examined the proposed Regulation. It noted that "the overwhelming weight of professional opinion…broadly supported the Proposal and was anxious to see it implemented as soon as possible"[5].

The US experience

The approach adopted by the EU draws on experience with the US system. Here, two pieces of complementary legislation to encourage clinical trials in children were introduced in 1997 and 1998. They have since been updated and modified by subsequent legislation. One provided an incentive – an additional 6 months' patent protection –to companies that perform clinical studies in children in response to a written request form the Food and Drug Administration. The other requires companies to perform studies and/or to develop formulations if the product is likely to be of use to a substantial number of children. This combined measure has stimulated the development of such medicinal products (see Box 3).

Box 3 US case study

Between the introduction of legislation to increase paediatric drug information in 1997 and 2005:

- additional labelling information on safety, efficacy, dosing and unique risks in children has been included on 100 drugs
- manufacturers have conducted more than 250 paediatric studies for 125 products.

In contrast, in the 7 year period before 1997 only 11 such studies were conducted[6].

Costs and rewards

The Regulation introduces incentives aimed at encouraging research on new and patent-protected products, off-patent (generic) products and orphan medicinal products (see Box 2). Without some kind of incentive, it is unlikely that industry would make the necessary investment in research. Much debate at the EU level has centred on the extent of these rewards.

There will be a cost to the generic medicines industry whose access to markets will be delayed by the six month patent extension. The European Generic Medicines Association argued that a patent extension of only 3-4 months would be adequate to recover the costs of paediatric clinical trials. However generic companies may have opportunities to benefit from developing medicines under the PUMA scheme (Box 2). As medicines under patent protection are more expensive, the Regulation will also increase the total medicine spend of national health services in Europe. The Government has estimated that the six month extension would cost the NHS in England an extra £30 to £120 million[5].

The House of Lords European Union Select Committee concluded that the package of incentives and rewards in the Regulation was essentially a leap of faith. It noted that it is impossible to judge whether these arrangements are likely to provide the necessary incentives to industry and be equitable and proportionate to all involved.

Assessing the Regulation

The European Commission will assess the application of the Regulation six years after it has been introduced.

However, the Association of the British Pharmaceutical Industry (ABPI) considers this period may not be long enough to determine whether the legislation is successful. It points out that the average paediatric clinical trial could take three to six years, followed by about a year to complete the regulatory process. The Commission has stated that the review may be deferred (for up to a further four years) if insufficient data are available after six years.

The Paediatric Committee (PC)
The PC will have expertise in research, development, authorisation and use of medicines in children, and will be central to the operation and success of the Regulation. This new EMEA Committee is required because none of the existing committees has sufficient specific paediatric expertise. As well as assessing, approving and checking compliance and results of PiPs, the PC will be responsible for the EU inventory of therapeutic needs in children. Many groups have commented on the make-up of the PC, with recommendations for expertise from pharmacy, paediatrics, clinical pharmacology, and patient representatives.

The EMEA established an expert group on paediatrics (PEG) in 2001 to provide recommendations to the Committee on Human Medicinal Products on all questions relating to the development and use of medicinal products in children. The PEG has begun to address the question of the unmet needs for the treatment of children in various disease areas. The PC will take over the work of the PEG, as well as carrying out the responsibilities set out in the Regulation.

Labelling of children's medicines
The Regulation will introduce a requirement for a symbol to be placed on the labelling for all products licensed for paediatric use. The symbol will be selected by the PC within one year of the Regulation coming into force. The symbol will not indicate the suitability for a particular age group; this would be contained within the product information. The Government does not believe that age specific symbols are necessary. However, the House of Lords European Union Committee is concerned this approach may overlook the danger that a product suitable for use in mature children may be highly dangerous for use in younger ones.

Clinical research issues

Age classification
Children are a heterogenous group. Within the paediatric population, (0 to 18), there are different sub-groups and international guidelines separate them into five groups[7]:

- preterm newborn infants;
- term newborn infants 0-27 days;
- infants 28 days – 23 months;
- children 2 – 11 years and;
- adolescents between 12 and 16/18 years.

As babies grow, numerous physiological processes develop and change. The effect of drugs may vary from one age group to another, as may the manner in which the drug is broken down. Some side effects occur in children only as their bodies grow and mature. As a consequence data obtained in adults cannot be extrapolated to children using a proportionality rule based on either weight or surface area.

Clinical trials
Design
As the number of children suffering from a specific disease is generally lower than in adults and as they need to be classified into different age categories, the design of the trial has to be robust enough to cope with problems in recruiting sufficient numbers. A well-coordinated research network should help to address this problem (see below). Clinical trials in children require specific expertise and methodologies, for example, to find the best ways of ensuring that parents and children understand all aspects of a trial or to measure the clinical outcomes in a child. While it might be straigtforward to measure lung function in adults in an asthma trial, this is much more challenging in children, in particular in young children. More research should inform better design of children's trials.

Clinical trials networks
The Regulation requires the EMEA to co-ordinate the establishment of a European Paediatric Clinical Trials Network. This will link existing national networks and clinical trial centres. This aims to build up the necessary competencies at European level and to facilitate the conduct of clinical trials, to increase cooperation and to avoid duplication of studies.

National networks are being established in a few European countries including the UK. The UK's Medicines for Children Research Network (MCRN) was set up in 2005 and will receive up to £4 million per year (depending on capacity) over five years from the Department of Health (DH). This covers the infrastructure costs but not the funding of actual clinical trials. The network will provide advice and support on all aspects of design, patient recruitment and management of trials of medicines for children. The ABPI hopes that the establishment of this network will lead to the UK becoming a prime place for paediatric research.

Formulations
Because childhood and adolescence span a variety of ages, weights, preferences and abilities, a range of medicine preparations (formulations) may be required. However, for many drugs, even those with a licence for paediatric use, formulations that suit children are not available. For example, particular problems arise for younger children unable to swallow tablets or capsules. Where medicines licensed for use in adults are adapted, activities such as crushing tablets and preparing suspensions may lead to potential problems with dosage and drug absorption. Developing ranges of formulations specifically for children is expensive and it is not clear that industry will be ready or able to fund all the necessary research in this area.

Ethics and consent

Medical research, including clinical trials, is subject to ethical scrutiny. In the UK no research study in children can take place unless it has received permission from a properly constituted ethical committee[8]. The EU Clinical Trials Directive lays down specific requirements to protect children taking part in clinical trials in the EU. This Directive requires a person with parental responsibility or a legal representative to give informed consent for any trial on a child. In addition, the explicit wish of the minor to refuse participation in, or to be withdrawn from, a clinical trial at any time must be considered. Exactly what this means in practice was highlighted by the House of Lords European Union Select Committee as in need of serious consideration. The European Commission (EC) is currently drafting specific guidance on the ethics of conducting clinical trials with children. This is expected to be published in autumn for consultation and to be in place by the time the new Regulation comes into force. In addition the Regulation has further measures in place to protect children taking part in clinical trials (see below).

Assessing proposals

Proposals for paediatric investigations will have to be agreed by the EMEA's PC. This has the option to refuse, waive or defer such proposals. It is required to veto trials (by removing any of the incentives) where the product concerned is likely to be unsafe, ineffective in children or targeted at a disease that occurs only in adults. The PC may also defer trials where it recommends initial experience of the use of the product in adults before children. The new Regulation requires the PC to take account of whether an appropriately authorised product already exists. It also requires studies undertaken before the entry into force of the Regulation to be submitted to avoid unnecessary participation of children in further trials in Europe.

Best practice

As many medicines have been used off-label/unlicensed in children for years, information about appropriate dose levels, efficacy and possible side effects already exists for some medicines. However such information is not always published and establishing best practice is not easy. The first edition of the British National Formulary for Children was produced by the British Medical Association, the Royal Pharmaceutical Society of Great Britain, the Royal College of Paediatrics and Child Health (RCPCH) and the Neonatal and Paediatric Pharmacists Group in 2005. Its distribution to health professionals in England was supported by £1.8 million from DH. It gives prescribers advice on which medicines are most appropriate for use in children, alongside information on child drug dosages and formulations, and will be updated annually. This information is validated against emerging evidence, best practice guidelines and advice from clinical experts.

Access to clinical data

Details of clinical trials on medicines in the EU are collected confidentially on the European Clinical Trials database (EudraCT) established by the Clinical Trials Directive. The Regulation requires that details of trials carried out under PiPs should be added to this database. Parts of the database, including results of trials, will be publicly available although exact details have yet to be finalised; the Commission will draw up guidelines on the elements of the database that should be public. Many including *Which?*, RCPCH and the Lords European Union Select Committee consider there should be full public access to prevent duplication of trials in children.

Research funding

It is likely that for some medicines research funding will be needed for clinical studies. This is most likely to be the case with old medicines that have been off-patent for a long time or for developing age-specific formulations. Here public funding, both national and European, will be needed. Although the Regulation makes provision for this through the European Research Framework programmes, details of exactly what and how much are not yet available. In the UK, the NHS Health Technology Assessment programme launched a call for research into children's medicines last year. So far, it has funded four studies[9]. It is also possible that the charitable sector will increase targeted funding on developing medicines for children in the next few years.

Overview

- Fewer than 50% of children's medicines have been tested in children. A new European regulation aims to increase their development and testing and will become law by the end of 2006.
- It is difficult to judge whether the Regulation's system of requirements and incentives will achieve this aim and be fair to all involved. The EC will review the Regulation six to ten years after it is introduced.
- Gaining consent for a child to take part in a clinical trial needs consideration. The EC will issue guidelines on this in autumn 2006.
- The children's British National Formulary, the UK children's clinical trials network, and increased funding, are key to improving children's medicines.

Endnotes

1 Clinical trials and children's medicines. Association of the British Pharmaceutical Industry briefing paper.
2 European Commission Staff Working paper 13880-04 (2004).
3 http://www.europarl.europa.eu/oeil/file.jsp?id=5210532
http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/index.htm
4 as amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC.
5 HL 101 of Session 2005-2006.
6 http://www.fda.gov/bbs/topics/NEWS/2005/NEW01280.html
7 http://www.emea.eu.int/pdfs/human/ich/271199en.pdf
8 See POSTnote 243, *Ethical scrutiny of research*, July 2005
9 http://www.hta.nhsweb.nhs.uk/calls/M4CUpdate.htm

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