

Paediatric inhalation products — an unmet challenge for the industry?

Academics, industrialists and regulators met at a workshop recently to discuss unmet needs and the regulatory framework in the rapidly developing field of paediatric inhalation technology. **Joseph Chamberlain** reports

Mark Everard, paediatric respiratory consultant at Sheffield Children's Hospital, strongly emphasised the importance of understanding the patient's needs in paediatric inhalation therapy and was critical of researchers and regulators for often overlooking this. At a recent international conference on aerosols, for instance, three and a half days passed before "the patient" was mentioned, and regulatory bodies often concentrated on irrelevancies. Clinicians did not escape criticism either; the tales of doctors and nurses demonstrating inhalers without removing the cap are apparently not apocryphal. The dose received by the lung has little to do with the prescribed dose and ultimately the need is to develop devices that patients can and will use effectively. Cognitive issues in young children pose special challenges, and sophisticated new technology, although making sense commercially, is unlikely to be the answer for most applications unless it meets patient needs, said Dr Everard, who set out to uncover the real unmet needs.

The perceived advantages of inhalation therapy were that there is a rapid speed of onset, the drug is delivered to the site of action, and otherwise poorly absorbed drugs can be used effectively. The fundamental differences between oral and inhaled therapy can be seen in that the lung has evolved to exclude foreign material. This it does effectively with just a window of opportunity, where particles of approximately 1-3µm in diameter can penetrate the deep airways. Even if the patient takes the medicine, no benefit may be derived because of inadequate regimen compliance or device compliance.

It is, therefore, most important to understand the factors that lead to the high failure rates of inhalation therapy. Delivering drug to the lungs requires a device that generates particles that can deposit in the lungs, and requires the patient to use the device effectively, whether this is a competence issue (the ability to use a device effectively) or one of contrivance (knowing what to do but contriving to use the device ineffectively).

Undoubtedly, said Dr Everard, poor regimen compliance is associated with increased morbidity but extensive surveys have failed to establish that regimen compliance is affected by age, sex, disease, socioeconomic status or even the real life-threatening nature of the disease. Nor does liking the device have any influence on compliance. Examples of contrivance include rapid inhalation, not shaking



the device or not holding the breath for pressurised metered dose inhalers (pMDI), and rapid inhalation and stopping on actuation for breath-actuated pMDIs.

To maximise true compliance it will be necessary to improve the education of health professionals as well as patients. Devices must be intuitive to use and visible feedback, such as disappearance of clouds from nebulisers, should be evident. The prescribed dose has little to do with lung drug availability because of unpredictable variations in the emitted dose and in anatomy and physiology. The best guide to prescribing an inhaler is to choose one that the patient can and will use correctly and the only guide to prescribed dose is to use the lowest dose that works.

Childhood has special problems, being a period of great change. Physical, physiologi-

cal, cognitive, emotional and social state all have a bearing on the effective use of medicines. Pre-school children (aged three to five years) favour "panting" and find deep breaths difficult. Depending on the stage of development, however, children as young as four years of age can learn to be proficient with devices such as dry powder inhalers.

In thinking about future devices, Dr Everard suggested we should consider safety and efficacy; efficiency was only a factor if the chemical entity was genuinely expensive. We need to consider the type of drug. Does it need to be targeted? What is its therapeutic index? Does it provide direct feedback? And does the dose need to be titratable? The needs of the patient to ensure that it is used reproducibly and regularly are paramount, concluded Dr Everard.

Regulatory framework

Paediatric studies of medicinal products are carried out to meet medical needs of children, to ensure compliance with legal and regulatory directives, and to benefit the development company by the reward of a period of paediatric exclusivity, said Julie Williams, head of regulatory chemistry, manufacturing and controls at Pfizer.

The International Conference on Harmonisation suggests in its "Clinical investigation of medicinal products in the pediatric population", that paediatric patients should be given medicines that have been appropriately evaluated for their use in those populations. Thus, the timing of studies, types of studies, ages of patients and ethics of study conduct are specified. Furthermore, the ICH's "Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals" states that safety data from adult human exposure is considered the most relevant information and expected to be available before paediatric clinical trials are started. There should be completion of repeated-dose toxicity studies, reproduction toxicity studies and genetic toxicity tests before the initiation of paediatric trials. Juvenile animal studies need to be considered on a case-by-case basis.

In the US, the regulatory environment is continually changing, using carrot and stick methods of encouraging development of paediatric medicines. The Pediatric Research Equity Act, which became law in December 2003, requires that paediatric data are generated for all new chemical entities via a written request, a legal document written and

The workshop organised by the Inhalation Focus Group of The Academy of Pharmaceutical Science took place at Burleigh Court, Loughborough, on 28 June

sent by the Food and Drug Administration to sponsors requesting studies in the paediatric population.

The Best Pharmaceuticals for Children Act, enacted in January 2002, gave six months' marketing exclusivity for completion of studies under a written request. A public fund was created to support studies for off-patent drugs or for drugs under patent that the manufacturer declines to study. The impact of these regulations has been that by the end of March this year, written requests had been issued for 275 active moieties, 120 exclusivities had been granted and, most importantly, 109 paediatric labelling changes had taken place. These included dosing recommendations, safety information, an expanded age group, and new paediatric formulations.

In the EU, draft legislation was released in September 2004 and approval is expected in 2006. The legislation has the same drivers as in the US, maintaining the important principles that there should be no delay of the authorisation of medicines for adults and that children should not be subjected to unnecessary clinical trials, along with full compliance with the EU Clinical Trials Directive. The key elements include the requirement for a paediatric investigation plan.

For the future, the global challenge is to accept that producing information for the safe use of medicines in children is a co-operative effort. We need to retain incentives, promote co-ordination and co-operation of international regulatory authorities, and encourage the development of paediatric drug delivery and formulation knowledge, concluded Dr Williams.

Responding to challenges

Manfred Keller, director of PARI Pharma business unit, PARI GmbH, said that the development scientists were indeed responding

Inhalation Focus Group

The Inhalation Focus Group is a group within the Academy of Pharmaceutical Sciences, explained Peter Seville, of Aston University, Birmingham, and chairman of the workshop. Its aim is to provide a forum for industry, academics and the regulators to discuss current issues in science, technology and regulation pertinent to pulmonary and nasal drug delivery. An acknowledged general lack of information and appropriate pharmaceutical formulations to support the administration of many medicinal products to children prompted the creation in Europe in 2001 of a paediatric working party to advise the European Medicines Agency and its scientific committees on all questions relating to the development and use of medicinal products in children.

As part of its ongoing work programme, the working party is making assessments of paediatric needs by therapeutic area, with obstructive lung diseases featuring in the 2006 work plan. Against this background, the Inhalation Focus Group organised the inaugural workshop reported here to consider the specific requirements when developing products for the paediatric market, with reference to the needs of the patients, the regulatory framework surrounding paediatric formulations and the approaches taken by the industry to overcome these challenges.

to the challenges of the clinicians and regulators. They recognise that both device and formulation play a crucial role for efficient pulmonary drug therapy. Whatever the device, lung deposition is highly affected by the breathing pattern. *In vitro* models are helpful in identifying and selecting drug formulations and devices for optimised pulmonary drug delivery.

Therapeutic aerosols contain particles or droplets with a range of diameters (ie, they are heterodisperse not monodisperse). Their overall behaviour is governed by the droplet size and drug distribution pattern. Small particles with low inspiratory flow rates result in greater delivery of drug to the lower respiratory tract. Reduced airway calibre results in proximal rather than distal deposition of drug. Droplets for children and infants must be smaller for substantial lung deposition and dose may need to be adjusted.

Non-electrostatic, small-volume, valve holding chambers (VHCs) should be used for children to reduce oropharyngeal deposition and eliminate co-ordination problems. VHCs should be assessed properly with pMDIs, including the close fit of face masks used for children aged under three years, where inhalation after actuation is important. Current dry powder inhalers are less suitable for drug delivery in children under six years of age.

Breath simulation tests mimicking children's breathing patterns with device and drug product are needed to obtain information on the delivered dose. Dr Keller emphasised that *in vivo-in vitro* correlations must be established to help in prediction of lung deposition.

The European Committee for Standardization (CEN) promotes voluntary technical harmonisation in Europe in conjunction with worldwide bodies. Its nebuliser standard, however, is inappropriate as it does not include any drug substance.

Approval of new drugs with sophisticated new devices will be associated with a burdensome, time-consuming and expensive regulatory process, said Dr Keller, and for this reason he did not agree with the contention that sophisticated devices were more commercially rewarding. Additionally, progress in child therapy is difficult due to reimbursement issues.

Group discussions — three relevant questions on paediatric inhalation products

The workshop included the opportunity for small groups to debate the issues raised in more detail and three relevant questions were reported on.

How do we deal with the paediatric patient?

The group agreed that the most important factor was for the patient to receive feedback, before, during and after dosing. What the market should provide, therefore, would be a fast-acting drug coupled with a simple device. However the group questioned the commercial viability of any such developments. The target population, although high on the emotional scale, was relatively small. The group also suggested that, for the present situation, better training of health professionals is needed and, for future unhindered development, the expectations of the regulatory authorities needs to change.

When, during the life-cycle of a new drug, should development of a paediatric formulation start?

Most industrialists, when questioned about the desirability of developing paediatric formulations, suggested the group, would not be enthusiastic. It is clinicians who are driving the demand. The conflicting attitudes need to be balanced. The group suggested the aggressive way forward would be to include paediatric considerations at the stage of "first time in man" or to apply for a waiver — ie, the sponsor may argue there is no therapeutic need in paediatric

populations. The details would then be fleshed out in Phase II, which is about the time when pharmacological testing switches from aerosols to the more probable product form of nebulisers. Adult Phase II trials are normally limited to subjects aged over 18 years, but subjects as young as 12 could be included and resulting data then used to support a robust paediatric product plan. The group also noted that the recruitment of children into clinical trials was likely to be problematic.

Do we need paediatric-specific inhalers?

Yes, said this group, as current inhaler devices were designed for use in adults, and have been adapted for the paediatric population. In particular, current inhalers were not considered to be particularly child-friendly. The use, for example, of flavoured face masks to improve patient acceptability was discussed. It was recognised that the needs of a 12-month-old infant were different from those of a four-year-old pre-school child whereas, with sufficient training, children older than six years of age can usually learn to use conventional inhalers correctly. The development of standard devices for particular age groups and acceptable to all developers was seen as a potential solution, although it was thought that companies would be unwilling to invest in developing a non-exclusive device. The group concluded that the development of intuitive, paediatric-specific inhalers would be beneficial in treating children, but that the development tools are lacking.