

# **MHRA/DEPARTMENT OF HEALTH STRATEGY ON MEDICINES FOR CHILDREN**

## **1 Introduction**

There is a need to develop new medicines for use in the paediatric population and to have full and proper evaluation and age-appropriate formulations for existing medicines which are currently used in children outside the licensing framework. The longer term strategy to produce changes to the regulatory structure is being taken forward at a European level in the form of a Regulation on medicines for paediatric use. This will not be adopted before 2006.

Meanwhile the UK needs a short- to medium-term strategy that will produce:

- a measurable increase in appropriately labelled and formulated medicines for children
- helpful and informed information for prescribers, carers and patients

and

- facilitate the conduct of paediatric clinical trials in the UK.

## **2 Background**

Until relatively recently there was a widespread reluctance to conduct studies of medicines used in the treatment of children. This was due to a number of factors including ethical concerns about, and the practical difficulties of, conducting trials in children, together with commercial considerations. As a result, most medicines have only been tested for safe and effective use in the adult population and there are comparatively few medicines on the market which are specifically licensed for the treatment of children. This leads to prescribers having no option but to prescribe unlicensed and off-label medications, often in unsuitable formulations. This may result in reluctance to use newly introduced drugs, medication errors, inappropriate dosing (both too high and too low), inadequate efficacy and unforeseen adverse events.

There has been a significant shift in opinion in recent years about conducting clinical trials in children as shown, for example, by the increasing number of trials carried out in the US over the last few years. The lack of such trials is now seen as the chief ethical concern.

The US has introduced legislation that provides financial incentives to industry to undertake clinical trials on products used in the treatment of children whilst they are still “patent protected”. This has succeeded to a point but has not encouraged trials of products for some important children's diseases, where the commercial incentive is still considered insufficient. For this reason the US has also introduced a legal obligation for companies to conduct trials on the paediatric use of medicines where there is a therapeutic need.

A European Regulation is being developed which will establish a system of requirements and incentives aimed at satisfying the need for medicines that are appropriately formulated and labelled for paediatric use. It draws on the experience with the US legislation. The Regulation will also result in improved information on the use of medicines in children and publication of information from clinical trials in children.

Given the constraints on the EU legislative process it is unlikely that the Regulation will be adopted before 2006. In the meantime a co-ordinated UK strategy will produce

concrete short to medium term gains and raise awareness in the pharmaceutical industry of the need to take action now to ensure that products are appropriately labelled and formulated for paediatric use.

### **3 Elements of the strategy**

The strategy is organised according to what is considered to be achievable in the short, medium and long term.

### **4 Short term strategy**

#### **4.1 Access to data from studies already completed**

A number of Marketing Authorisation Holders (MAHs) already possess data which may impact on the safe and effective use of their products in the paediatric population. Many of these data relate to studies conducted in accordance with US legislation.

The US Food and Drug Administration (FDA) publishes a list of the approved active substances for which the FDA has granted “paediatric exclusivity”. This indicates that paediatric data have been generated in accordance with a formal FDA Written Request and have been submitted to the FDA. The FDA also publishes a list of labelling changes that result from the evaluation of these data. These changes do not necessarily involve new paediatric indications. They may relate to the safe use of the product. In addition, the FDA publishes a list of labelling changes that have resulted from the evaluation of studies conducted according to the FDA’s “paediatric rule” which mandates paediatric studies in certain circumstances. The majority of these data have not been submitted to the MHRA.

#### ***Action***

The MHRA has requested the MAHs concerned to submit the data to the MHRA for evaluation and variation of the Marketing Authorisation as appropriate. The Association of the British Pharmaceutical Industry has encouraged its members to comply with the requests.

#### **4.2 Regulatory incentives**

There is little scope for providing incentives within the current regulatory framework. However, two opportunities have been identified.

#### ***Action***

The MHRA is offering paediatric scientific advice without charge and fee waivers for applications to include paediatric safety information in the summary of product characteristics. The MHRA will be consulting on extending fee waivers to all paediatric-specific applications, where it is judged to be in the public health interest.

#### **4.3 Paediatric development plans**

The need to consider the inclusion of a paediatric development plan as a part of medicinal product development is set out in European guidance.

#### ***Action***

The MHRA will systematically raise the subject of paediatric development plans at appropriate stages in product development, where there is a therapeutic need. This will include when advising companies on product development, assessing an application for marketing authorisation, assessing a variation to a marketing authorisation and renewing the marketing authorisation.

## **5 Medium term strategy**

### **5.1 Discontinued medicines**

A number of useful medicines used in the paediatric population have been discontinued although the formulations intended for adults remain licensed and available. The MHRA has no power to prevent a company from discontinuing a product.

#### ***Action***

The MHRA will write to a company which has signalled its intention to discontinue manufacture of a medicine for which there is a paediatric therapeutic need, alerting the company to the paediatric usage and asking the company what steps they are taking to ensure that this therapeutic need continues to be met. The MHRA will explore the scope for securing an alternative source of supply. This work will be coordinated with, and will not duplicate, the work of DH in relation to discontinued medicines.

### **5.2 Importation of medicines**

There are many examples of suitable licensed paediatric preparations available in other countries with similar licensing arrangements to those in the UK, yet companies have chosen not to apply for a licence in the UK. Importation is possible but is expensive.

#### ***Action***

The MHRA will identify needed paediatric medicines that are licensed outside the UK and invite the companies to submit applications for authorisation. The exercise will focus on medicines authorised elsewhere in the EU.

### **5.3 Extemporaneous Formulations**

Extemporaneous formulations (made to order or specially prepared) may not be of the same quality as licensed formulations but sometimes they are unavoidable. In addition standards of quality and bioavailability of the formulations may vary throughout the UK depending on the supplier.

#### ***Action***

Work is in progress to include best practice guidance in the forthcoming British National Formulary for Children. In addition the MHRA will explore the direct actions which may be taken to standardise the quality throughout the UK of extemporaneous formulations for paediatric use.

### **5.4 Off-patent medicines - paediatric formulations and indications**

Liquid oral formulations and suppositories are needed for a number of established medicines. MHRA has contacted individual manufacturers, occasionally with positive results, but without incentives it is difficult to persuade companies to allocate resources to develop paediatric formulations. Appropriate studies are needed to support applications for paediatric indications for off-patent products. Sometimes there may be sufficient data in the published literature or in the company archives.

#### ***Action***

The MHRA will continue to contact companies to encourage the development of appropriate paediatric formulations for established medicines, focussing activity using a short priority list (see section 5.8).

### **5.5 On-patent medicines - paediatric formulations and indications**

The same considerations and actions apply as for off-patent medicines. In addition, paediatric studies may be conducted on on-patent medicines that are marketed in the US

in order to benefit from or comply with US legislation. Any studies that have at least one center in the EU will be entered on an EU clinical trials database in compliance with the EU directive on clinical trials. A summary report of the clinical trial will be submitted to the EU competent authority(ies) within one year of trial completion.

**Action**

The MHRA will set up a system to monitor information on paediatric trials conducted within the EU. The summary reports produced after trial completion will be used to request further information from the companies as appropriate.

## **5.6 Priorities**

Work is on-going at European level to produce a comprehensive prioritised list for the EU. A short priority national list will help to focus efforts in the UK.

**Action**

The UK will establish and publish a list of 10 or 20 products where efforts will be focussed in the UK, with the emphasis on what is achievable in licensing terms.

## **5.7 Regulatory guidance**

The UK will take a leading role in preparing European guidance on topics relating to paediatric drug development.

**Action**

The UK is rapporteur for a guideline on paediatric pharmacovigilance and will contribute to a guideline which includes information on paediatric dose response.

## **5.8 Paediatric Research and development**

When the European regulation is adopted the incentives and obligations will result in the potential for a great number of paediatric clinical studies to be conducted in the EU. This will include pharmacokinetic, pharmacodynamic and dose-finding studies, as well as phase III trials. The pharmaceutical industry needs centers of excellence and a functioning network in which to conduct these studies. If the UK is to benefit from this opportunity and to become a country of choice for conducting paediatric clinical trials in Europe it needs to develop and strengthen its capacity to conduct such trials.

**Action**

In June 2004 the Health Minister, Lord Warner, announced the creation of the UK Clinical Research Collaboration (UKCRC)<sup>1</sup>. It brings together the NHS, Medical Research Council, medical charities and industry to speed up the development of new medicines and treatments. Extra funding amounting in due course to £100 million per annum to support NHS R&D in the five therapeutic areas announced by the Secretary of State for Health in March 2004 will be made available to UKCRC<sup>2</sup>. One of these areas is medicines for children. In this area the extra funding will be used to bring together existing paediatric research centres to deliver faster progress in developing drugs for use in children.

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[http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT\\_ID=4086850&chk=FAIm2P](http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4086850&chk=FAIm2P)

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[http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT\\_ID=4077103&chk=OhPMZ8](http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4077103&chk=OhPMZ8)

The Research and Development Directorate of the Department of Health is in the process of developing detailed plans, in discussion with stakeholders, for a managed clinical research network for medicines for children. It is intended that the network should provide the NHS infrastructure for research in this area in much the same way as that provided by/through the National Cancer Research Network. Infrastructure support for experimental medicine / translational research will also be strengthened and funding will be set aside to support research in the networks on medicines for children.

## **5.9 Information for health professionals, carers and patients**

### **5.9.1 Children's British National Formulary (BNF-C)**

Health professionals wish to have authoritative, regularly updated information on paediatric prescribing in a single source. The external working group on the use of medicines in children (Children's NSF<sup>3</sup>) considered this a priority. Preliminary work has begun on the development of a Children's BNF with the intention of producing the first edition by mid- 2005. A web-based version will be available simultaneously.

#### **Action**

The Department of Health will support the distribution of the BNF-C as it supports the distribution of the regular BNF to doctors, pharmacists and Extended Formulary Nurse Prescribers in England.

### **5.9.2 Patient Information leaflets**

The Patient Information leaflet (PIL) is frequently either not written in a child-friendly manner or may be confusing to the patient/carer if the use is off-label. An exercise is currently underway within the MHRA to improve the readability of PILs. It will also address the improvement of paediatric specific information.

## **6 Long term strategy**

The UK supports the proposed European Regulation on medicines for paediatric use and will work to maintain the important elements contained within it, in particular striking the right balance of costs and benefits for the UK's National Health Service and for the pharmaceutical industry. At the same time it will strive to achieve provisions that are practical and workable and do not create problems for existing UK arrangements.

## **7 Conclusion**

The longer term strategy to produce changes to the regulatory structure is being taken forward at a European level. In the meantime, the MHRA/DH strategy should achieve a measurable increase in the number of products appropriately labelled and formulated for paediatric use, better information for prescriber, patient and carer, a change in the attitude of the pharmaceutical industry, and create positive conditions for the conduct of paediatric clinical trials in the UK.

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<sup>3</sup> <http://www.publications.doh.gov.uk/nsf/children>

