

## INHALED THERAPIES

# Patient and industry views on inhalers

*A one-day symposium on inhaled therapies, held with the European Pharmaceutical Aerosol Group, was part of the science programme at this year's British Pharmaceutical Conference. The session, held on 25 September and chaired by Dr Steve Nicholls of Aventis, included presentations on a spectrum of topics from inhalation devices and trends in their design to the incidence and treatment of respiratory disease*

## Patients often failing to use inhalers correctly

Up to 80 per cent of patients fail to actuate and inhale simultaneously when using a pressurised metered dose inhaler (pMDI), DEBBIE CAMPBELL, Royal Brompton Hospital, London, said, describing her experiences as a nurse working with patients who use inhaled therapies.

Other problems include positioning the canister close to the chest or otherwise away from the mouth, and inhalation of objects such as coins, earrings, insects and pen tops, after they have become lodged in the device which can occur if the cap is not used or is lost. Spacer devices are bulky and inconvenient, require cleaning, and may be difficult for older patients who lack dexterity.

Dry powder inhalers are portable, easy to co-ordinate and have a dose counter, but have disadvantages, such as irritation caused by the powder, and mouth rinsing is still required.

The consequences of poor inhaler technique include reduced disease control, more doses are administered than are required, and increased drug costs. Inhaler technique should be checked at least annually or ideally at every visit. Ms Campbell warned that good inhaler technique can relapse and there is a need to check constantly and reinforce good technique. Factors to consider when selecting a device for a particular patient include:

- 1 The patient's cognitive and physical capabilities
- 1 Psychological factors
- 1 Lifestyle
- 1 Convenience, shape and portability of device
- 1 Personal preference
- 1 Stigma and peer pressures

Concluding, she said that collaboration between industry and healthcare professionals in the development of inhaler devices may help to reduce some of the common errors that occur.

### INCIDENCE OF RESPIRATORY DISEASE

Respiratory disease includes over 30 different diseases and is a major cause of morbidity and mortality, said Dr MARK EVERARD, consultant respiratory paediatrician, Sheffield Children's Hospital. It is a huge health and economic burden and is the most common cause for medical consulta-



*Patients may fail to maintain good inhaler use technique and should have their technique checked at least annually*

tion. The cost of respiratory disease to the National Health Service is more than £2.5bn a year. In the United Kingdom, more people die from respiratory disease than from coronary heart disease or cancer.

The three main causes of death from respiratory disease are pneumonia, lung cancer and chronic obstructive pulmonary disease (COPD). Asthma causes less than 2,000 deaths per year, but is a major contribution to morbidity. The total number of patients with asthma in the UK has increased since 1991, although this is partly due to better labelling of disease. Nevertheless, the UK's record in relation to asthma is not good when compared with countries such as Finland where use of dry powder inhalers and inhaled corticosteroids (ICS) is popular. "We should be pushing inhaled steroids if we want to make an impact on asthma", said Dr Everard.

Other important respiratory diseases are cystic fibrosis (CF) and tuberculosis (TB). CF forms a large part of the work of respiratory paediatricians and patients require a complex treatment regimen. The incidence of TB in London has increased by 50 per cent over the last 10 years, partly due to immigration and AIDS. The problem of multi-drug resistance is increasingly important, Dr Everard said.

### NEW INHALED THERAPIES AND THE TREATMENT OF ASTHMA

The cost to the NHS of poorly controlled asthma is more than £850m per year, according to data from the National Asthma Campaign (NAC), said Dr BRIAN O'CONNOR (Guy's, King's and St Thomas' School of Medicine, London). Around half of health care costs associated with asthma arise from the 22 per cent of patients who experience an asthma attack. However, there is no National Service Framework (NSF) for asthma. The burden on primary care is substantial, and the number of deaths per year from asthma is "too many for what is a preventable disease".

The introduction of long-acting beta-agonists (LABAs), such as salmeterol, met with several concerns, such as the perceived implication that the use of LABAs could prevent an asthma attack, and that use of LABAs might mask inflammation.

However, research showed that LABAs given in addition to low- or high-dose ICS reduces asthma exacerbations and that LABAs do not mask inflammation. Nevertheless, ICS remain "the cornerstone" of treatment and LABAs should never be used as monotherapy.

Dr O'Connor showed data suggesting that combination therapy with ICS and LABAs could have complementary effects on tissue inflammatory cells because they act on different pathways. There are several hypotheses that have been put forward to explain the complementary effects of LABAs and ICS, he said. Corticosteroids increase beta-receptor synthesis, and LABAs seem to have the ability to switch on corticosteroid receptors through mechanisms that involve MAP kinase and which are related to the duration of occupancy of the beta-receptor.

Dr O'Connor uses combination therapy with ICS and LABAs to treat patients with persistent asthma. He suggested that, in the future, this combination approach could be contemplated across the range of asthma severity from step 2 upwards.

Dr O'Connor concluded by saying that updated British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines have been drafted and it is hoped that they will be published by the end of the year. — *Contributed by Dr Jo Barnes MRPharmS, School of Pharmacy, University of London*

# Inhaler innovations and the pharmaceutical industry

The pharmaceutical industry is trying to satisfy both patients and regulators as customers, but manufacturers of inhaler devices are sometimes driven by regulators to produce devices that are not necessarily suitable for patients, said Dr ANDY CLARK, Inhale Therapeutic Systems.

There are three types of devices, each of which has slightly different requirements:

- 1 **Nebulisers** Drug in solution
- 1 **Pressurised MDIs** Drug in solution or suspended in a propellant mixture
- 1 **Dry powder inhalers** Drug as powder

Important properties for solutions used in inhalation devices are neutral pH and isotonicity to avoid causing a challenge to the airways. The viscosity and surface tension of the solution are also important as they can affect atomisation. For dry powder inhalers, particles need to be flowable. Spray drying and supercritical fluid precipitation are now beginning to replace solvent crystallisation and micronisation as techniques for producing fine dry powders. Spray drying tends to generate an amorphous material; this can be engineered and allows control of the surface morphology. In this way, the technique offers "some terrific advantages" over other methods, Dr Clark said.

Nebulisers are a popular device for the delivery of inhaled solutions, but delivery efficiency is low — around 50 per cent of the dose is lost in the nebuliser and, of the remaining 50 per cent, half is lost during exhalation. Thus, only around 12 per cent of the dose reaches the lungs and is deposited. There has been some success with developing nebulisers that nebulise only during inhalation, although as a consequence, the time taken to deliver the dose is longer — up to 20 or 30 minutes. New "soft mist" inhalers are being developed in an attempt to deliver the dose more quickly. The dose is taken from a reservoir, and up to 40 per cent can reach the lungs in a short time period.

Moving on to pressurised metered dose inhalers (pMDIs), Dr Clark said that drugs in solution, rather than in suspension, are usually better for delivering a dose to the lungs. However, whether a drug is formulated as a solution or suspension ultimately depends on its physicochemical properties. Concluding, Dr Clark said that inhaler development "is not for the faint hearted". The process probably takes around a decade, and needs "huge commitment and a lot of patience".

## FROM CFCs TO HFAs

The driver for the change from ozone-depleting chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) was the Montreal protocol, said the next speaker Dr PAUL COLTHORPE, 3M Health Care. This legally binding international agreement — to phase out CFCs (by 1996 for developed countries) — was signed in 1987 and now has more than 160 signatures.

CFCs for use in pMDIs continue to receive an "essential use" exemption but, according to Dr Colthorpe, essential use exemptions were never intended to be permanent.

There are several technical challenges involved with the transition to HFA inhalers. Product performance depends on the product valve/container, the formulation and the actuator. "You cannot tinker with any one [of these] without influencing the others", Dr Colthorpe said. In the early 1990s, two HFAs were identified:

- 1 **HFA 134a** Tetrafluoroethane
- 1 **HFA 227** Heptafluoropropane

However, it was "not just a case of substitution" — there are differences in the physicochemical properties of HFAs and CFCs. For example, the dielectric constants of HFAs are greater than those for CFCs.

The industry has been reasonably innovative in overcoming the technical challenges presented by the CFC to HFA transition. There was an explosion of inhalation patents after the Montreal protocol was drafted. Seven HFA pMDIs were launched over the period 1995 to 2001, and others are in development, including HFA pMDIs for new chemical entities, such as tiotropium and ciclesonide, that had not existed in CFC pMDIs. However, these successes have not been achieved without significant cost to the industry. By 1999, around \$1bn (£640m) had been spent developing HFA pMDIs. Considerable further investment, including educational initiatives for health care professionals, is still required.

## THE FUTURE FOR HFA pMDIs

There are several perceived issues relevant to the future of HFA pMDIs. One is that because HFA 227 and HFA 134a are greenhouse gases, at some point, emissions may need to be controlled under the Kyoto climate change protocol. However, the estimated contribution of the pMDI sector to European Union global warming emissions by 2010 is only 0.09 to 0.16 per cent, which Dr Colthorpe said was negligible. He refuted another perceived issue — that HFA pMDIs are not suitable for the delivery of proteins and peptides — saying that there are a lot of encouraging data for the use of HFA pMDIs for the delivery of these substances. Summing up, Dr Colthorpe said: "The future for HFA pMDIs is bright". There has been generation of significant intellectual property during the transition to HFA pMDIs, and significant advances in closure system design and formulation are ongoing.

## DEVICE TRENDS

Up to the late 1980s, trends in device development were relatively unremarkable, compared with the innovation — stimulated by the crisis with CFCs, the increasing inci-

dence of asthma, emergence of COPD, patent termination and development of biotech molecules — that followed in the next decade. According to JOHN BELL, Clinical Designs, improvements in powder technology mean that even simple devices, such as those using drug contained in capsules, may have a new lease of life. An improved pMDI makes user co-ordination easier, but such devices are expensive. Development work with pMDIs has shown that adding non-volatile materials, such as glycerol, to HFAs can shift the particle size distribution. Other devices in development include breath-actuated nebulisers. Delivery of biotech molecules is a potential market. At present, around 97 per cent of biotech molecules are delivered parenterally; pulmonary delivery accounts for only a very small proportion.

Device trends result from adequate technology and marketing effort, but innovation is slowed by regulatory, clinical and cost barriers. There is no new "killer" technology around — powders are still important. It is possible that dry powder inhalers could cannibalise the pMDI market, said Mr Bell.

## MODELLING INHALER BEHAVIOUR

Dr ROB CLAYBOROUGH, Aventis, described an initiative which aims to develop a better understanding of how particles deposit in the respiratory system by creating a validated, predictive model for respiratory deposition and systemic uptake of particles. The Computer-Optimised Pulmonary Delivery in Humans of Inhaled Therapies (COPHIT; [www.scf.tware.aeat.com/cfx/european\\_projects/cophit/index.html](http://www.scf.tware.aeat.com/cfx/european_projects/cophit/index.html)) project is a European Community funded partnership between industry and academia and is due to be completed in March 2003.

The respiratory system has evolved to prevent particles getting into the lungs, Dr Clayborough said. The dimensions of the conductive airways vary during breathing and, in disease, the dimensions of the airways may be altered. Hundreds of other variables affect particle deposition in the lungs, such as device characteristics, user co-ordination and drug formulations. The most cost-effective way to optimise these is to use modelling. The ideal model would incorporate information on device behaviour, drug characteristics, the patient's inhalation profile and so on, and would be able to provide data on particle deposition, systemic uptake and effectiveness.

The consortium has taken a compartmental approach to developing the model and has drawn from several techniques. For example, data from medical imaging were used to create the geometry of the upper respiratory tract, and data from high-resolution computed tomography (CT) scans were used to create the tracheo-bronchial tree. The group is currently investigating ways in which it can further build up the geometry of the respiratory system.