

FACTORS FOR DOSE COMPLIANCE IN PAEDIATRIC PATIENTS

- Devices must provide feedback before, during and after dosage.
- Devices should be intuitive to use.
- Devices used should not be intimidating.

BREATHING LESSONS

Commercial and regulatory realities can be obstacles to progress towards paediatric-specific inhalers currently used for adults. Ken Bruce, Ben Forbes and Nilesh Patel, King's College London, explore the rationale for passively targeting the lung via inhalation for the treatment of respiratory infection, and discuss the need for more research.

In 2001, the lack of information and appropriate pharmaceutical formulations to support the administration of many medicines to children prompted the creation in Europe of a Paediatric Working Party to advise the EMEA. As part of its ongoing work programme, the PEG is making assessments of paediatric needs by therapeutic area, with obstructive lung diseases featuring in the 2006 work plan. The needs of the patient, the regulatory framework surrounding paediatric formulations and approaches taken by industry to overcome these challenges are considered.

At a workshop in June 2006 hosted by the Academy of Pharmaceutical Sciences in Great Britain, Dr Mark Everard, paediatric respiratory consultant, Sheffield Children's Hospital, UK, led discussions on 'Defining the unmet needs'. Dr Julie Williams, head of regulatory CMC, Pfizer, UK, led discussions on 'Current and future regulatory framework', and Dr Manfred Keller, director of PARI GmbH, Germany, led the discussion on 'Responses from product developers'. Delegates debated the issues raised by the speakers in breakout sessions that were themed to consider:

- the needs of the patient population
- the regulatory framework surrounding paediatric formulations
- approaches taken by industry to meet the challenge of developing paediatric products.

Children's needs

The paediatric population can be divided into three groups according to ability to use inhalation devices. The youngest children, under two years, require relatively little inhaled

Author profiles



Ken Bruce is lecturer in molecular microbiology, King's College London. He was appointed to his academic post in 1999. He has teaching roles in biochemistry, pharmaceuticals and forensic sciences. The research carried out in Bruce's laboratory is focused on developing a more accurate understanding of the activities of microbes in health and disease.



Dr Ben Forbes is senior lecturer in pharmaceuticals at King's College London. Between 1987 and 1990 he worked in hospital pharmacy in London and Sydney, and from 1990-91 worked for Inveresk Clinical Research in Edinburgh. Forbes performed post-doctoral work in respiratory drug delivery at King's College London from 1995 until he was appointed to the academic staff in 1997.



Dr Nilesh Patel is lecturer in clinical pharmacy at King's College London. He teaches clinical pharmacy at undergraduate and postgraduate level and is also involved in teaching in the MPharm4 drug delivery elective.

therapy and are dependent on the assistance of healthcare deliverers to provide the therapy. Pre-school children of three to five years find deep breaths difficult and inhale by panting, requiring nebulisers or inhalers with spacers. Above the age of five, children can be proficient with the inhalers used by the adult population, with or without the use of spacers (Table 1).

The huge variability in received dose (as a result of patient factors in the use of inhalers) means that the principal need of

children with respect to their delivery devices is not efficiency, but rather factors that will improve compliance. These factors were identified as devices that provide feedback before, during and after dosing; devices that are intuitive to use, simple, fast, discreet, portable and importantly, not intimidating. By taking the approach to prescribing inhaled therapy that the lowest dose that works is the correct dose, the desirability of a titratable dose inhaler is clear. In the absence of any prospect of such a device, then the generation of data on which to base recommendations for device-spacer combinations for existing products and nomination of new chemical entity pMDI-spacer combinations would be a good way forward.

Regimen and device compliance is a challenge in inhaled therapy generally and the problem is exacerbated for paediatric populations. Device compliance can be affected

Table 1. Breathing patterns depend on age and disease

Age	6 months	1 year	3 years	5 years	10 years	adult
Tidal volume	50	75	125	150	225	500
Rate (breaths per minute)	30	28	24	20	16	15
1:E ratio	40:60	40:60	40:60	40:60	40:60	50:50

The highly variable breathing profiles of children make dosing difficult when efficiency of drug delivery systems is breathing-pattern dependent.

by competence-affecting and contrivance-affecting product factors. Poor compliance may result from deficiencies in competence (the ability to use the device) or contrivance (contriving to use the device in an ineffective manner). While device competence is a recognised problem, contrivance to use devices ineffectively (for example, spacer disuse and shallow rapid inhalation) is an issue that is less appreciated.

Regulatory framework

The International Conference on Harmonisation (ICH) suggests that medicines for paediatric patients should have been appropriately evaluated for their use in those populations. The requirement for different dosage forms for children in different age ranges is apparent, along with the importance of the timing, type, ages and ethics of the study.

Over the last decade a number of legal and regulatory directives have been issued in the US and EU aimed at promoting the development of specific products for the paediatric market. To date, no inhaled medicines have been developed specifically for the treatment of children or infants, but the regulatory framework aims to encourage the development of such products to complement adult therapies.

In the US, a carrot and stick regulatory approach exists. The Best Pharmaceuticals for Children Act (2002) gives six months' marketing exclusivity on completion of paediatric clinical trials. The Paediatric Research Equity Act (2003) requires paediatric data to be generated for all new dosage forms. EU draft legislation (2004) suggests a Paediatric Investigation Plan should be submitted during the registration of new medicinal products, with marketing exclusivity incentives to conduct

paediatric studies submission on off-patent drugs. However, important principles are that there should be no delay in the authorisation of medicines for adults, and that children should not be subject to unnecessary clinical trials.

Product developers' responses

The various challenges that are posed by the needs of the paediatric population and the regulatory authorities are being addressed by the pharmaceutical industry. Product developers have long recognised that efficient pulmonary drug delivery is dependent on the formulation, the device by which it is delivered and the breathing patterns to which the device and formulation are subjected.

Although currently available inhalers may be considered to be non-child friendly, various devices are available to improve pulmonary deposition in the paediatric population. These include non-electrostatic small-volume valve holding chambers (spacers), which are effective at reducing oropharyngeal deposition and eliminate the coordination issues surrounding the use of pMDI devices. Dry powder inhalers provide an alternative method of inhalation and can be effective for use in children as there are no coordination issues.

A more aesthetic approach to use of inhalers in general has been to improve their use by producing fashionable inhalers with child-friendly designs. The challenge for product developers is apparent from the observation that the needs of a 12-month-old infant, a three-year-old child at nursery and a ten-year-old schoolchild are considerably different. The development of age-specific devices would be the solution, although it was recognised that the industry was unlikely to be willing to invest funds in developing products for such small, specialised markets.

Development requirements

The clinical necessity for improved inhaled products for the paediatric patient is evident, but communication between clinicians, regulators and product developers will be essential for the development of this field. Presently, it seems that the important requirements of a device in the clinic may not be concordant with priorities of the regulatory authorities. This may be exacerbated as technical advances enhancing understanding of respiratory disease, such as the studies describing the microbiology of the CF lung described herein, lead to new indications for inhaled therapy in the paediatric population.

The development of paediatric-specific devices is recognised as desirable, but the technical tools required to guide product development are currently inadequate. Rather than focusing on the development of increasingly sophisticated devices, it has been suggested that the industry should focus on intuitive devices than can be used by patients of all ages. Increased awareness of the needs of the patient by the regulators and product developers is the important first step towards generating a framework that will enable innovation in this area. **WPF**