A new regulatory approach to nebuliser testing

A new Pharmacopoeial monograph reflects the changes triggered by the decision of the EMEA (European Medicines Agency) to issue regulatory guidance on the drug delivery aspects of nebulisers. **Mark Copley** from Copley Scientific reviews the monograph

Nebulisers convert liquids into a cloud of droplets suitable for respiration. Unlike other inhalation devices they do not deliver a pre-metered dose and may be used with a range of different drugs, as directed by the prescribing clinician. Consequently, nebulisers are classified as medical equipment rather than pharmaceutical products.

For a number of years nebulisers were tested in accordance with the European Committee for Standardisation (CEN) Standard for Respiratory Therapy Equipment EN 13544-1. In 2006 the EMEA issued guidance which recognised that the safety and efficacy of a nebulised product depends on the nebuliser/drug combination. The proposed monograph (Ph.Eur. Pharmeuropa Vol 18, No 2, April 2006, and USP Pharmacopoeial Forum 32(4) July – August 2006) defines a testing approach similar to that for other inhaled pharmaceuticals, requiring delivered dose uniformity and aerodynamic particle size distribution for each inhaled drug/device combination.

Delivered dose

Unlike other inhalers, nebulisers operate continuously once loaded and activated. User breathing pattern determines the inhalation rate of the drug and ultimately the amount of active delivered to the patient. It is recommended that a breath simulator is used in assessing these aspects of performance.

The new monograph describes tests for Active Substance Delivery Rate and Total Active Substance Delivered. It defines standardised flow conditions, specified to reflect an adult breathing pattern: 500 mL tidal volume; sinusoidal waveform; 15 cycles per minute; 1-to-1 inhalation/exhalation ratio. Other test conditions may be used, for example if

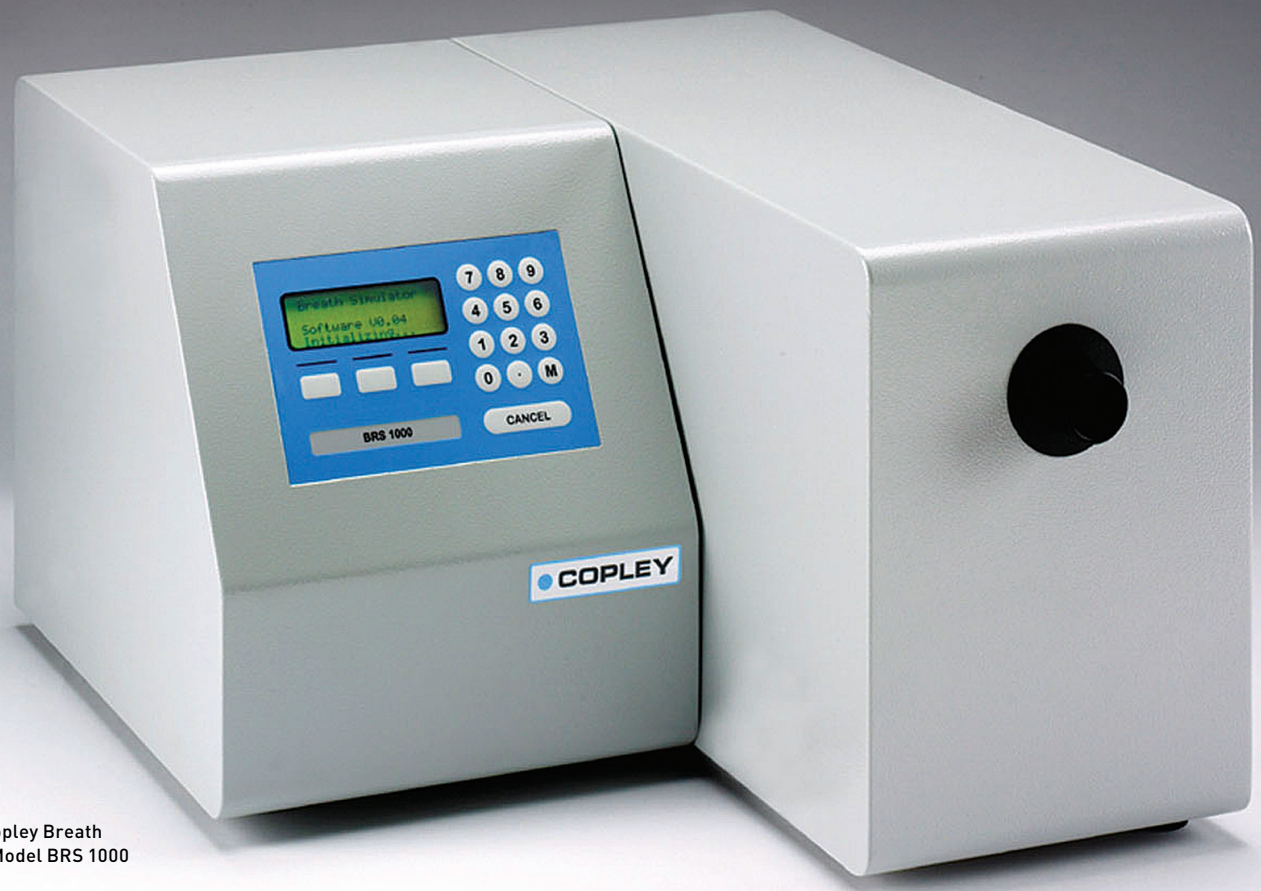

Figure 1: Copley Breath Simulator Model BRS 1000

the drug is specified for paediatric use. Copley Scientific has developed the Breath Simulator Model BRS 1000 (see figure 1) specifically for nebuliser testing. Simple to use, it generates breath profiles in accordance with CEN standard EN 13544-1 and the proposed Ph.Eur. monograph .

Aerodynamic particle size distribution

CEN standard EN 13544-1 specifies the use of a multiple stage cascade impactor to characterise the size of droplets produced during nebulisation. The recommendation is for an instrument with five to eight stages, with calibrated performance at a flow rate not exceeding 15 L/min (typical of the mid-inhalation flow rate of a healthy adult).

In 2002, following the successful development of the Next Generation Pharmaceutical Impactor (NGI), the European Pharmaceutical Aerosol Group (EPAG) launched an initiative to calibrate the NGI's performance at a flowrate of 15 L/min[1]. This extension to the original archival calibration[2] shows that the NGI meets nebuliser testing requirements, and the document provides guidance for use.

In the proposed Pharmacopoeial monograph the test method for Aerodynamic Assessment of Nebulised Aerosols is based on the NGI. The draft monograph addresses a number of issues, including: the possibility with some nebulisers/formulations that the thermal capacity of the impactor can cause evaporation of the droplets during testing; stage over-loading; and re-entrainment.

In conclusion

The new monograph for nebulisers defines test methods for assessing delivered dose, delivery rate and particle size distribution. Breath simulators are specified for accurate characterisation of dose delivery, while the method for particle size measurement is based on the NGI. This new approach harmonises nebulisers with other inhalation products.

References

[1] Next Generation Pharmaceutical Impactor (A new impactor for pharmaceutical inhaler testing). Part II : Archival Calibration. V.Marple *et al.* *Journal of Aerosol Medicine*, Volume 16, Number 3, 2003, p. 301-324

[2] Next Generation Pharmaceutical Impactor: A new impactor for pharmaceutical inhaler testing. Part III. Extension of Archival Calibration to 15 L/min. V.Marple *et al Journal of Aerosol Medicine*, Volume 17, Number 4, 2004, p. 335-343

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