COPLEY SCIENTIFIC

Quality Solutions for Inhaler Testing

2015 EDITION

METERED-DOSE INHALERS • DRY POWDER INHALERS • NEBULISERS • NASAL SPRAYS

Who are Copley Scientific?

Copley Scientific was founded in 1946 in Nottingham, UK by Frank Copley to supply laboratory equipment to the local pharmaceutical industry.

Today, still family owned and managed, we are recognised as the world's leading manufacturer of inhaler test equipment, in addition to being a trusted provider of test instrumentation for other pharmaceutical dosage forms.

This focus on pharmaceutical test instrumentation began in 1957.

Subsequent decades saw marked expansion and today we manufacture a range of innovative equipment for tablet dissolution, disintegration, friability and hardness testing, and for testing creams, ointments, powders, suppositories and transdermal patches.

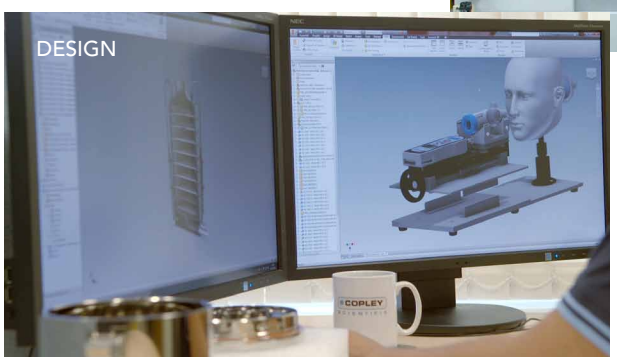
The 1980s saw respiratory drug delivery gain commercial momentum and, in parallel, the development of new solutions for the testing of orally inhaled and nasal drug products (OINDPs).

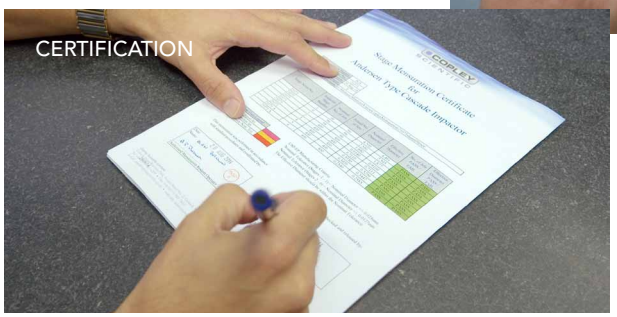
Early success was boosted in 2000, with the signing of a strategic partnership agreement with MSP Corporation which enabled us to become the first company to offer the full range of cascade impactors specified by the European and US Pharmacopoeias for measuring the aerodynamic particle size distribution of all OINDPs.

Our comprehensive range for inhaled product testing now extends to equipment, software and services for every stage of development and manufacture, for both innovator and generic products, topical and systemic.

We continue to work closely with industry groups and leading experts to bring relevant new products to market, with all equipment backed by expert training and lifetime support.

Company headquarters remain in Nottingham, in a purpose-built facility, but we also have a well-established sales and service company in Switzerland and secure partnerships in place to serve a growing number of dynamic international markets.





ISOQAR REGISTERED
UKAS MANAGEMENT SYSTEMS
0026
Certificate Number 7391
ISO 9001

Our Philosophy

Copley Scientific is a strong, stable company with a track record of success, but equally important we are agile and forward-looking, with a philosphy closely aligned to the needs of the market we serve.

Accurate, precise, reproducible data drives pharmaceutical development and ensures product safety, but high productivity in testing is increasingly important.

Equipment that is rugged, robust and simple to use is essential.

To deliver instrumentation with the necessary accuracy and reproducibility hard-wired into its design we adopt the same Quality by Design principles that our customers rely on to control product performance.

Continuous improvement is a core element of this approach and we strive to exceed the expectations of the industry, not only by enhancing equipment performance but also through unrivalled service.

These commitments are exemplified by our investment in the **ISO 9001: 2008 Quality Management System** for which we have certification to the latest standard for all aspects of our business, including equipment design.

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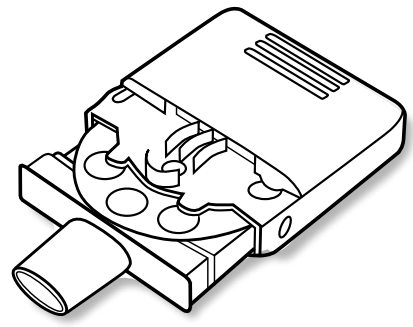
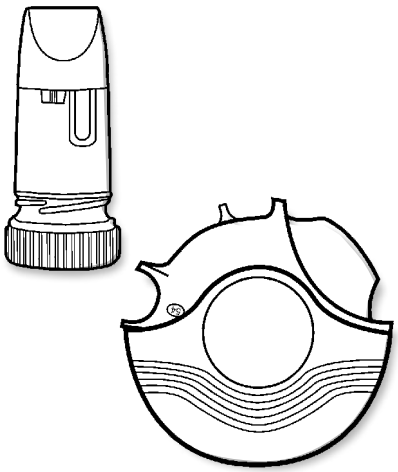
Inhaled Drug Products

INTRODUCTION





The devices used for inhaled and nasal drug delivery are collectively referred to as orally inhaled and nasal drug products (OINDPs).

The range of products available is broad, encompassing inhalers (metered-dose, dry powder and aqueous droplet), nebulisers (jet, ultrasonic and vibrating mesh) and nasal (aqueous based, dry powder and propellant based).

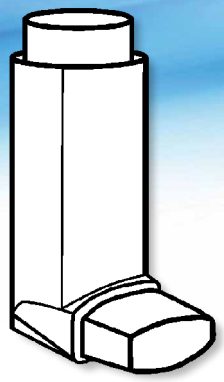
Pressurised metered-dose inhalers (pMDIs or simply MDIs) use a propellant to deliver a fixed volume of liquid solution or suspension to the patient in the form of an aerosol. They are small, inexpensive, convenient for the user and suitable for a wide range of drugs. At the same time, the use of MDIs requires good coordination and technique, and the actuation force needed means they are not always suitable for elderly or paediatric users. Spacers (or valved holding chambers) and new breath-actuated MDIs can resolve these problems.

Dry Powder Inhalers (DPIs) are an attractive option to an industry well used to powder formulations. Typically, the active drug is mixed with an excipient containing much larger particles, for example lactose, to which it attaches. During aerosolisation the active is stripped from the carrier and inhaled whilst the carrier particles impact on the mouth and throat and are ingested. DPIs synchronise drug delivery with inhalation. However, their relatively high cost and reliance on inhalation strength and duration are potential drawbacks.

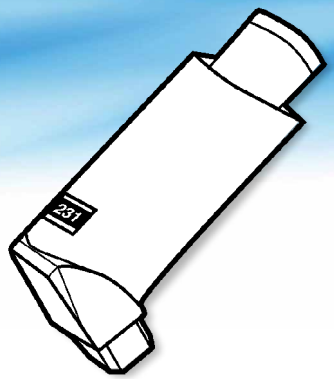
Aqueous droplet inhalers are a new generation of devices that deliver a pre-metered dose of liquid formulation without using a propellant. They actively aerosolise the liquid, producing a "soft mist" of fine particles. These inhalers generally deliver a higher fine particle fraction to the lungs than MDIs or DPIs. As with any multi-dose liquid system, microbial contamination can be a problem.

Nebulisers, like aqueous droplet inhalers, actively aerosolise a liquid formulation. Nebulisers, however, normally operate continuously once loaded. They are widely used at home and in hospital and demand little or no coordination for effective use. The disadvantage is that they tend to be cumbersome and require either compressed air or an electrical supply. New vibrating mesh technology is an improvement, delivering portable, silent battery-operated devices.

Historically used to treat allergic or seasonal rhinitis, there is now increasing interest in the use of **Nasal Sprays** for systemic drug delivery. Like inhalers, nasal sprays can be liquid or powder based. Aqueous systems can be manually actuated or propellant driven. They are commonly multi-dose although unit dose devices are popular for delivering vaccines and pain relief.



Metered-Dose Inhaler (MDI)



MDI incorporating Dose Counter

DRUG DELIVERY DEVICES

APPLICATIONS (LOCAL/SYSTEMIC)

Inhaled drug products are becoming increasingly popular as a means of delivering local or systemic therapy via the lungs or nasal mucosa.

Inhalation therapy has been in use for a number of years:

a) **locally** (directly) to treat lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), and to deliver locally acting drugs such as antibiotics and antivirals directly to the lungs to curb infection, and
b) **systemically** (absorption), for example in pain relief and anaesthetic applications

Pulmonary delivery offers a number of advantages compared to the more traditional oral and parenteral (subcutaneous injection) routes:

- Directly targets the lungs
- Rapid onset of drug action
- Drugs effective in relatively low doses
- Fewer side effects
- Avoids hepatic metabolism
- Injection-free administration

More recently, considerable research and development has been devoted to delivering new drugs to the systemic circulation via the inhaled route – no doubt attracted by the large surface area and easy air/blood interface provided by the respiratory system.

Such drugs include treatments for for diverse applications including **diabetes, erectile dysfunction, migraine, osteoporosis and for vaccine delivery.**

DRUG DELIVERY DEVICES

Collectively described as **orally inhaled and nasal drug products (OINDPs),** these can be divided into the following categories:

1. Metered-Dose Inhalers (MDIs)

Whilst there are non-pressurised MDIs on the market, this term is normally reserved to describe the pressurised version of the inhaler (pMDI) so familiar to people with asthma.

The pMDI comprises a pressurised canister containing the medication and propellant, together with a delivery device – normally a metering valve linked to an actuator. Pressing down on the canister releases the drug in the form of an aerosol cloud – this is then inhaled into the lungs.

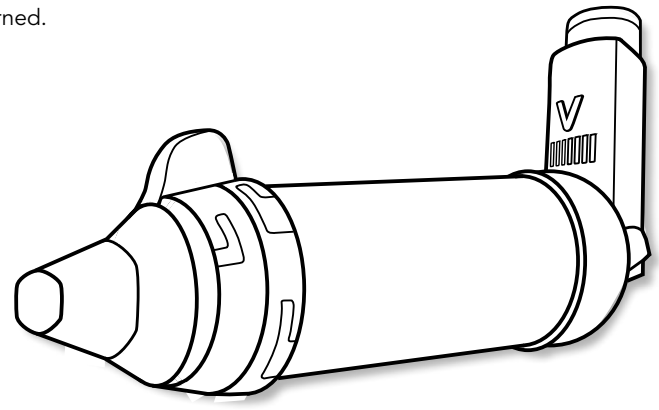
The pMDI is convenient, rugged and cheap to manufacture. It works well with the bronchodilators and corticosteroids traditionally used to treat respiratory disorders because of the potency and wide therapeutic window of the drugs concerned.

Comparatively recent developments have seen the replacement of the traditional CFC (chlorofluorocarbon) propellants with more ozone friendly and efficient alternatives in the form of hydrofluroalkane (HFA) propellants, and the incorporation of dose counters into the pMDI.

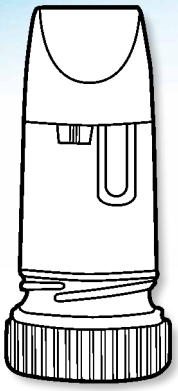
Patient coordination of actuation with inhalation can be a problem with pMDIs, particularly in the young, old or chronically ill.

Breath-Actuated MDIs seek to overcome this problem by sensing the patient's inhalation through the actuator and synchronising dose delivery with it.

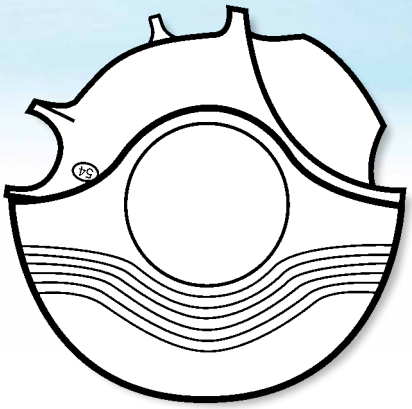
Other methods of overcoming this problem include **Add-on Devices** such as **Spacers** and **Valved Holding Chambers (VHCs)** which reduce or eliminate the need for coordination between actuation and inhalation together with the cold freon effect that is often the cause of the problem.



MDI with Valved Holding Chamber (VHC)



Dry Powder Inhaler - Passive Type (device metered)



Dry Powder Inhaler - Passive Type (pre-metered)

DRUG DELIVERY DEVICES

2. Dry Powder Inhalers (DPIs)

Historically, the DPI was limited to single dose capsule systems and the inhaler market was dominated by the chlorofluorocarbon (CFC) propelled MDI.

When, in 1997, the Montreal Protocol effectively banned the ozone depleting CFCs, the pharmaceutical industry was faced with the option of:

a) finding an alternative propellant (as in the HFA propelled MDI), or
b) developing new ways of delivering drug to the lungs

It is the latter that has provided a resurgence of interest in the DPI. As the name suggests, in the DPI the medication comes in the form of a dry powder.

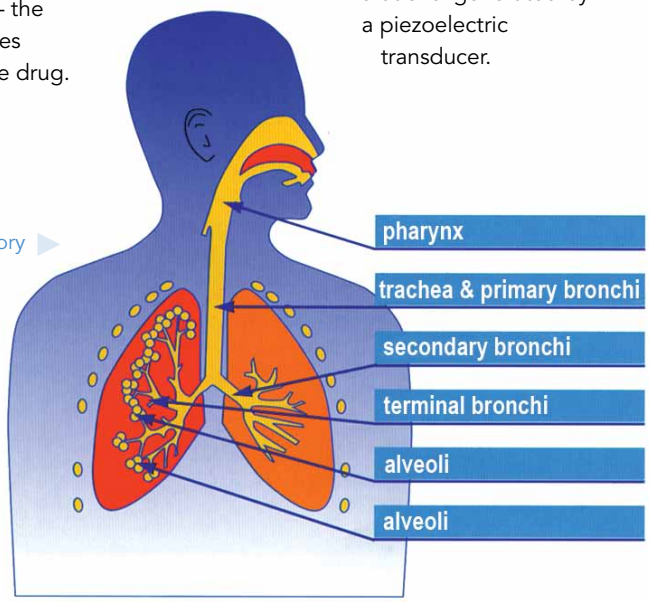
The majority of DPIs are **passive** devices, that is to say they rely on the patient's inspiration to operate. There is no need to coordinate breathing with the activation – the patient simply inhales deeply to access the drug.

The passive DPI can be sub-divided into two categories:

a) **pre-metered** (single or multi-dose) where the dose is pre-measured during manufacture as, for example, blisters, capsules or similar cavities
b) **device metered** where the drug is contained in a reservoir within the device which pre-measures each dose on actuation

Some DPIs have devices for assisting the patient's inspiration whilst simultaneously improving the accuracy and reproducibility of the delivered dose.

Such devices are normally termed **active** DPIs and are particularly useful where the patient's own inspiration capability is compromised. Assistance normally comes in the form of pressurised/compressed air or through vibrations generated by a piezoelectric transducer.



The Human Respiratory System

3. Aqueous Droplet Inhalers (Solution Metering Inhalers)

Both Metered-Dose (MDIs) and Dry Powder Inhalers (DPIs) suffer from the same two inherent problems: low lung deposits (typically 5-20%) and dose variability (often due to patient difficulties in coordination or inspiration).

Aqueous Droplet Inhalers (often known as **"Solution Metering"** or **"Soft Mist"** Inhalers), are a new generation of inhaler designed to overcome these problems.

The Aqueous Droplet Inhaler is effectively a propellant-free Metered-Dose Liquid Inhalers (MDLIs) sharing the following common characteristics:

- Precision-dosed liquid-based metering (normally water or ethanol)
- "Active" aerosol generation (mechanical or electromechanical)
- Patient-independent, accurate and reproducible dosing
- High fine particle fraction
- Require sterile production and addition of bacteriostatic agents to prevent microbial contamination in the case of multi-dose solution reservoirs

Methods of aerosol generation vary: (a) forcing liquid through nozzles, (b) electrospraying, (c) thermal generation, and (d) vibration mesh all being typical examples.

As far as testing is concerned, most **Aqueous Droplet Inhalers** are treated as MDIs unless their particular design dictates otherwise.

DRUG DELIVERY DEVICES

4. Nebulisers

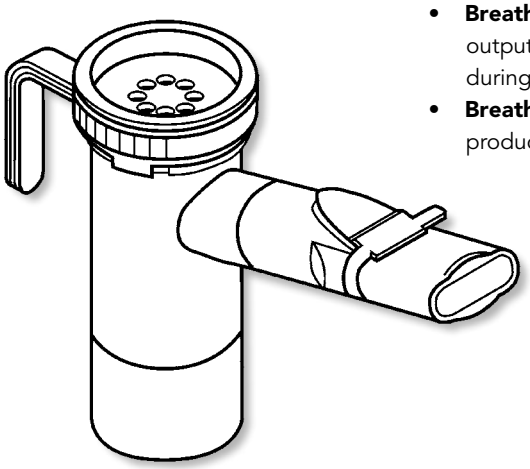
A nebuliser may be defined as a device that can convert a liquid into aerosol droplets to produce a respirable cloud suitable for inhalation.

Normally it must be loaded with the drug before each treatment. Once activated it operates on a continuous basis.

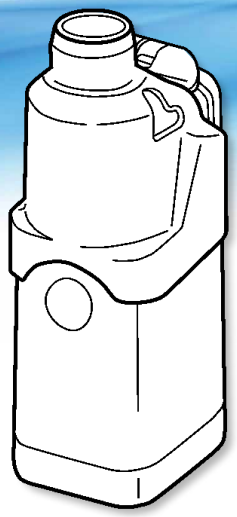
It should not be confused with the Aqueous Droplet Inhaler described in the preceding section which delivers a **pre-metered dose** or bolus of medication.

This difference is important since the regulatory bodies have traditionally classified nebulisers as medical equipment. This is regulated differently, and hitherto less stringently, than the other drug delivery devices described in this brochure which are classified as pharmaceuticals.

Conventional nebulisers are widely used in both hospital and home. Their main advantage is that unlike other devices, they require little or no coordination on the part of the patient in order to use them.



Jet Nebuliser



Ultrasonic Nebuliser

Their disadvantages include their size and weight (a compressed air or electrical supply is normally required for operation), expense, inefficiency and inter-brand variability.

Conventional nebulisers fall into two categories, namely **Jet** and **Ultrasonic.**

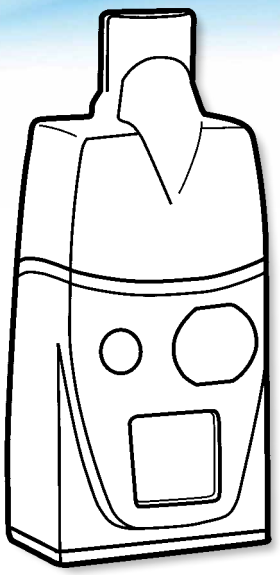
More recent years have seen the introduction of a new wave of portable nebulisers based on **Mesh** technology.

a) Jet Nebulisers

Jet Nebulisers use a compressed air supply to atomise liquid drug to produce a fine mist using the Bernoulli principle.

The Jet Nebuliser itself can be sub-divided into three types depending on their output during exhalation:

- **Standard** – constant output throughout the respiratory cycle
- **Breath-Enhanced** – constant output but provides higher output during inhalation
- **Breath-Actuated** – aerosol produced only during inhalation



Mesh Nebuliser

b) Ultrasonic Nebulisers

Ultrasonic Nebulisers use electricity to vibrate a piezoelectric crystal at high frequency.

The resultant vibrations are transmitted to a reservoir containing the liquid drug, creating a series of waves from which liquid droplets separate to form an aerosol.

c) Mesh Nebulisers

A new generation of portable, efficient, silent, battery operated nebulisers based on vibrating mesh technology has recently been introduced to the market.

Mesh nebulisers use the ultrasonic principle to generate droplets which are then pushed through a static or vibrating mesh or plate (either electro-formed or laser drilled) to form a cloud prior to inhalation.

Some mesh nebulisers incorporate sensing devices to detect the patient's inspiration in order to provide **breath enhanced, breath activated** or **breath integrated** systems.

DRUG DELIVERY DEVICES

5. Nasal Delivery Systems

Traditionally, nasal preparations have been used for the local administration of anti-histamines, decongestants and steroids in order to alleviate cold or allergy symptoms and nasal congestion.

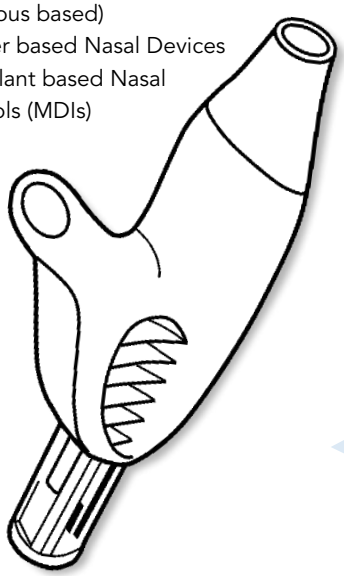
More recently attention has focused on two other areas:

a) The potential rapid drug absorption into the **systemic circulation** provided by the turbinates and lymphoid tissues located at the back of the nasal cavity. This is already in use in a number of areas, e.g. migraine and pain relief, osteoporosis, vaccines, etc., and

b) The potential of the "Nose to Brain" entry to the **central nervous system** presented by the olfactory region at the top of the nasal cavity for the treatment, for example, of diseases of aging such as Alzheimers Disease, etc.

Conventional nasal technologies fall into three main categories:

- Metered Spray Pumps (Aqueous based)
- Powder based Nasal Devices
- Propellant based Nasal Aerosols (MDIs)



Powder based Nasal Device

Metered Nasal Spray Pump

a) Metered Spray Pumps (Aqueous based)

Mechanical Metered-Dose Spray Pumps have largely replaced droppers and squeeze bottles as the drug delivery of choice because of the latter's inability to deliver an accurate and consistent dose.

Hitherto, **multi-dose** spray pumps have dominated the nasal market and are widely available through a number of device manufacturers.

Unit dose devices that deliver one or two shots (one per nostril), usually based on the syringe principle, are also becoming increasingly popular for delivering certain drugs, e.g. pain relief and vaccines.

Where drugs are formulated as aqueous solutions or suspensions then undesirable preservatives are normally added to prevent microbiological contamination. This problem can also be addressed by using unit dose devices.

b) Powder based Nasal Devices

Available in both multi- and unit-dose formats, powder based devices provide another solution to preservative-free delivery and can produce longer nasal retention times than liquids.

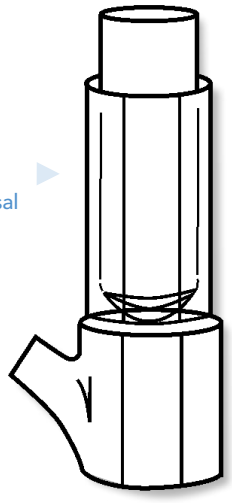
Powder based nasal sprays are ideal for peptides, hormones and antigens (more stable) and where high dose concentrations are required and can be produced using conventional manufacturing techniques.

c) Propellant based Nasal Aerosols (MDIs)

Pressurised Metered-Dose Inhaler (MDI) technology provides another method of delivering drug to the nasal mucosa. Similar to a regular MDI for oral use, a Propellant based Nasal Aerosol usually features a nosepiece (nozzle) designed at an angle for insertion into the nostril.

d) Novel Nasal Devices

Two examples of novel drug delivery systems starting to receive attention are (a) a bi-directional nasal device which uses the body's natural reaction to close the soft palate whilst exhaling to prevent lung deposition and (b) a nebuliser using ampoules employing "controlled particle dispersion" to dispense the drug.



Propellant based Nasal Aerosol

Organisations and their roles

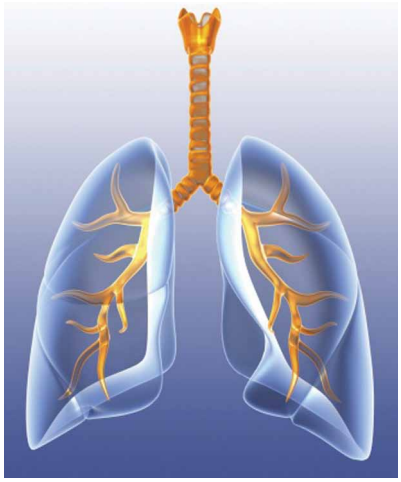
INTRODUCTION

The ultimate responsibility for the safety, quality and efficacy of medicines and medical devices lies with the various national regulatory bodies designated to safeguard public health.

In Europe and in the USA this function is performed by the **European Medicines Agency (EMA)** and by the **Food and Drug Administration (FDA)** respectively.

The regulatory authorities are supported in this role by:

a) the **Pharmacopoeias** whose job is to define the standards with which the drug formulation shall comply and the methods by which compliance will be adjudged, and



b) in the case of OINDPs, by the **International Standards Organisation (ISO)** whose function is to define the standards and methods relating to the medical device, e.g. inhaler, nebuliser, etc., concerned.

In 2002 the FDA launched a new initiative "Pharmaceutical cGMPs for the 21st Century" in which it proposed a new risk-based approach to pharmaceutical manufacturing.

This initiative gave birth to **Process Analytical Technology (PAT)**, a framework for understanding and improving the processes involved in Pharmaceutical Development, Manufacturing and Quality Control, described in FDA's Guidance of September 2004.

PAT operates on the premise that quality cannot be tested into products; rather, it should be built-in or should be by design.

The goal is to ensure final product quality by understanding and controlling the processes involved in the manufacturing operation.

The **Quality by Design (QbD)** approach agreed and recently recommended for adoption by the EMA, FDA and the Japanese MWHL in the form of the five quality related guidelines, ICH Q8, Q9, Q10, Q11 and Q12 published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), extends this philosophy to all parts of the product cycle from product development, transfer through to manufacturing, manufacturing and finally product end.

ICH Q8 Pharmaceutical Development describes the suggested contents of a regulatory submission based on the QbD format.

ICH Q9 details a systematic approach to quality risk management whilst ICH Q10 describes a new quality management system based on the complete product lifecycle and referred to as the Pharmaceutical Quality System.

ICH Q11 provides a Guideline to the "Development and Manufacture of Drug Substances" including the type and extent of information to be submitted in regulatory dossiers.

Finally, ICH Q12 (final concept stage) is intended to work with ICH Q8-Q11 guidelines to provide a framework to facilitate the management of the entire "Pharmaceutical Product Lifecycle" focusing particularly on the Commercial Manufacturing phase.

GUIDELINES AND REGULATIONS

Regulatory Draft	Metered-Dose Inhaler (MDI)	Dry Powder Inhaler (DPI)	Aqueous Droplet Inhaler	Nasal Spray (Aqueous)	Nebuliser
EMA Guidelines	Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (2006)				
EMA Guidelines	Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence between Two Inhaled products for use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for the use of Asthma in Children and Adolescents (2009)				
FDA Guidance for Industry (Chemistry, Manufacturing & Controls Documentation)	Metered-Dose Inhaler (MDI) & Dry Powder Inhaler (DPI) Drug Products (1998) - Draft				
FDA Guidance for Industry (Chemistry, Manufacturing & Controls Documentation)				Nasal Spray, Inhalation Solution, Suspension & Spray Drug Products (2002)	
				Nasal Aerosols and Nasal Sprays for Local Action (2003) - Draft	
Drug Efficacy					
European Pharmacopoeia 2014 (8th Edition)	Preparations for Inhalations (Dosage Forms 0671) Aerodynamic Assessment of Fine Particles (Chapter 2.9.18)			Nasal Preparations (Dosage Forms 0676)	Preparations for Nebulisation (Chapter 2.9.44)
US Pharmacopeia 2015 (USP 38)	Inhalation & Nasal Drug Products - General Information & Product Quality Tests <5> Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry Powder Inhalers <601> Uniformity of Dosage Units <905> Pharmaceutical Dosage Forms (Aerosols - Inhalations) <1151>				Products for Nebulization <1601>
	Spacers & VHCs <Draft 1602>				
Device Efficacy					
International Standards Organisation	Aerosol Drug Delivery Devices - Requirements and test methods (ISO 20072: 2013)				Nebulizing Systems (ISO 27427: 2013)
Expert Groups					
European Pharmaceutical Aerosol Group (EPAG)	EPAG European based industry expert group involved in orally inhaled and nasal drug products				
International Pharmaceutical Consortium on Regulation & Science (IPAC-RS)	IPAC-RS US based industry expert group involved in orally inhaled and nasal drug products				
Product Quality Research Institute (PQRI)	PQRI A collaborative research organisation involving FDA's CDER, industry and academia				

ORGANISATIONS INVOLVED IN OINDPs

1. REGULATORY BODIES IN THE EUROPEAN UNION, JAPAN AND USA

At present, there are no worldwide standards that are specifically applicable to OINDPs.

In Europe, the ultimate responsibility for the regulation of medicines and medical devices lies with the **European Medicines Agency (EMA)** in the form of the Committee for Medicinal Products for Human Use (CHMP).

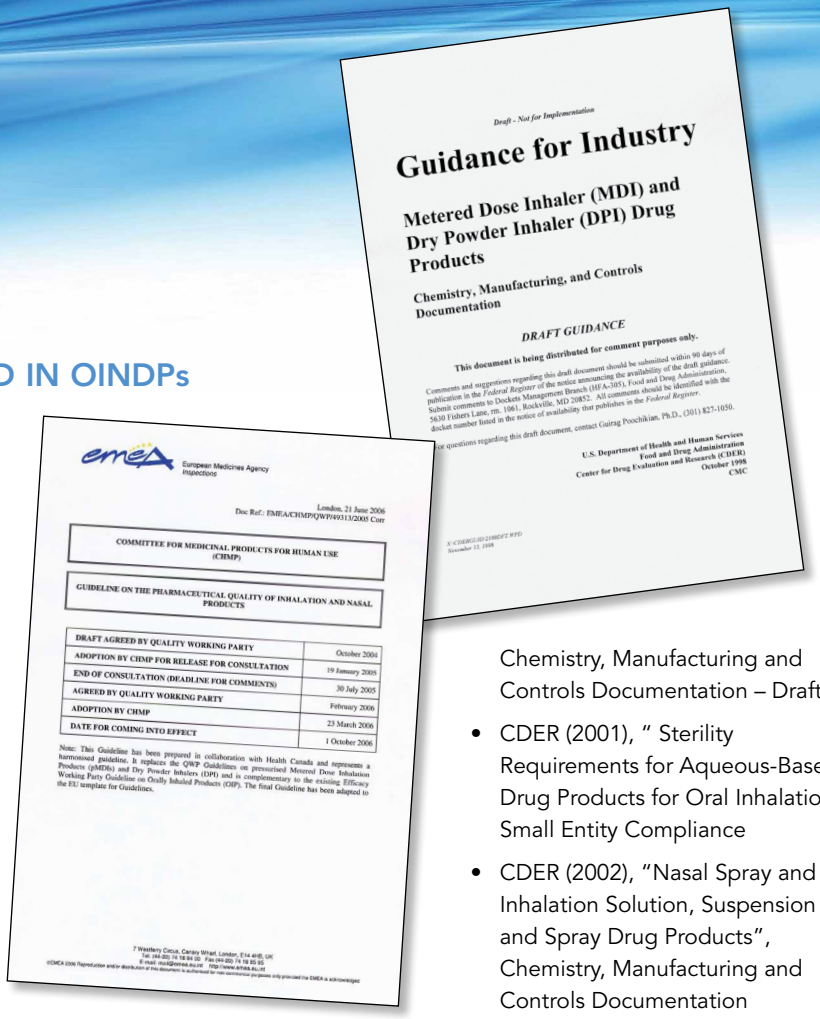
The EMA was set up in 1995 to harmonise the work of existing national regulatory bodies in Europe.

The main guidance from the EMA relating to OINDPs is contained in two guidelines:

- CPMP (2006), "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products"
- CPMP (2009), "Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents"

These guidelines give a comprehensive list of the parameters that should be taken into account dependent on the specific type of inhaled or nasal product concerned.

The parameters are limited to those that specifically relate to inhaled products and which are critical to the safety, quality and efficacy of the final product.


Draft - Not for Implementation

Guidance for Industry

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

Chemistry, Manufacturing, and Controls Documentation

DRAFT GUIDANCE

This document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1998
CMC

emea
European Medicines Agency
Inspections

London, 21 June 2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

DRAFT AGREED BY QUALITY WORKING PARTY	October 2004
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 January 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 July 2005
AGREED BY QUALITY WORKING PARTY	February 2006
ADOPTION BY CHMP	23 March 2006
DATE FOR COMING INTO EFFECT	1 October 2006

In the USA, the regulatory function is performed by the **Food and Drug Administration (FDA)** through two centers, the Center for Drug Evaluation and Research (CDER) in respect of medicines and the Center for Devices and Radiologic Health (CDRH) in respect of medical devices.

The relevant current thinking from the FDA is reflected in the following regulatory Guidelines for industry:

- CDER (1998), "Metered-Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products", Chemistry, Manufacturing and Controls Documentation – Draft
- CDER (2001), " Sterility Requirements for Aqueous-Based Drug Products for Oral Inhalation", Small Entity Compliance
- CDER (2002), "Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products", Chemistry, Manufacturing and Controls Documentation
- CDER (2003), "Integration of dose-counting mechanisms into MDI products", Clinical Medical
- CDER (2003), "Bioavailability and bioequivalence studies for nasal sprays for local action", Biopharmaceutics – Draft

Since December 2013, the FDA has issued a series of product specific guidances relating to various actives including **fluticasone propionate** and **salmeterol** intended to help generic manufacturers navigate the Abbreviated New Drug Application process (see Pages 100 - 102).

ICH Quality Guidelines	
Q1A - Q1F Stability	Q7 - Good Manufacturing Practice
Q2 - Analytical Validation	Q8 - Pharmaceutical Development
Q3A - Q4B Impurities	Q9 - Quality Risk Management
Q4 - Q4B Pharmacopoeias	Q10 - Pharmaceutical Quality System
Q5A - Q5E Quality of Biotechnological Products	Q11 - Development and Manufacture of Drug Substances
Q6A - Q6B Specifications	Q12 - Lifecycle Management

ORGANISATIONS INVOLVED IN OINDPs

2. INTERNATIONAL REGULATION AND HARMONISATION

The **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** is a unique organisation consisting of representatives from the regulatory authorities in the European Union (EMA), Japan (MHLW) and the USA (FDA), and experts from the pharmaceutical industry in the three regions, in a single forum.

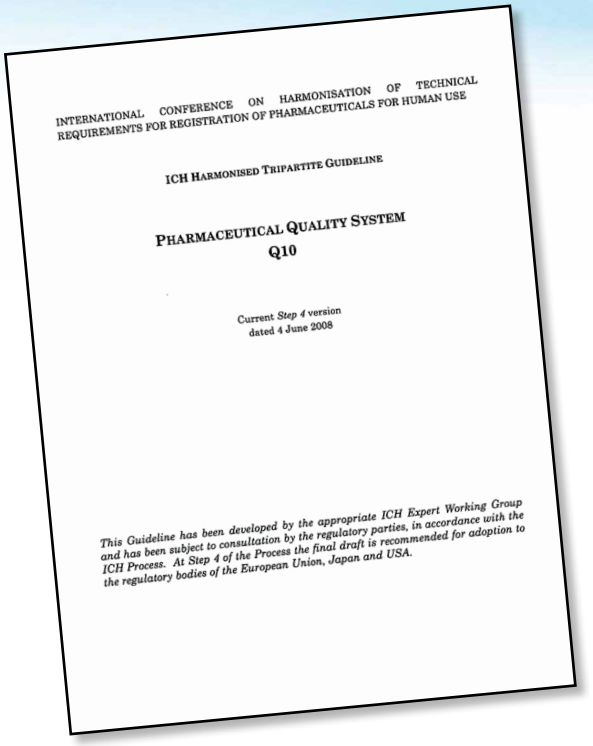
The purpose of the ICH is to promote greater harmonisation in the way in which the individual regulatory bodies regulate new drugs such that the medicine reaches the patient economically and with the minimum delay whilst maintaining the standards of safety, quality and efficacy necessary to safeguard public health. (Note: A similar organisation, the **Global Harmonisation Task Force (GHTF) exists for medical devices).**

Whilst not OINDP specific, over the past few years, ICH has concentrated on the preparation of four new quality related guidelines:

- ICH Q8(R2) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- ICH Q11 Development and Manufacture of Drug Substances

all of which have now been recommended for adoption by the regulatory authorities concerned (EMA. FDA and MHLW).

Collectively, these provide the guidelines for a new Pharmaceutical Quality System (PQS) described in ICH Q10. Based on International Standards Organisation (ISO) quality concepts, the new system includes Good Manufacturing Practice (GMP) regulations where applicable and complements ICH Q8 and ICH Q9.



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current *Step 4* version
dated 4 June 2008

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

One of the key features of the new PQS is the decision to extend the system to include all parts of the product lifecycle, namely:

- Pharmaceutical Development
- Technology Transfer, e.g. from development to manufacturing
- Manufacturing
- Product Discontinuation

This decision to extend the PQS to include Pharmaceutical Development through a concept known as **Quality by Design (QbD)** is described in more detail in ICH Q8(R2) Part II Pharmaceutical Development – Annex.

The ICH Q8(R2) Annex describes the principles and gives examples of many of the essential concepts employed in QbD including **Critical Quality Attributes (CQAs),** Design Space and Control Strategy and its implementation through **Process Analytical Technology (PAT)** Tools.

ICH Q9 describes the principles of quality risk management and their application in a pharmaceutical environment.

ICH Q10 provides a model PQS covering the different stages of a product life cycle and thus a link between pharmaceutical development and manufacturing. As a guideline, ICH Q10 is not enforceable – however, it is likely that the regulators will consider it as standard best practice.

The practical implementation of the guidelines with respect to OINDPs is not easy because of (a) the complexities involved in manufacturing inhalation products, (b) the difficulties in applying real time test methods to them, and (c) the lack of clear *in vitro – in vivo* correlations for most formulations. This continues to be an area of considerable discussion in pharmaceutical development, quality and regulatory circles.

ICH Q11 provides a Guideline to the "Development and Manufacture of Drug Substances" including the type and extent of information to be submitted in regulatory dossiers.

Finally, mention should be made of ICH Q12 currently in conceptual stage but which when completed is intended to work with ICH Q8-Q11 guidelines to provide a framework to facilitate the management of the entire "Pharmaceutical Product Lifecycle".

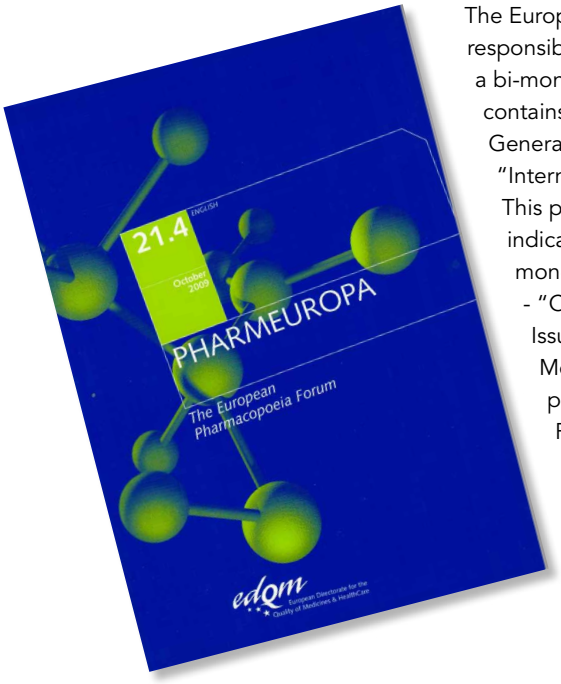
Current Ph.Eur.

ORGANISATIONS INVOLVED IN OINDPs

3. DRUG SAFETY, QUALITY AND EFFICACY – THE PHARMACOPOEIAS

The main role of the Pharmacopoeias is to define the standards with which medicines shall comply and the methods by which compliance will be adjudged.

As with the regulatory groups, the leading Pharmacopoeias tend to be those of the European Union, Japan and USA.



Pharmeuropa

a) European Pharmacopoeia

In the **European Pharmacopoeia (Ph. Eur.)**, the initial information relating to the control of OINDPs is contained in the monograph relating to the dosage form concerned, e.g. Preparations for Inhalation (0671) with cross references to appropriate methods of testing, e.g. 2.9.18. Preparations for Inhalation: Aerodynamic Assessment of Particles.

The European Pharmacopoeia is also responsible for "**Pharmeuropa**", a bi-monthly publication which contains "Draft Monographs and General Texts for Comment" and "International Harmonisation". This publication is a good indicator of new and/or amended monographs, e.g. - "Calibration and Mensuration Issues for the Standard and Modified ACI" Vol.12.4, p.584-588 (2000) - "2.9.44 Preparations for Nebulisation: Characterisation" Vol. 18.2, p.280-283 (2006).

b) United States Pharmacopeia

Hitherto, the **United States Pharmacopeia (USP)** has adopted a similar approach but placed more emphasis on the Physical Tests and Determinations, e.g. Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry Powder Inhalers <601> than the type of dosage form, e.g. Pharmaceutical Dosage Forms <1151>.

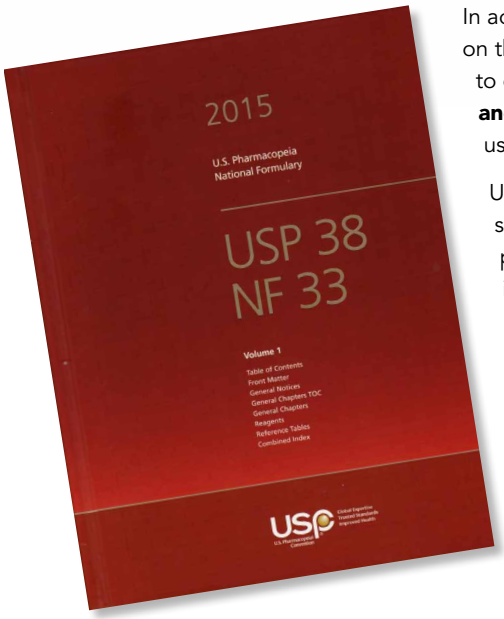
However, in USP 38 the Pharmacopeia has introduced a series of new chapters, <1> through to <5>, which provide general information and the critical quality attributes applicable to the various dosage forms based on their route of administration.

The five chapters concerned detail the test procedures relevant to each dosage form, divided between those relating to product **quality** and those to product **performance**.

Product **quality** tests assess physical, chemical and microbial attributes. Product **performance** tests assess drug release from the dosage form concerned.

In the case of "Inhalation and Nasal Drug Products", the quality tests are described in Chapter <5> whereas the performance tests are described in Chapter <601>.

Both Ph.Eur. (2.9.44) and USP <1601> now include chapters on tests designed to characterise those products used for nebulisation.

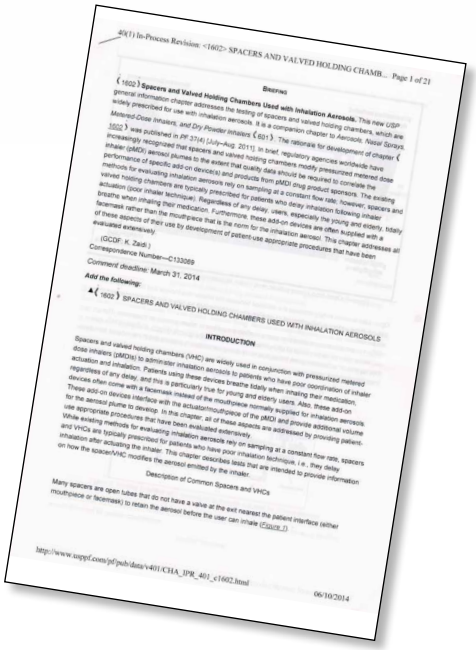


In addition, USP are currently working on the draft of a new Chapter <1602> to cover the testing of the **Spacers and Valved Holding Chambers** used with Inhalation Aerosols.

USP have also taken the unusual step of introducing a series of product-specific monographs intended to assist the developers of generic inhaled drugs call for the clarification of the testing of such generics not specifed in the more general chapters (see Pages 100-102).

◀ Current USP

USP Draft Chapter <1602> ▶


4(01) In-Process Revision: <1602> SPACERS AND VALVED HOLDING CHAMB... Page 1 of 21

Biorims

〈1602〉 **Spacers and Valved Holding Chambers Used with Inhalation Aerosols.** This new USP general information chapter addresses the testing of spacers and valved holding chambers, which are widely prescribed for use with inhalation aerosols. It is a companion chapter to Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers 〈601〉. The rationale for development of chapter 〈1602〉 was published in PF 37(4) [July–Aug. 2011]. In brief, regulatory agencies worldwide have increasingly recognized that spacers and valved holding chambers modify pressurized metered dose inhaler (pMDI) aerosol plumes to the extent that quality data should be required to correlate the performance of specific add-on device(s) and products from pMDI drug product sponsors. The existing methods for evaluating inhalation aerosols rely on sampling at a constant flow rate; however, spacers and valved holding chambers are typically prescribed for patients who delay inhalation following inhaler actuation (poor inhaler technique). Regardless of any delay, users, especially the young and elderly, totally breathe when inhaling their medication. Furthermore, these add-on devices are often supplied with a facemask rather than the mouthpiece that is the norm for the inhalation aerosol. This chapter addresses all of these aspects of their use by development of patient-use appropriate procedures that have been evaluated extensively.

(GCDF: K. Zaidi)

Correspondence Number—C133089

Comment deadline: March 31, 2014

Add the following:

▲〈1602〉 SPACERS AND VALVED HOLDING CHAMBERS USED WITH INHALATION AEROSOLS

INTRODUCTION

Spacers and valved holding chambers (VHC) are widely used in conjunction with pressurized metered dose inhalers (pMDIs) to administer inhalation aerosols to patients who have poor coordination of inhaler actuation and inhalation. Patients using these devices breathe totally when inhaling their medication, regardless of any delay, and this is particularly true for young and elderly users. Also, these add-on devices often come with a facemask instead of the mouthpiece normally supplied for inhalation aerosols. These add-on devices interface with the actuator/mouthpiece of the pMDI and provide additional volume for the aerosol plume to develop. In this chapter, all of these aspects are addressed by providing patient-use appropriate procedures that have been evaluated extensively.

While existing methods for evaluating inhalation aerosols rely on sampling at a constant flow rate, spacers and VHCs are typically prescribed for patients who have poor inhalation technique, i.e., they delay inhalation after actuating the inhaler. This chapter describes tests that are intended to provide information on how the spacer/VHC modifies the aerosol emitted by the inhaler.

Description of Common Spacers and VHCs

Many spacers are open tubes that do not have a valve at the exit nearest the patient interface (either mouthpiece or facemask) to retain the aerosol before the user can inhale (Figure 1).

http://www.uspnf.com/pf/pub/data/v401/CHA_IPR_401_c1602.html 06/10/2014

NEW USP 38 CHAPTERS <1> TO <5>

ROUTE OF ADMINSTRATION	Site of Release	Typical Dose Forms	Product Tests for QUALITY	Product Tests for PERFORMANCE
Injections & Implanted Drug Products (Parentals) Draft Chapter <1>	Body tissues and fluids	Injections, particles, liposomes, implants, stents	<1>	<1001> Under development
Oral Drug Products Chapter <2>	Oral	Tablets and Capsules, Liquids	<2>	<701> <711>
Topical and Transdermal Drug Products Chapter <3>	Skin	Semisolids, Transdermal Patches	<3>	<724> <1724>
Mucosal Drug Products Chapter <4>	Ear, eye, nose, throat, urether, vagina, rectum	Various see <4>	<4> Under development	<1004> Under development
Inhalation and Nasal Drug Products Chapter <5>	Lung, nasal cavity	Aerosols, sprays, powders	<5>	<601>, <602> <603>, <604> <1601>, <1602>

Pharmacopeial Forum

Like Ph.Eur., USP produce a bi-monthly publication which contains discussion documents relating to new and/or amended chapters and monographs. "Pharmacopeial Forum" features items relating to "In-Process Revision", "Harmonisation" and "Stimuli to the Revision Process", e.g.

- "Verification of Operating the Andersen Cascade Impactor at Different Flow Rates" Vol. 22(2), p. 2211-2215 (1996)
- "ACI: Procedure for Powder Inhalers: Modified Configuration" Vol. 28(2) p. 601-603 (2002)

4. DEVICE SAFETY, QUALITY AND EFFICACY - ISO

Most orally inhaled and nasal drug products (OINDPs) are unique dosage forms in so far as that they comprise two components:

(a) The drug formulation

(b) The medical device delivering that formulation to the patient

The responsibility of defining the standards relating to the medical device resides with the **International Standards Organisation (ISO).**

The relevant standards are "ISO 20072 Aerosol drug delivery device verification – Requirements and test methods" for Inhalers and "ISO 27427 Anaesthetic and respiratory equipment – Nebulising Systems and Components" for nebulisers.

5. EXPERT GROUPS

In addition to the above, there are a number of industry and quasi-industry expert groups whose role is to assist the regulatory bodies in establishing best practice in their thinking and guidance.

- **European Pharmaceutical Aerosol Group (EPAG)**

A group of 20 member companies active in the OINDP market within Europe formed to establish scientifically based best practice, provide consensus comment to industry and government agencies on safety and quality issues and recommend harmonised standards and methodology.

EPAG
European Pharmaceutical Aerosol Group

- **International Pharmaceutical Consortium on Regulation and Science (IPAC-RS)**

A group of 19 international companies including suppliers, that is committed to advancing consensus-based, scientifically driven standards and regulations for orally inhaled and nasal drug products worldwide.

IPAC-RS

- **Product Quality Research Institute (PQRI)**

PQRI is a collaborative organisation involving FDA's CDER, industry and academia. A research organisation, it was formed to provide consensus advice on the scientific information to be submitted in a regulatory filing to CDER and has been involved in a number of OINDP related products.

CURRENT PHARMACOPOEIAL SPECIFICATIONS

As can be seen from the preceding pages, there are many advantages to using inhaled drugs for targetting the lungs or nasal mucosa as a means of providing local or systemic therapy.

These advantages have led to a growing number of new types of device designed to provide the accuracy and sophistication necessary to deliver the drugs concerned.

Other challenges have presented themselves over the last few years involving drug delivery device changes, not least the ban on ozone depleting chlorofluorocarbons (CFCs) used as propellants in MDIs and the incorporation of dose counters into multi-dose devices.

The regulatory bodies (EMA, FDA, MHWL, ICH and others) are constantly evolving their requirements (both in terms of pharmaceutical development and manufacture) to meet the challenges of these new technologies and to ensure their safety, quality and efficacy in the global marketplace.

This effort has been matched by the Pharmacopoeias whose role it is to lay down suitable quality standards and test methods to meet the regulatory requirements and to harmonise their approach to the *in vitro* testing of these devices.

Apart from the mandatory testing for leachables, extractables and microbial contaminants, two of the main factors largely recognised as Critical Quality Attributes (CQAs) in the testing of OINDPs (in both pharmaceutical development and batch release) are:

- **Delivered Dose (Emitted Dose)**

The total amount of drug emitted from the drug device and hence available to the user and

- **Particle Size (Aerodynamic Size Distribution)**

The size of the particles or droplets that make up the emitted aerosol cloud. Particle size determines the percentage of the total emitted dose that actually reaches the lungs or nasal mucosa during inhalation and is thus, therapeutically effective.

These two physical tests form the basis of many of the parameters used by the regulators to characterise inhalation and nasal products.

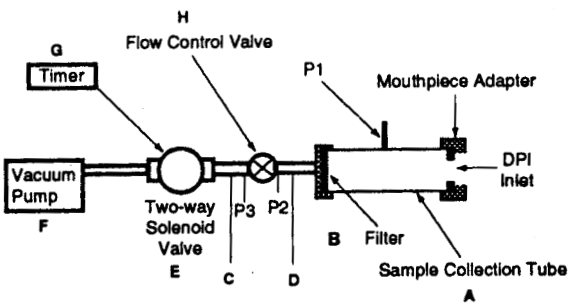
6A. DELIVERED DOSE

The Sampling Apparatus used for determining the amount and uniformity of the delivered dose for Metered-Dose Inhalers (MDIs) was originally designed by Charles Thiel who was then at 3M Laboratories, Minneapolis, USA.

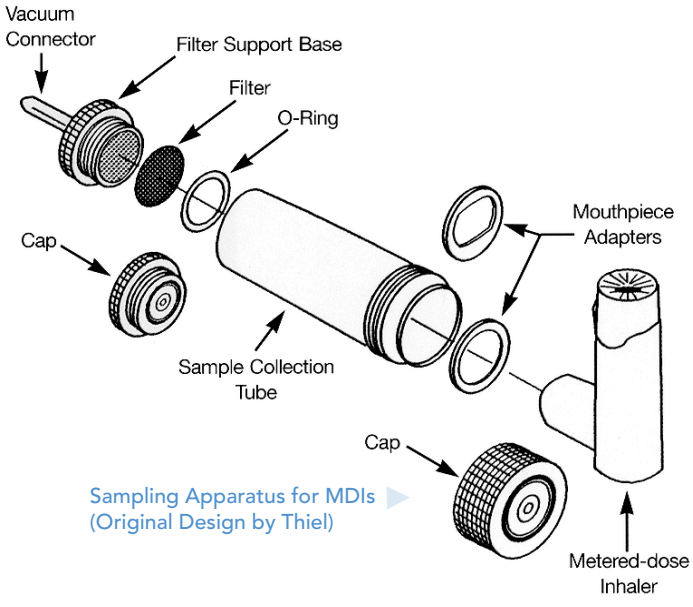
The design has subsequently been amended to replace the original screw fittings with easier-to-use bayonet fittings, whilst maintaining the critical internal dimensions of the original design.

A second and larger sampling apparatus, the Sampling Apparatus for Dry Powder Inhalers, has been introduced for DPIs based on a similar design by Byron and Hindle, Virginia Commonwealth University.

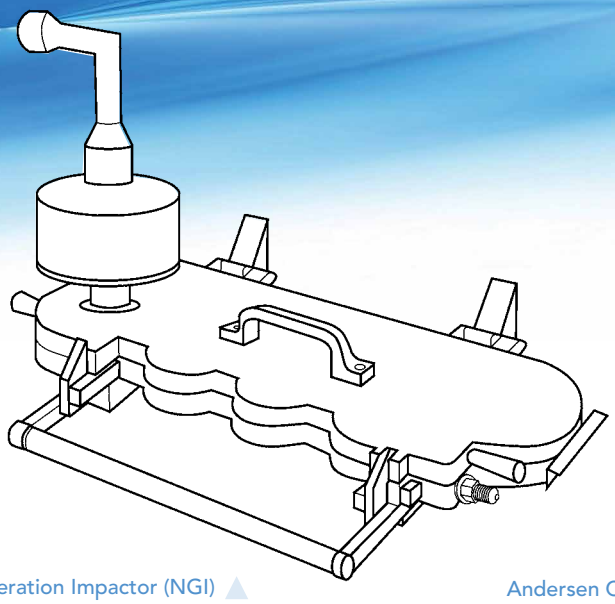
Both types of apparatus appear in the European Pharmacopoeia under Dosage Forms - Preparations for Inhalation <0671> and in the US Pharmacopeia under Section <601>.



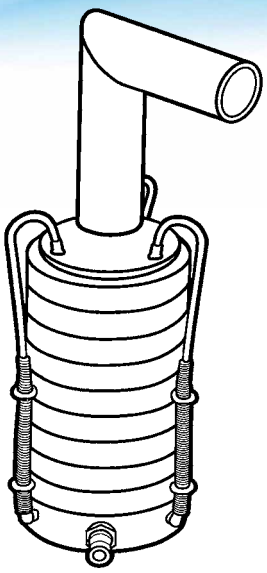
Sampling Apparatus for DPIs



Sampling Apparatus for MDIs (Original Design by Thiel)



Next Generation Impactor (NGI)



Andersen Cascade Impactor (ACI)

CURRENT PHARMACOPOEIAL SPECIFICATIONS

6B. PARTICLE SIZE (AERODYNAMIC SIZE DISTRIBUTION)

The cascade impactor is the instrument of choice for both regulators and Pharmacopoeias when measuring the aerodynamic size distribution (particle size) of inhaled products.

The aerodynamic size distribution of an aerosol cloud defines where the particles in that cloud are likely to deposit following inhalation. It is generally accepted, for example, that to be therapeutically effective the particles should be in the range of 1 to 5 microns in order to deposit in the lungs. The particle mass below 5 microns is normally described as the fine particle mass.

Particles having an aerodynamic size in excess of 5 microns will generally impact in the oropharynx and be swallowed whereas below 1 micron the possibility exists that the particles will remain entrained in the air stream and be exhaled.

The **European Pharmacopoeia (Ph. Eur.) Method Chapter 2.9.18** currently specifies one twin and three multi-stage impactors for the aerodynamic assessment of fine particles in both MDIs and DPIs:

- Ph.Eur. Apparatus A: Twin Impinger (Glass)
- Ph.Eur. Apparatus C: Multi-Stage Liquid Impinger (MSLI)
- Ph.Eur. Apparatus D: Andersen Cascade Impactor (ACI)
- Ph.Eur. Apparatus E: Next Generation Impactor (NGI)

Procedures for Apparatus E - NGI (Chapter 2.9.44) are also specified for nebulisers.

The United States Pharmacopeia (USP) Test Chapter <601> specifies six impactors suitable for aerodynamic size distribution:

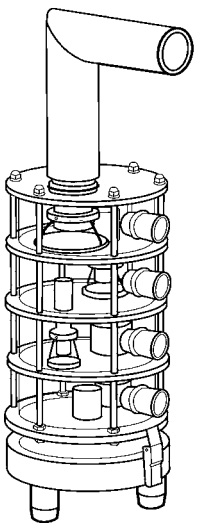
- USP Apparatus 1 for MDIs: Andersen Cascade Impactor (ACI)
- USP Apparatus 2 for DPIs: Marple Miller Impactor (MMI)
- USP Apparatus 3 for DPIs: Andersen Cascade Impactor (ACI) + Preseparator
- USP Apparatus 4 for DPIs: Multi-Stage Liquid Impinger (MSLI)
- USP Apparatus 5 for DPIs: Next Generation Impactor (NGI) + Preseparator
- USP Apparatus 6 for MDIs: Next Generation Impactor (NGI)

At the current time, only three impactors appear in both Ph.Eur. and USP:

- Multi-Stage Liquid Impinger (MSLI)
- Andersen Cascade Impactor (ACI)
- Next Generation Impactor (NGI)

Both Pharmacopoeias specify test methods for all three impactors for use with DPIs and for the NGI for nebulisers - see Ph.Eur. Chapter 2.9.44 and USP Chapter <1601>.

In the case of USP however, the use of the MSLI is restricted to DPIs only, which leaves just the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) as suitable candidates for testing both DPIs and MDIs if both Pharmacopoeial standards are to be satisfied.



Multi-Stage Liquid Impinger (MSLI)

Delivered Dose Uniformity

INTRODUCTION

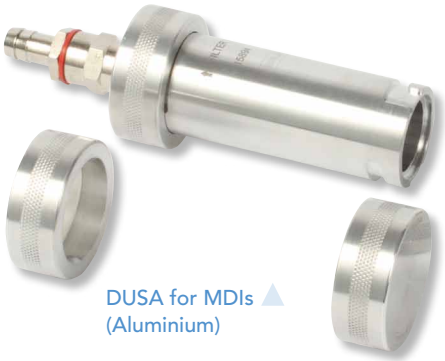
The devices used for inhaled and nasal drug delivery are collectively referred to as orally inhaled and nasal drug products (OINDPs).

The safety, quality and efficacy of OINDPs is dependent on four critical quality attributes:

- the delivered dose (the amount of drug that the user actually receives)
- the aerodynamic particle size distribution of that dose (or more precisely the fraction of the delivered dose of the appropriate size to reach the target site)
- the presence and possible inhalation of leachables or microbial contaminants
- in some instances, the spray pattern or plume geometry of the device under test

The Delivered Dose is measured by firing the test device into a sampling apparatus containing a filter.

The dose is captured, the active drug is dissolved in solvent and an aliquot is then analysed, normally using High Pressure Liquid Chromatography (HPLC).



DUSA for MDIs (Aluminium)

During testing, air is drawn through the sampling apparatus to broadly simulate inhalation. The manner in which the air is drawn through the apparatus is dependent on the device under test.

Pressurised Metered-Dose Inhalers (pMDIs) are relatively insensitive to changes in flow rate because the aerosolisation and dispersion mechanism is dependent on the force generated by the propellant.

Therefore, for MDIs, the air flow rate is fixed at an arbitrary rate of 28.3 L/min equivalent to 1 cubic foot per minute.

For Dry Powder Inhalers (DPIs), the test regime is more complex. The aerosolisation of DPIs depends on the strength and duration of a single inhalation on the part of the user.

When inhaling in this manner, the typical adult produces a pressure drop over the device of approximately 4 kPa. Depending on the **device flow resistance** this will yield a flow rate, typical of the mean patient inhalation flow rate, that is then used for all the required testing of that device.

Similarly, the duration of the test is set on the basis of the **total air volume** typically inhaled in one adult breath, adjudged to be 4 litres in the case of the Ph.Eur. and 2 litres in the case of the FDA and USP.

In the case of nebulisers and MDIs with spacers or VHCs, the user inhales the drug as part of tidal breathing at rest. In this instance, the breathing cycle *in vitro* is replicated by means of a breath simulator.

DELIVERED DOSE UNIFORMITY (DDU)

The **Delivered Dose** measures the mass of the drug that is emitted from the mouthpiece of an inhaler when the device is actuated according to the manufacturer's instructions.

The tests described under DDU are designed to demonstrate:

1. The consistency of drug emitted from a number of inhalers within a specified batch.
2. In the case of multi-dose inhalers, the consistency of drug emitted from various actuations throughout the life of a specified inhaler.
3. That the number of deliveries per inhaler is equal to or or greater than the labelled amount.
4. In the case of DPIs, that the effect of varying flow rates as demonstrated by various patients has been taken into account.

The sampling procedure and acceptance criteria for delivered dose uniformity of orally inhaled products (OIPs) varies according to the Regulatory Authority concerned (see below).

EUROPEAN MEDICINES AGENCY (EMA)

The EMA guidance for OINDPs is contained in the 2006 publication "Guideline on the Pharmaceutical Quality of Inhalation and Nasal products" and is divided into two sections, one relating to pharmaceutical development and a second relating to product manufacture.

In the case of DDU, it applies to all MDI (pressurised and non-pressurised) and DPI products.

The main study applicable to pharmaceutical development relates to the **DDU through container life**.

A further study is required in the case of DPIs, **DDU over patient flow rate range**. This is because DPIs rely on the patient's inspiration for their therapeutic effectiveness.

As far as manufacture is concerned, tests are required to determine both the **Delivered Dose Uniformity** and the **Mean Delivered Dose**.

The "Mean Delivered Dose" is the amount of drug in one actuation and is determined by calculating the mean of the DDU test results. Limits of +/-15% of the label claim apply.

Regarding the method to be employed, the EMA simply states that the DDU test should be conducted according to "*an accepted pharmacopoeial method, or a suitably validated alternative*".

EUROPEAN PHARMACOPOEIA (PH.EUR. 8.0)

The references in the European Pharmacopoeia to the "**Uniformity of delivered dose**", the "**Number of deliveries per inhaler**" and, in the case of DPIs, the "Number of deliveries per inhaler for multidose inhalers" are to found under "Preparations for Inhalation" (0671) in the chapter on Dosage Forms.

In the case of DDU, the same sampling procedure applies to both pressurised and non-pressurised MDIs and DPIs.

Ph.Eur. specifies that a total of 10 doses are to be collected in order to obtain a representative sample over the life time of the inhaler, basically 3 at the beginning, 4 in the middle and 3 at the end.

To comply, 9 out of the 10 results must lie between 75% and 125% of the average value and all between 65% and 135%.

If 2 or 3 values lie outside the 75% - 125% limits then the test must be repeated for 2 more inhalers whereupon not more than 3 of the 30 values lie outside the 75% -125% band and no value lies outside the 65% - 135% band.

If the inhaler contains more than one active, then a separate test should be carried out for each individual drug.

Checks are also required to ensure that the number of deliveries from the device are within the stated label claim.

Note: For pre-metered systems, collect and analyse 10 individual doses.

FOOD & DRUG ADMINISTRATION (FDA)

The FDA guidelines on MDIs and DPIs is contained in the Draft Guidance of that name published in 1998. FDA suggests two tests applicable to both MDIs and DPIs, namely, "Dose Content Uniformity" and "Dose Content Uniformity through container life".

The **Dose Content Uniformity** test recommends one sample be taken from 10 separate inhalers. To comply, 9 out of the 10 results must lie between 80% and 120% of the label claim, all are between 85% and 115% of the claim and the mean does not lie outside 85% -115% of the label claim.

If 2 or 3 values lie outside the 80% - 120% limits (all other criteria being met), an additional 20 inhalers should be sampled. To comply to this second tier of testing, 3 out of the 30 results must lie between 80% and 120% of the label claim (all other criteria being met).

The **Dose Content Uniformity through container life** recommends the collection of 9 samples throughout the life of one individual inhaler, basically 3 at the beginning, 3 in the middle and 3 at the end.

To comply, 8 out of the 9 results must lie between 80% and 120% of the label claim, all are between 85% and 115% of the claim and the means for the beginning, middle and end samples do not lie outside 85% -115% of the label claim.

If 2 or 3 values lie outside the 80% - 120% limits (all other criteria being met), an additional 6 inhalers (1 beginning, 1 middle, 1 end) should be sampled. To comply to this second tier of testing, not more than 3 out of the total of the 27 results must lie between 80% and 120% of the label claim (all other criteria being met).

UNITED STATES PHARMACOPEIA (USP 38)

The references in USP 38 to **Delivered-Dose Uniformity (including dose uniformity over the entire unit life)** are to be found in Chapter <601>.

The USP specifies that samples should be taken from 10 separate inhalers and in the case of dose uniformity over the entire unit life, a sample at the beginning and end of each inhaler making a total of 20 determinations.

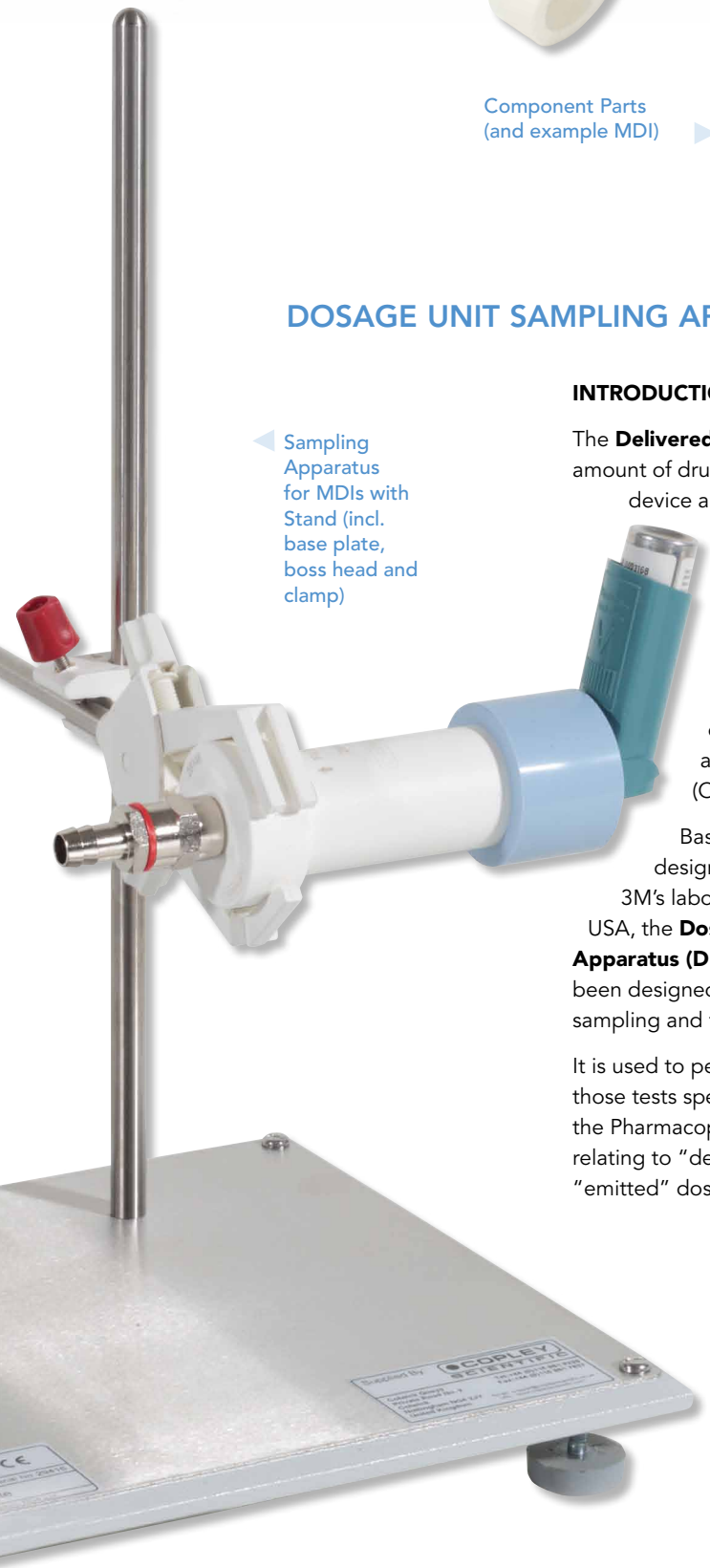
As at today, USP 38 no longer states specfic acceptance criteria for orally inhaled products.

DELIVERED DOSE UNIFORMITY - KEY CRITERIA

REGULATORY AUTHORITY	1st Test Tier No. of Inhalers	1st Test Tier Criteria	2nd Test Tier No. of Inhalers	2nd Test Tier Criteria
EMA 2006				
Delivery Dose Uniformity	1 Inhaler / 10 doses	9/10 doses to be 75-125% of Average Value	3 Inhalers / 30 doses	27/30 doses to be 75-125% of Average Value
DDU through container life	1 Inhaler / 10 doses		3 Inhalers / 30 doses	
DDU over patient flow rate range	As appropriate	As appropriate	As appropriate	As appropiate
Ph.Eur. 8.0 (0671)				
Uniformity of delivered dose	1 Inhaler / 10 doses	9/10 doses to be 75-125% of Average Value	3 Inhalers / 30 doses	27/30 doses to be 75-125% of Average Value
Number of deliveries per inhaler	1 Inhaler	> Label Amount	N/A	N/A
FDA 1998				
Dose Content Uniformity	10 Inhalers / 1 dose	9/10 doses to be 80-120% of Label Claim	30 Inhalers / 1 dose	27/30 doses to be 80-120% of Label Claim
DCU through container life	1 Inhaler / 9 doses	8/9 doses to be 80-120% of Label Claim	7 Inhalers / 27 doses	24/27 doses to be 80-120% of Label Claim
Effect of Varying Flow Rates (as appropriate)				
USP 38 <601>				
Delivered Dose Uniformity	10 Inhalers / 1 dose	Not applicable	Not applicable	Not applicable
DDU over the entire unit life	10 Inhalers / 2 doses			

Component Parts (and example MDI)

DOSAGE UNIT SAMPLING APPARATUS (DUSA) FOR MDIs



Sampling Apparatus for MDIs with Stand (incl. base plate, boss head and clamp)

INTRODUCTION

The **Delivered Dose** is the **total** amount of drug emitted from the device and hence available to the patient.

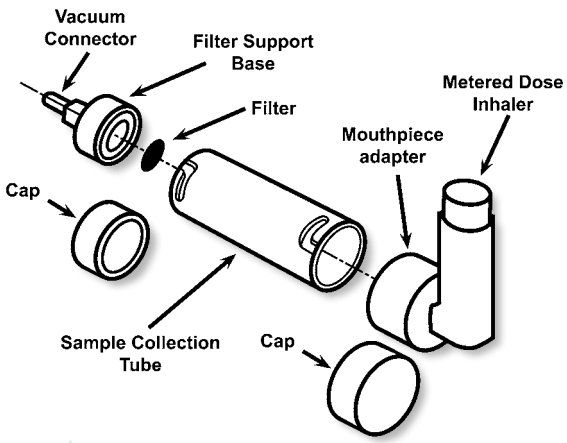
Its uniformity is a Critical Quality Attribute (CQA) in determining the safety, quality and efficacy of an orally inhaled and nasal drug product (OINDP).

Based on an original design by Charles Thiel in 3M's laboratories in Minneapolis, USA, the **Dosage Unit Sampling Apparatus (DUSA) for MDIs** has been designed specifically for the sampling and testing of MDIs

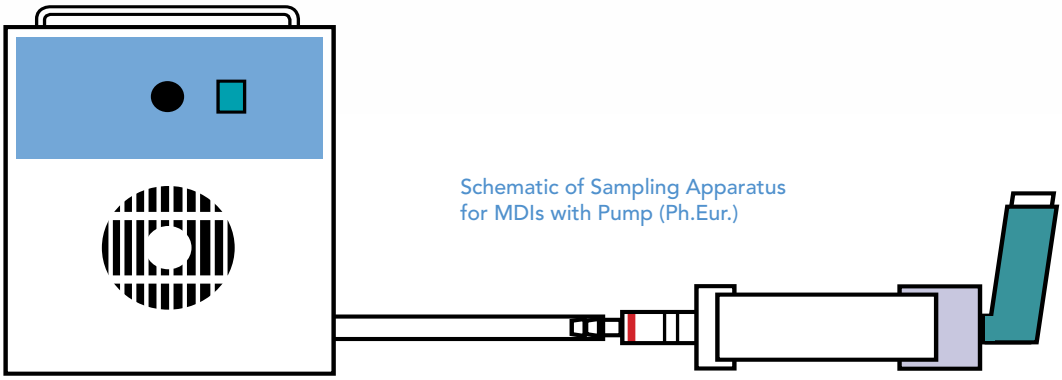
It is used to perform those tests specified in the Pharmacopoeias relating to "delivered" or "emitted" dose, namely "Uniformity of Delivered Dose", "Dose Content Uniformity" and "DDU or DCU through container life".

Over the years, the design of the sampling apparatus has been refined to improve user-friendliness and productivity whilst maintaining the critical internal dimensions specified by the Pharmacopoeias.

"Quick Release" Bayonet Caps and Adapters, for example requiring a simple quarter-turn, have now replaced the more cumbersome screw thread fittings. The old fixed disk type mouthpiece adapter has been superseded by the interchangeable, and hence more versatile, sheath type mouthpiece adapter.



Schematic of Sampling Apparatus for MDIs



Schematic of Sampling Apparatus
for MDIs with Pump (Ph.Eur.)

DESCRIPTION

The Dosage Unit Sampling Apparatus (DUSA) for MDIs consists of one collection tube, two rinsing caps, one filter support cap, one flow meter adapter and a starter pack of filters supplied in a handy carrying case.

Spare collection tubes and caps are available.

The standard collection tube itself and rinsing caps are manufactured from **TecaPro MT**, an FDA approved inert polypropylene specifically formulated for medical and pharmaceutical applications.

Alternative materials are available on request, e.g. aluminium or 316 stainless steel. All tubes and caps are **laser numbered** to assist in traceability.

The sample collection tube is fitted with a 25 mm glass fibre filter having a typical aerosol retention of 0.3 microns.

It has a volume of approx. 50 mL which equates to that of the human oropharynx.

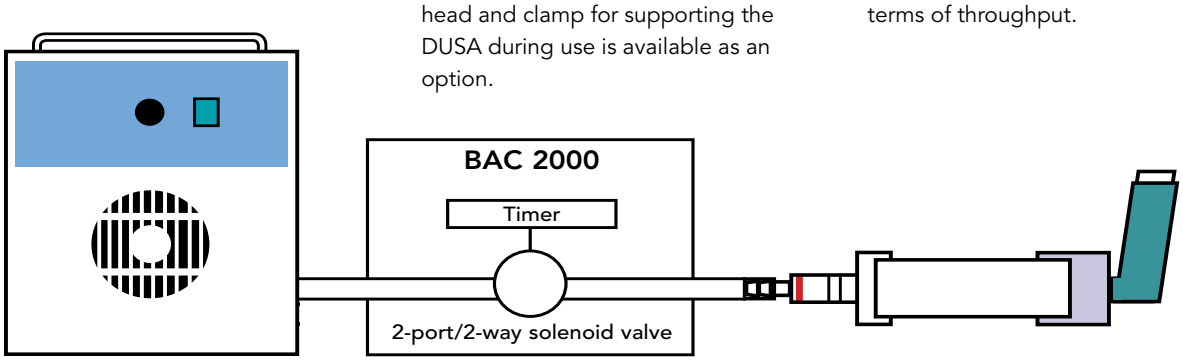
The standard unit comes with silicone rubber seals. LDPE seals are available as an option, in the event of extractables being an issue with silicone rubber.

A stand comprising base plate, boss head and clamp for supporting the DUSA during use is available as an option.

The combination of the clamp to secure the filter support cap and the boss head to alter its angle allows collection tubes to be quickly connected to the vacuum system prior to testing and removed once the test is complete.

A further base plate option includes mounting fixtures for the Waste Shot Collector (see Page 31) and Switching Valve.

Using a Waste Shot Collector and a suitable Switching Valve mounted on the Base Plate used as the stand for the DUSA, in conjunction with two mouthpiece adapters (one for the DUSA and one for the WSC2) and a number (say, 10) of spare collection tubes, can provide substantial gains in terms of throughput.



Schematic of Sampling Apparatus
for MDIs with BAC 2000 and Pump
to control maximum volume (USP)

System for Testing the Dose Uniformity of MDIs (incl. Waste Shot Collector and Switching Valve)

DOSAGE UNIT SAMPLING APPARATUS (DUSA) FOR MDIs

PROCEDURE (PH.EUR. 8.0)

The minimum set-up for delivered dose testing as specified by Ph.Eur. comprises a sample collection tube, fitted at one end with a suitable mouthpiece adapter to accept the inhaler under test and connected at the other end to a vacuum pump capable of continuously drawing 28.3 L/min through the assembled system (including the filter and inhaler).

A flow meter should be used to adjust the flow at the inlet to the correct rate prior to testing, using the flow meter adapter (see Pages 90-91).

Once the device has been shaken, primed and actuated and the test is complete, the collection tube together with the filter is removed. Solvent is then added and the tube capped and agitated to assist in drug dissolution prior to recovery and analysis.

PROCEDURE (USP 38)

In addition to the specifications laid down in Ph.Eur., the FDA recommends, and USP 38 specifies, that the volume of air sampled should not exceed 2 litres, this being the volume of air adjudged to be typical of the average patient.

This additional criterion can be met by positioning an electrically operated, timer controlled, two-way solenoid valve, such as that incorporated in the **Breath Actuation Controller BAC 2000** (see Page 84), in the line between the collection tube and the vacuum pump to control the air flow supply to the inhaler.

The BAC 2000 provides near instantaneous starting and stopping of the air flow during testing and has both delay and inhaled time functions.

This allows the time that the test flow is applied to the inhaler to be adjusted to a specific volume, for example, the 2 litres required by USP.

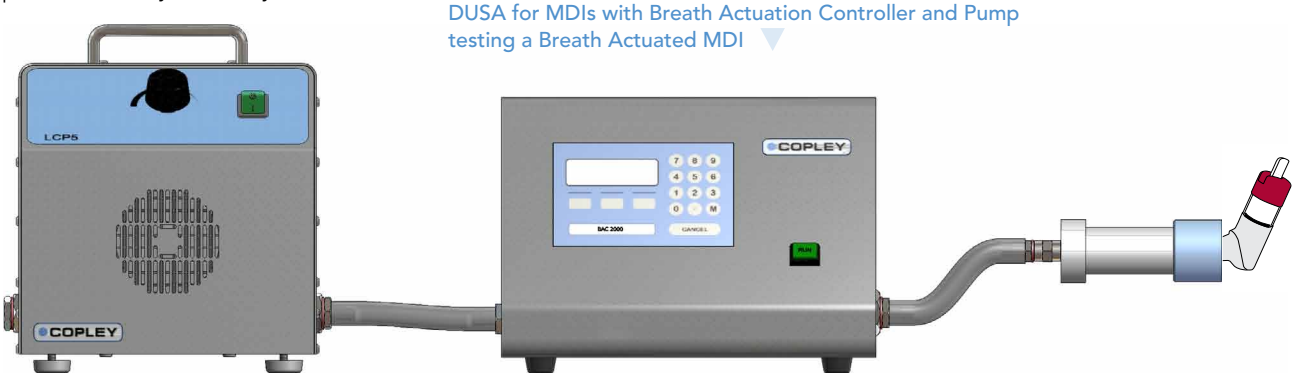
Operation can be triggered via the instrument front panel, foot switch or RS 232 interface.

The BAC 2000 can also be used for the testing of **Breath Actuated (or Breath Operated) MDIs.**

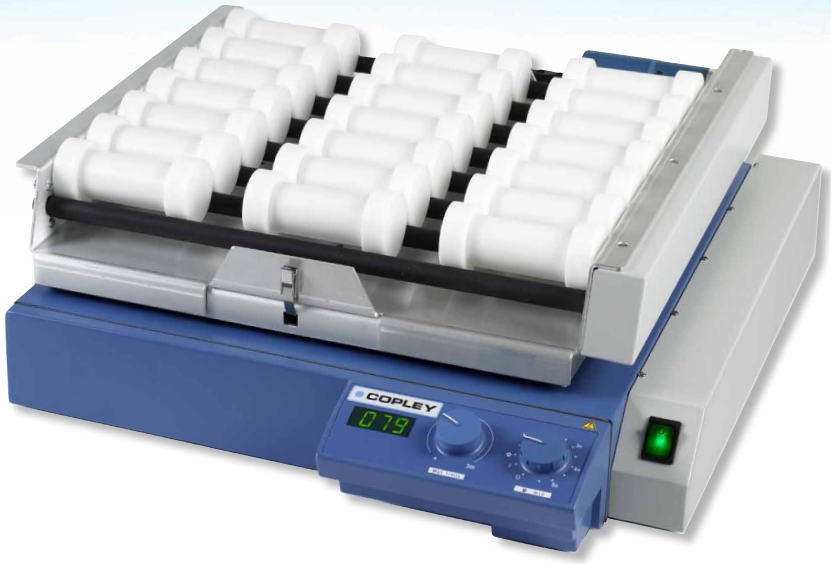
In this case, the BAC 2000 is used to initiate the flow and hence trigger the breath actuated inhaler simultaneously.

An optional DUSA Shaker for holding up to 21 DUSA for MDI collection tubes is available as an option (see Page 106).

DUSA for MDIs with Breath Actuation Controller and Pump testing a Breath Actuated MDI



Stand for 10 Collection Tubes



Shaker for DUSA for MDIs

BRITISH PHARMACOPOEIA

It is important to note that the **British Pharmacopoeia** has its own unique apparatus for determining the "Content of Active Ingredient delivered by actuation of the valve" (see below), likely retained for historical reasons.

This comprises a stainless steel base plate having three legs and a central hole to accept the actuator stem in a small vessel (to which solvent is added) suitable for shaking.

BP Content Uniformity Apparatus for MDIs

ANCILLARIES

The following ancillaries are recommended to complete a fully operating test system for the delivered dose testing of MDIs:

- **Mouthpiece Adapter (see Page 92)**
- **Vacuum Pump (see Page 93)**
- **Breath Actuation Controller (see Page 84)**
- **Flow Meter (see Page 90)**
- **Waste Shot Collector (see Page 31)**
- **DUSA Shaker for DUSA for MDIs (see Page 106)**

Cat. No.	Description
8201	Dosage Unit Sampling Apparatus for MDIs (Silicone Rubber Seals)
8201A	Dosage Unit Sampling Apparatus for MDIs (LDPE Seals)
Accessories	
8111	Stand (incl. Base Plate, Boss Head and Clamp)
8211	Stand for 10 Collection Tubes
Spare Parts	
8202	Set of 3 Silicone Rubber Seals
8202A	Set of 3 LDPE Seals
8203	Collection Tube
8204	Filter Support Cap
8205	Rinsing Cap (Silicone Rubber Seal)
8205A	Rinsing Cap (LDPE Seal)
8206	Flow Meter Cap (Silicone Rubber Seal)
8206A	Flow Meter Cap (LDPE Seal)
8207	Stainless Steel Filter Support Disc
8210	Pack of 500 Glass Fibre Filters 25 mm
Note: Aluminium or 316 stainless steel DUSAs are available on request	
8212	BP Content Uniformity Apparatus for MDIs

System for Testing the Dose Uniformity of DPIs (incl. Waste Shot Collector and Switching Valve)

DOSAGE UNIT SAMPLING APPARATUS (DUSA) FOR DPIs

INTRODUCTION

A second and larger version of the Sampling Apparatus for MDIs, capable of sampling at a variety of flow rates up to 100 L/min, is available for use with Dry Powder Inhalers (DPIs).

The **Dosage Unit Sampling Apparatus (DUSA) for DPIs** is used to perform those tests specified by the Pharmacopoeias that relate to "delivered" or "emitted" dose, namely "Uniformity of Delivered Dose", "Dose Content Uniformity" and "DDU or DCU through container life".

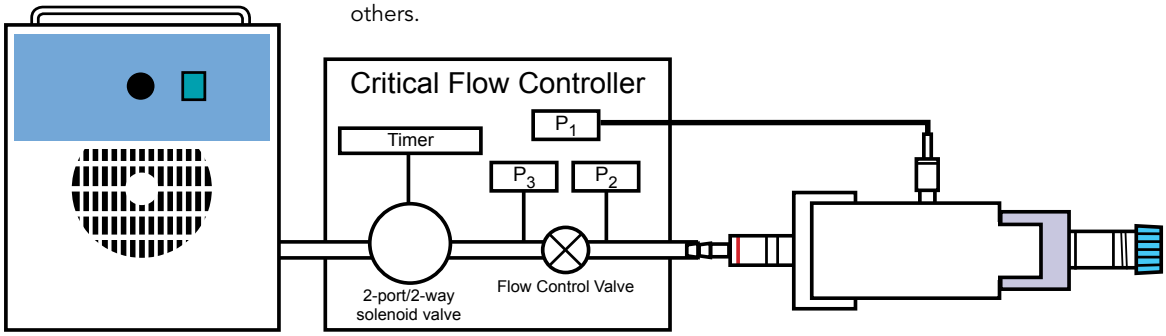
As with the system suggested for testing MDIs according to USP 38 <601>, an electrically operated, timer controlled, two-way solenoid valve is positioned in the line between the collection tube and the vacuum pump to control the air flow supply to the inhaler.

In the case of DPIs this is mandatory because, unlike MDIs, the majority of these devices are passive breath-actuated devices which rely on the patient's inspiration rather than a propellant for dose emission.

The testing of DPIs is further complicated by the fact that different inhalers provide varying degrees of resistance to flow, i.e. some require more effort to inhale than others.

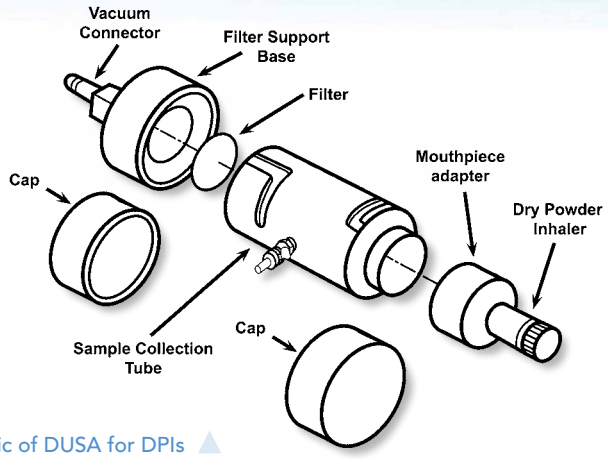
Instruments such as the Critical Flow Controller Model TPK 2000 (see Page 82) interposed between DUSA and vacuum pump simplify set-up in accordance with these pharmacopoeial recommendations, measuring and recording all the parameters required for testing and controlling flow conditions and ensuring critical (sonic) flow conditions during testing.

They also allow the time that the test flow is applied to the inhaler to be adjusted to a specific volume, for example 2 or 4 litres, thus equating to the inhaled volume of a typical patient.



Schematic of Sampling Apparatus for DPIs with Pump and Critical Flow Controller

Component Parts (and example DPI)



Schematic of DUSA for DPIs

DOSAGE UNIT SAMPLING APPARATUS (DUSA) FOR DPIs

DESCRIPTION

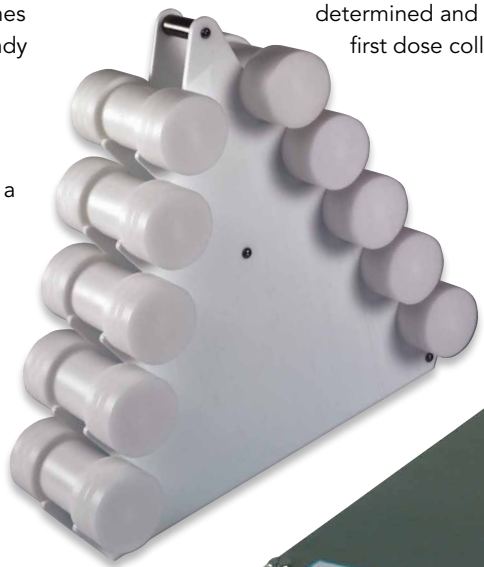
The Dose Unit Sampling Apparatus (DUSA) for DPIs utilises the same materials of construction as the unit for MDIs. However, alternative materials are available on request, e.g. aluminium or 316 stainless steel.

The apparatus comprises one collection tube, two rinsing caps, one filter support cap, one flow meter adapter and a starter pack of filters, and comes complete in a handy carrying case.

In this case, the sample collection tube is fitted with a 47 mm glass fibre filter enabling dosage collection at the higher flow rates – up 100 L/min – necessary.

The collection tube also differs from that employed for MDIs in having a pressure tap (P1) in its wall that is used in conjunction with the Critical Flow Controller to measure the pressure drop across the device.

Spare collection tubes without a pressure tap (P1) are also available for subsequent dose collections, once the test flow rate has been determined and the first dose collected.



Stand for 10 Collection Tubes

DUSA for DPIs with Stand (incl. base plate, boss head and clamp)

DOSAGE UNIT SAMPLING APPARATUS (DUSA) FOR DPIs

PROCEDURE

The minimum start-up requirement for DPI delivered dose testing is the same as that for MDI testing described in the preceding section, namely DUSA, mouthpiece adapter, pump and flow meter plus the addition of the Critical Flow Controller (e.g. TPK) to measure the pressure drop across the device and control the flow conditions during testing accordingly.

Proceed as follows:

1. Assemble the system as per the schematic of the DUSA for DPIs.
2. Connect the inhaler to the Collection Tube using a suitable mouthpiece adapter.
3. Connect the tube marked P1 on the Critical Flow Controller to the pressure tap on the Collection Tube.
4. Switch on the Pump, open the 2-way Solenoid Valve and adjust the flow control valve until the differential pressure on the display reads 4 kPa.
5. Check that critical (sonic) flow is being achieved through the flow control valve by checking the P2 and P3 values on the display.
6. Replace the inhaler with a flow meter and measure the flow rate, Q. Then, using the pre-determined flow rate, Q, and the Critical Flow Controller timer controls, adjust the test flow duration to give an inspiration volume of 4 (or 2) L.
7. Replace the inhaler and discharge the dose into the collection tube by activating the timer on the Critical Flow Controller controlling the solenoid valve. Repeat as necessary to achieve the desired number of doses.
8. Add solvent to the collection tube, apply rinsing caps and then shake the tube vigorously before assaying the contents.

An optional DUSA Shaker for holding up to 12 DUSA collection tubes is available (see Page 106).

ANCILLARIES

The following ancillaries are recommended to complete a fully operating test system for the delivered dose testing of DPIs:

- **Mouthpiece Adapter (see Page 92)**
- **Vacuum Pump (see Page 93)**
- **Critical Flow Controller (see Page 78)**
- **Flow Meter (see Page 90)**
- **Waste Shot Collector (see Page 31)**
- **Shaker for DUSA for DPIs (see Page 106)**

Cat. No.	Description
8601	Dosage Unit Sampling Apparatus for DPIs (Silicone Rubber Seals)
8601A	Dosage Unit Sampling Apparatus for DPIs (LDPE Seals)

Accessories

8111	Stand (incl. Base Plate, Boss Head and Clamp)
8604	Stand for 10 Collection Tubes

Spare Parts

8602	Set of 3 Silicone Rubber Seals
8602A	Set of 3 LDPE Seals
8603	Pack of 100 Glass Fibre Filters 47 mm
8606	Filter Support Cap
8607	Rinsing Cap (Silicone Rubber Seal)
8607A	Rinsing Cap (LDPE Seal)
8608	Collection Tube with P1 Port
8608A	Collection Tube without P1 Port
8609	Flow Meter Cap (Silicone Rubber Seal)
8609A	Flow Meter Cap (LDPE Seal)
8610	Stainless Steel Filter Support Disc
8622	Pack of 10 Plugs (to plug P1 Port when using the DUSA Shaker)
8502	Induction Port P1 Measurement Adapter

Note: DUSAs constructed from aluminium or 316 stainless steel on request

Waste Shot Collector Model WSC2 (Stand Alone)

Waste Shot Collector Model WSC2 mounted on Stand with Switching Valve

Waste Shot Collector Model WSC2 showing Disposable Cartridge

WASTE SHOT COLLECTOR MODEL WSC2

INTRODUCTION

Both European and US Pharmacopoeia state that Delivered Dose Uniformity tests should be carried out on all OIPs and that in the case of **multiple-dose devices** tests should be carried out throughout the life of the inhaler i.e. **Dose Uniformity over the Entire Contents.**

In the case of Ph.Eur., this involves the collection of 10 doses throughout the life of each individual inhaler: three doses at the beginning, four in the middle and three at the end.

In the case of an inhaler with 100 labelled doses, for example, then tests would be carried out on dose numbers 2, 3 and 4 (at the beginning of the test), numbers 49, 50, 51 and 52 (in the middle) and numbers 98, 99 and 100 (at the end).

For an inhaler having a label claim of 200 doses, this could mean firing each unit 200 times with no less than 190 shots being fired to waste for each individual container.

Traditionally, this firing to waste is carried out in a fume cupboard or into some specially built evacuation system which removes the drug particles from the atmosphere, or to a large filtering system which traps the drug. Such facilities may not always be available or suitable for this application.

DESCRIPTION

The Waste Shot Collector WSC2 is a compact vacuum filtration system suitable for use in both MDI and DPI applications.

It can be used in either stand alone mode or integrated into the Base Plate for the Dosage Unit Sampling Apparatus, via a Switching Valve, whereby the vacuum pump used on the Sampling Apparatus powers both sampling and waste collection units.

Using a Waste Shot Collector and a suitable Switching Valve mounted on the Base Plate that serves as the stand for the DUSA, in conjunction with two mouthpiece adapters (one for the DUSA and one for the WSC2) and a number (say, 10) of spare collection tubes, can provide substantial gains in terms of throughput.

The external dimensions of the inlet of the WSC2 are identical to those of the Dosage Unit Sampling Apparatus.

This means that the same mouthpiece adapter (and therefore inhaler) can be used with both pieces of equipment.

This approach also ensures that the two pieces of equipment are immediately switchable within the system and that consequently all shots are collected or discharged to waste under identical conditions.

PROCEDURE

The user simply places the inhaler in the mouthpiece of the Waste Shot Collector and fires a shot in the normal manner. A separate tally counter to record the number of shots fired is available.

The waste dose is captured in a disposable cartridge capable of collecting of shots and trapping the contents in an integral HEPA filter, retaining 99.97% of particles over 0.3 microns.

The Waste Shot Collector measures 150 x 150 x 140 mm (L x W x H) and weighs approximately 2 kg.

Cat. No.	Description
5000	Stand with Switching Valve
5001	Waste Shot Collector WSC2 (including 1 Cartridge)
5002	Spare Filter Cartridge for Waste Shot Collector
8060	Flow Meter Adapter (WSC2 to Flow Meter)
5007	Waste Shot Tally Counter

Angle Adapter for Breath Simulator BRS 1100

DELIVERED DOSE SAMPLING APPARATUS FOR NEBULISERS

INTRODUCTION

Nebulisers convert liquids into a cloud of droplets suitable for respiration. In the past, nebulisers have been designed to be used with a variety of drugs, the choice of nebuliser and/or drug being dependent on the prescribing clinician. For this reason, the nebuliser and drug were normally marketed and sold as two distinct entities.

This is in direct contrast with inhalers which normally deliver a pre-metered dose of medication and which have always been marketed as integrated products.

These differences are important since, hitherto, the regulatory bodies have classified nebulisers as medical equipment rather than pharmaceuticals for testing purposes and for that reason there have been no specific guidelines on characterising the drug preparation itself.

Filter Holder and Adapter for Breath Simulator BRS 1100

In 2006, the European Medicines Agency (EMA) issued a new "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" in which they included regulatory guidance on the drug aspects of nebulisers.

This was on the grounds that the safety and efficacy of nebulisers is dependent on the nebuliser/drug combination and not just on the nebuliser alone.

As a result of the EMA initiative and recognising the lack of suitable test methods for nebulisers, the Pharmacopoeias have now introduced a new Chapter on **"Preparations for Nebulisation: Characterisation"** (Ph. Eur. 2.9.44 and USP Chapter <1601>).

It is these proposals that form the basis for the tests specified in Annex C of the new **ISO 27427:2013** requirements for the "safety, performance and testing for general purpose nebulising systems intended for continuous or breath-actuated delivery of liquids in an aerosol form, to humans through the respiratory system" and the tests and equipment outlined below.

DELIVERED DOSE IN NEBULISERS

The effectiveness of any nebuliser is dependent on:

a) the total active drug delivered to the user
b) the rate at which that active is delivered and
c) the aerodynamic size of the particles/droplets generated

The breathing pattern employed in the testing of nebulisers is particularly important since *in vivo* this determines the amount of active available to the user.

For this reason, the two tests proposed in the Pharmacopoeias to characterise delivered dose, **Active Substance Delivery Rate** and **Total Active Substance Delivered**, are based on standardised tidal flow conditions generated by a breath simulator, as opposed to fixed flow rates.

The standard breathing pattern employed is intended to simulate that of an adult. Different breathing patterns may be used where appropriate, for example in the case of drugs intended for paediatric use (see Table on Page 33).

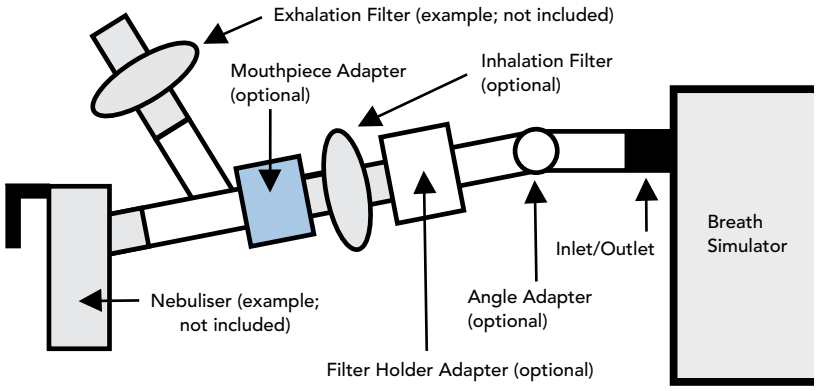
Delivered Dose Sampling Apparatus for Nebulisers

DELIVERED DOSE SAMPLING APPARATUS FOR NEBULISERS

DESCRIPTION

The **Sampling Apparatus for Nebulisers** consists of a breath simulator to generate the specified breathing profile, a filter holder containing the filter to capture the active drug and a suitable mouthpiece adapter to connect the filter holder to the nebuliser under test.

An angle adapter can be provided as an optional extra where required to adjust the angle of the nebuliser mouthpiece to that representative of actual operating conditions.



Representative Tidal Breathing Patterns for Nebuliser Tests

Parameter	Adult	Neonatal	Infant	Child
Total Volume	500 mL	25 mL	50 mL	155 mL
Frequency	15 cycles/min	40 cycles/min	30 cycles/min	25 cycles/min
Waveform	sinusoidal	sinusoidal	sinusoidal	sinusoidal
I/E Ratio	1:1	1:3	1:3	1:2

Copley Scientific supply a range of Breath Simulators specifically designed to meet the requirements of the tests concerned (see Pages 73-77).

PROCEDURE

Use a suitable Breath Simulator to generate the breathing pattern required in conjunction with the **Filter Holder** and **Adapter**, **Angle Adapter** and a suitable **Mouthpiece Adapter** to perform these two tests.

Proceed as follows:

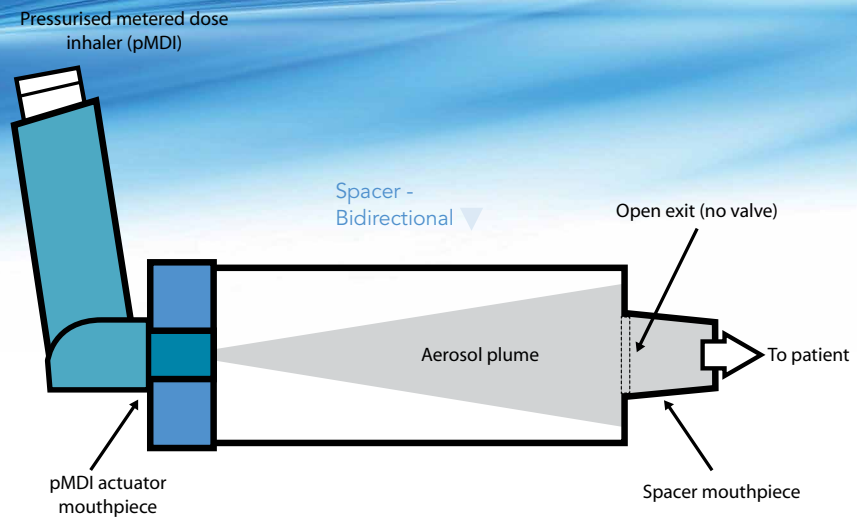
1. Assemble the system as per the schematic.
2. Connect the nebuliser to the system using a suitable mouthpiece adapter.
3. Use the Angle Adapter to ensure that the nebuliser is positioned in the same orientation as intended for use and that the environmental conditions are as stated.
4. Set the breath simulator to generate the specified breathing pattern.
5. Start both nebuliser and simulator and run for 60 seconds (or for such time that sufficient active is collected on the filter for analysis).
6. Pause both units and remove the filter from the holder.
7. Place a fresh filter in the holder and continue the test until nebulisation ceases, i.e. the reservoir is empty.
8. Using a suitable method, determine the amount of active on each filter.

Determine the ***active substance delivery rate*** by dividing the mass of active collected on the first filter by the time taken to collect it.

Determine the ***total active substance delivered*** by summing the mass collected on both filters.

Cat. No.	Description
9102	Filter Holder and Adapter for Breath Simulator BRS 1100
9102A	Filter Holder and Adapter for Breath Simulator BRS 2000/3000
9103	Pack of 100 filters for above
9104	Angle Adapter for Breath Simulator BRS 1100
5003	Mouthpiece Adapter
5004	Tooling Charge for above

Note: A range of Breath Simulators capable of generating all of the wave patterns described in the table below may be found on Pages 73-77.



DELIVERED DOSE SAMPLING APPARATUS FOR SPACERS AND VHCs

INTRODUCTION

Pressurised metered dose inhalers (pMDIs) are an inexpensive and convenient means of treating asthma and other pulmonary diseases.

However, patient coordination of actuation with inhalation can be a problem when using pMDIs particularly in the young, old or chronically ill.

Add-on devices such as **Spacers**, **Valved Holding Chambers** and **Reverse Firing VHCs,** which reduce or eliminate the need for coordination between actuation and inhalation and also the cold freon effect associated with them, are widely used in conjunction with pMDIs to overcome this problem.

A **Spacer** is an open tube placed between the inhaler and the mouthpiece, or in some instances facemask of the patient. In practical terms, they extend the distance between the inhaler and patient and thus provide additional volume for the aerosol plume to develop.

A **Valved Holding Chamber (VHC)** is similar but normally incorporates a one way valve close to the mouthpiece or facemask. This opens to release the aerosol cloud once the patient starts to inhale but prevents emptying the holding chamber during exhalation as in the case of a simple spacer device. **Reverse Firing Spacers** and **VHCs** are designed with an integral actuator to accept an inhaler canister directly. In this instance, the pMDI is actuated into a bag in a direction pointing away from the body (hence the description, Reverse Firing) and then the patient inhales slowly from the bag.

All three "Add-on" devices result in the patient inhaling the drug from a reservoir of aerosolised particles, not dissimilar to a nebuliser, rather than directly from the pMDI.

IN VITRO ASSESSMENT

When a patient uses a pMDI without an add-on device, the emitted dose and hence the drug particles contained within it are inhaled almost instantaneously as the formulation is aerosolised.

In contrast, when an add-on device is used, the patient inhales drug from a reservoir of aerosolised particles.

The additional dead volume provided by the reservoir not only provides a reservoir for aerosol expansion, but also particle impaction, settling and/or electrostatic deposition within the chamber itself, all of which can change the emitted dose ahead of inhalation.

As the use of add-on devices has become more widespread, the regulatory authorities responsible for the safety and efficacy of OIPs have become increasingly aware of the need to test add-on devices as distinct from pMDIs used on their own.

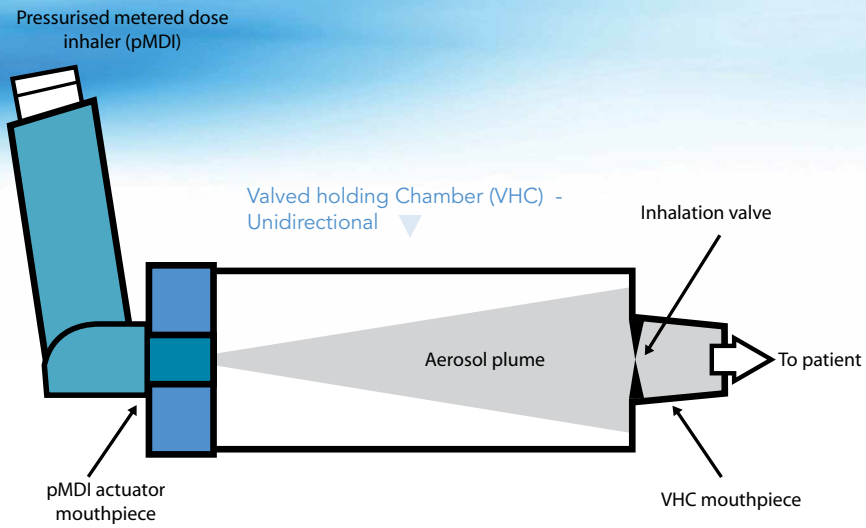
As a result, USP has released a new draft chapter for testing **Spacers and Valved Holding Chambers used with Inhalation Aerosols <1602>**.

The tests set out in the new draft chapter are based on experience in Canada gained over a ten year period culminating in the release of a new standard "Spacers and Holding Chambers for use with Metered-Dose Inhalers" by the Canadian Standard Association in 2011.

The new methods reflect that, as with a nebuliser, the amount of drug received by the patient employing an add-on device with a pMDI will be directly influenced by the inhalation profile of the user concerned.

For that reason, the tests in the new chapter call for the application of specific breathing profiles to reflect the physiology of the intended user (see Page 35).

Delivered Dose Sampling Apparatus for Spacers and VHCs



DESCRIPTION - TEST PART 2 (Mouthpiece based products)

Two DDU tests are described in Chapter <1602> to determine the "Total mass of drug delivered from a spacer/VHC while simulating patient tidal breathing".

Test Part 2 is designed to be used with standard **mouthpiece** based products.

Test Part 3 is described for spacers / VHCs supplied with a **facemask** (see Pages 36-37 overleaf).

Like the DDU test for pMDIs, the total active is collected on a filter mounted in this case as close as practically possible to the mouthpiece/mouth spacer/VHC/facemask concerned in order to minimise dead volume.

In this instance however, the constant 28.3 L/min air flow rate applied during the testing of pMDIs is replaced by a specific patient relevant breath profile more representative of the conditions applicable to add-on devices *in vivo*.

In the case of VHCs, tests are also carried out to compare the dose received when use is coordinated or uncoordinated with device actuation.

Performance is optimal and directly comparable with a normal pMDI if the patient inhales from the add-on as the device is actuated. This near perfect patient-inhaler technique is called "**coordinated use**".

In contrast, the worst case scenario is if actuation coincides with exhalation i.e., "**uncoordinated use**".

The **standard sampling apparatus for mouthpiece based products** consists of a breath simulator to generate the specified breath profile, a filter holder containing the filter to capture the active drug and a suitable mouthpiece adapter to connect the filter holder to the mouthpiece of the spacer / VHC concerned.

Copley Scientific supply a range of Breath Simulators specifically designed to meet the requirements of the test concerned (see Page 73).

PROCEDURE - TEST PART 2 (Mouthpiece based products)

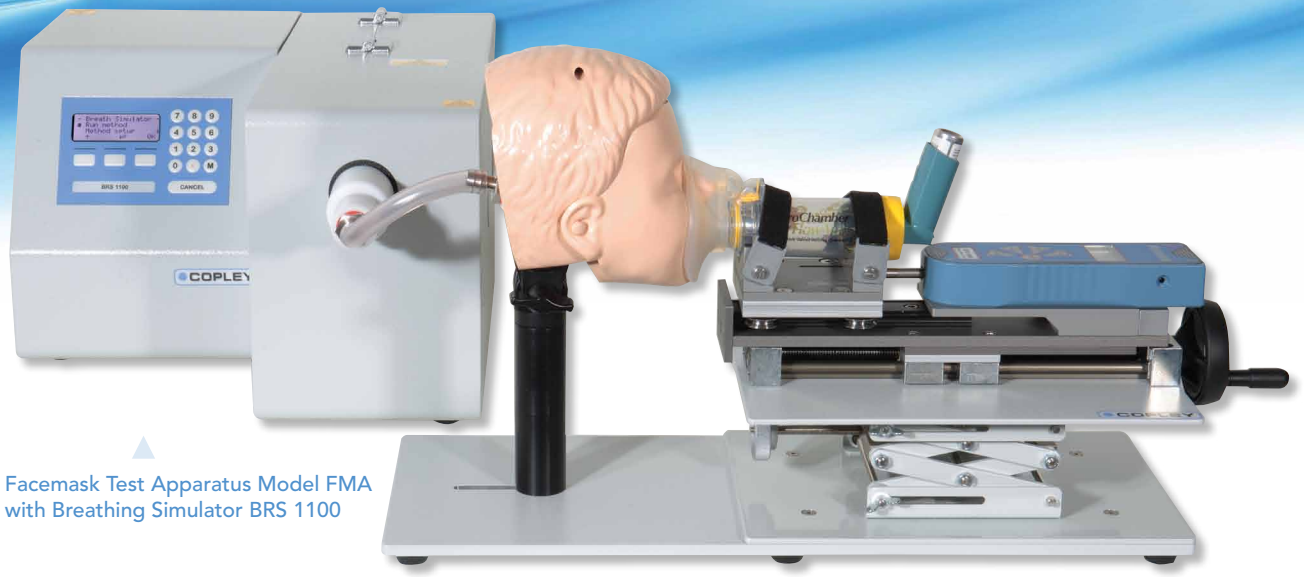
Use a suitable Breath Simulator to generate the breathing pattern required in conjunction with the filter holder and a suitable mouthpiece adapter to perform these two tests.

Proceed as follows:

1. Assemble the system as per the manufacturer's instructions.
2. Set the breath simulator to generate the specified breathing pattern ensuring that the start position is set for "Inhalation" (coordinated) and check that it is operating correctly.
3. Connect the spacer/VHC to the test system using a suitable mouthpiece adapter.
3. Actuate the pMDI whilst simultaneously starting the breath cycle.
4. At the end of the test, remove the filter from the holder.
5. Repeat the test ensuring that the start position is set for "Exhalation" (uncoordinated) - **VHCs only**.
6. Using a suitable method, determine the amount of active on each filter.
7. Determine the ratio of delivered dose for coordinated and uncoordinated use to assess valve efficiency.

Representative Tidal Breathing Patterns for MDI with Spacer/VHC Tests

	Paediatric			Adult	
Parameter	Neonate	Infant	Child	Normal 1	Normal 2
Tidal Volume (mL)	25	50	155	770	500
Frequency (cycles/min)	40	30	25	12	13
I/E Ratio	1:3	1:3	1:2	1:2	1:2
Minute Volume (mL)	1000	1500	3875	9240	6500



Facemask Test Apparatus Model FMA with Breathing Simulator BRS 1100

DELIVERED DOSE SAMPLING APPARATUS FOR SPACERS AND VHCs

DESCRIPTION - TEST PART 3 (Facemask based products)

The purpose of this test is to confirm that the emitted dose from a spacer/VHC used in conjunction with a facemask is comparable to that obtained in the fully coordinated simulation with the facemask removed.

A critical component of the test apparatus is the face model employed. This should be appropriate to the age group for which the spacer/VHC is intended, e.g. infant, child or adult.

The face model should be such as to:

1. Achieve realistic dead space and at the same time ensure the absence of leaks between the mask and model.

2. Simulate *in vivo* conditions in having physiologically accurate soft facial tissue.

3. Provide a means of mounting the spacer/VHC such that the facemask is in correct alignment with the face model as in "real life" conditions.

The system from Copley Scientific seeks to address all of these requirements, whilst also giving sufficient flexibility to allow users to utilise their own validated face models, if desired.

The FMA System comprises two key elements:

1. The **Device Securing Fixture** which secures the spacer/VHC and its associated facemask into position prior to testing. The device securing fixture has been designed to accommodate various sizes of spacer/VHC. The fixture is adjustable in two axes:

- x (horizontal) and
- y (height)

by means of handwheels.

An in-built digital gauge (Range 0 - 2.5 kg) measures the force applied to the face model in Newtons or kg (e.g. 1.6 kg) as suggested in USP <1602>.

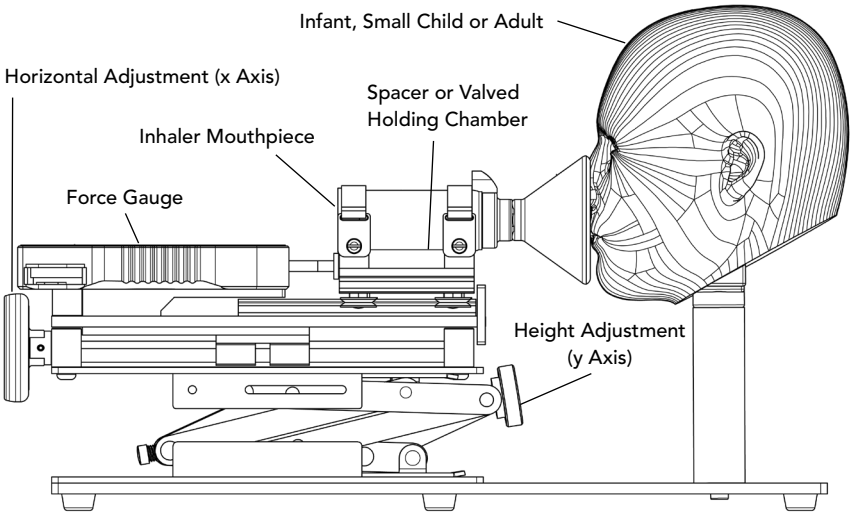
2. The **Face Model Support** accepts three different models: infant, child and adult. All models are fitted with replaceable face skins representative of "real life" tissue.

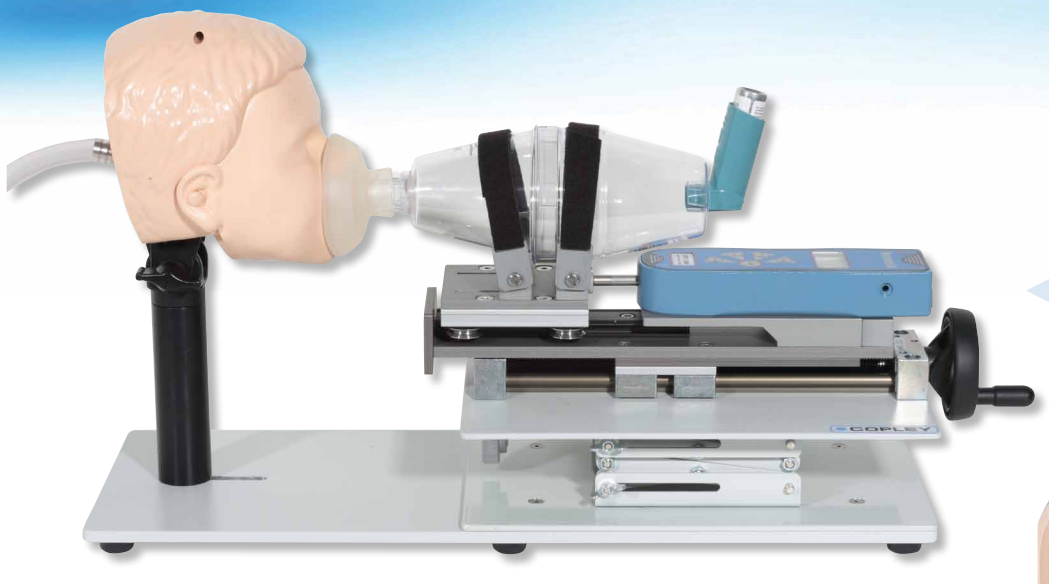
The support also can be adjusted in both axes to tilt the head from front to back or orientate it from side to side.

In this instance, the filter holder is located in a cavity behind the face model's lips.

As with the mouthpiece based product, the specified breathing profile is provided by a Breath Simulator, details of which can be found on Page 73.

DUSA for testing Spacers and VHCs in conjunction with a Facemask





Facemask Test Apparatus Model FMA (with child head) supporting a large spacer

Filter Holder and Adapter

PROCEDURE - TEST PART 3 (Facemask based products)

Use a suitable Breath Simulator to generate the breathing pattern required in conjunction with the FMA holder to perform these two tests.

Proceed as follows:

1. Assemble the system as instructed and check that the system is air tight using the procedure described in Chapter <1602>.
2. Set the breath simulator to generate the specified breathing pattern ensuring that the start position is set for "Inhalation" (coordinated) and check that it is operating correctly.
3. Connect the spacer/VHC to the test system using a suitable mouthpiece adapter.
3. Actuate the pMDI whilst simultaneously starting the breath cycle.
4. At the end of the test, remove the filter from the holder.
5. Repeat the test ensuring that the start position is set for "Exhalation" (uncoordinated) - **VHCs only**.
6. Using a suitable method, determine the amount of active on each filter.
7. Determine the ratio of delivered dose for coordinated and uncoordinated use to assess valve efficiency.

Infant, Child and Adult Heads

Cat. No.	Description
Mouthpiece based devices	
9102	Filter Holder and Adapter for Breath Simulator BRS 1100
9102A	Filter Holder and Adapter for Breath Simulator BRS 2000/3000
9103	Pack of 100 Filters for above
5003	Mouthpiece Adapter
5004	Tooling Charge for above
Facemask based devices	
9141	Facemask Test Apparatus for Spacers & VHCs Model FMA
9142	FMA Filter Holder and Adapter for BRS 1100
9143	FMA Filter Holder and Adapter for BRS 2000/3000
9103	Pack of 100 Filters for above
9144	Adult Head and Adapter for FMA
9145	Child Head and Adapter for FMA
9146	Infant Head and Adapter for FMA
9147	Re-calibration Certificate for FMA Force Gauge
9152	IQ/OQ Documentation for FMA
9148	FMA Qualification Tools
9149	Replacement Face Skins for Adult Head (Pack of 6)
9150	Replacement Face Skins for Child Head (Pack of 6)
9151	Replacement Face Skins for Infant Head (Pack of 6)
9005	Compact Printer (Force Gauge)

Note: A range of Breath Simulators capable of generating all of the wave patterns described in the table below may be found on Page 73.

Aerodynamic Particle Size

INTRODUCTION

Together with delivered dose, the Aerodynamic Particle Size Distribution (APSD) is widely recognised as a Critical Quality Attribute (CGA) in the *in vitro* characterisation of OINDPs since it is the APSD of an aerosol cloud that defines where the particles in that cloud are deposited following inhalation.

It is generally accepted, for example, that to be therapeutically effective, the particles should be in the range of 1 to 5 microns. Particles in excess of 5 microns will generally impact in the oropharynx and be swallowed whereas below 1 micron the possibility exists that the particles will remain entrained in the air stream and be exhaled.

The preferred instrument of choice for measuring the APSD of inhaled products for both regulators and pharmacopoeias alike is the cascade impactor.

This is because:

1. Cascade impactors measure **aerodynamic** particle size (APSD).
2. Cascade impactors measure **active** pharmaceutical ingredient (API).
3. Cascade impactors measure the **entire** dose.

Cascade impactors are precision engineered instruments that separate a sample on the basis of particle inertia (which is a function of velocity and aerodynamic particle size) without the need to know either particle density or shape.

The Pharmacopoeias recommend several commercially available impactors for the routine testing of OINDPs including the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) both of which are used globally for the testing of MDIs, DPIs and ADIs (Aqueous Droplet Inhalers).

Special versions are available for the testing of nasal delivery systems, nebuliser systems and the add-on devices such as spacers and valved holding chambers sometimes used with pMDIs.

Following on from FDA's Guidance on Process Analytical Technology (PAT) in 2004, in the last few years considerable interest has focused on the Quality by Design (QbD) approach to pharmaceutical development and manufacture.

Because of the amount of APSD data demanded by these new initiatives, attention has once again turned to faster methods of APSD determination and in particular to the concept of Abbreviated Impactor Measurement (AIM).

In order to meet these demands and to provide a basis for the proof-of-concept work to validate them, Copley Scientific has introduced a number of different versions of Abbreviated Impactors for use in a QbD environment. These are based on reduced stage versions of the ACI and NGI respectively (see Page 60).

CASCADE IMPACTORS

Andersen Cascade Impactor (28.3 L/min Version) with Induction Port

INTRODUCTION

The cascade impactor forms the basis of most systems used to measure the size distribution (particle size) of inhaled products.

This is because it has three unique features which currently no other technique can replicate:

1. Cascade impactors measure **aerodynamic particle size.**

Cascade impactors measure aerodynamic particle size which is a function of density and viscosity as well as the physical dimensions and shape of the particles concerned.

This is important since it helps to explain how particles behave in a moving air stream (as exemplified by the respiratory tract) as opposed to simple "geometric" size.

2. Cascade impactors measure **active pharmaceutical ingredient.**

Cascade impactors provide a direct means of recovering and quantifying the **active pharmaceutical ingredient (API)** contained in the aerosol cloud as opposed to the overall formulation.

This is important since the aerosol clouds generated by pharmaceutical inhalers typically comprise a combination of API and other excipients or components, the latter having no effect on therapeutic efficacy.

3. Cascade impactors measure the **entire dose.**

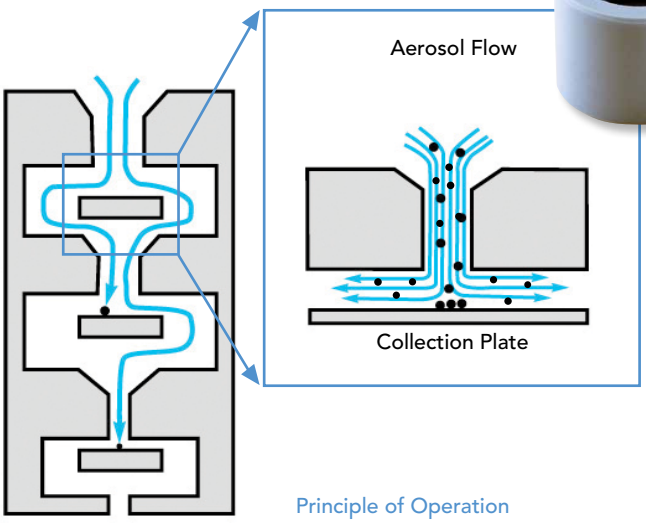
Cascade impactors, unlike other techniques which just provide a snap-shot of part of the dose, capture the entire dose allowing complete characterisation of the formulation concerned.

IMPACTOR SYSTEMS

In its simplest form, an inhaler particle sizing system comprises the following components:

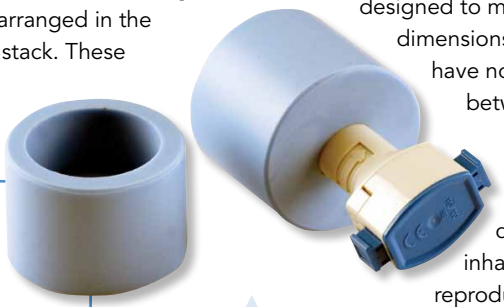
- Mouthpiece Adapter (see Page 92)
- Induction Port (Throat)
- Cascade Impactor
- Vacuum Pump (see Page 93)

The **cascade impactor** itself consists of one or more stages normally arranged in the form of a stack. These separate the particles entrained in the aerosol stream, passing through them into a series of size bands or fractions, broadly corresponding to their likely deposition sites in the respiratory tract.



Principle of Operation

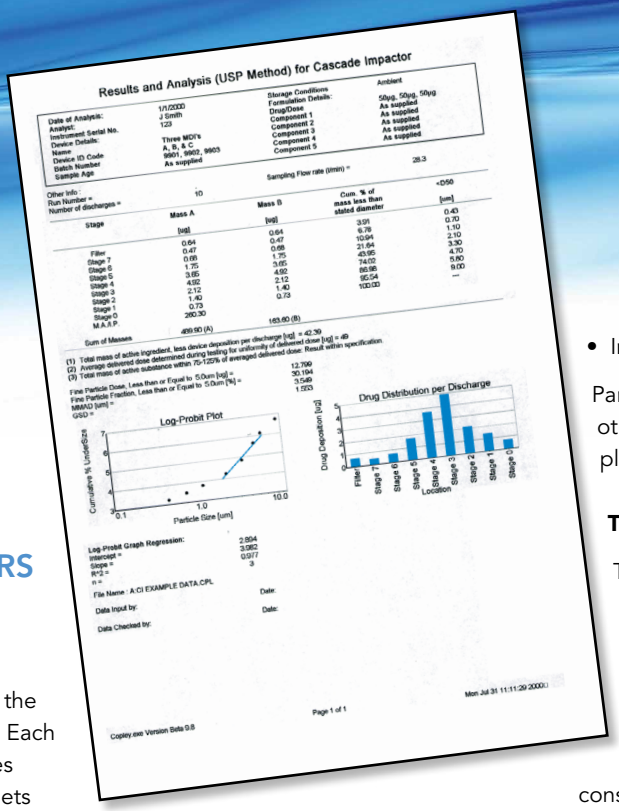
For most inhaler related applications, the entrance to the impactor is fitted with a right angled **induction port** designed to mimic the throat. The dimensions of this induction port have now been standardised between the various Pharmacopoeias and serve to ensure that the aerosol cloud produced by the inhaler is sampled in a reproducible manner.



Mouthpiece Adapters

The inhaler is connected to the induction port by means of a **mouthpiece adapter** which provides an airtight seal between the induction port and the medical device under test.

Once discharged from the inhaler, the aerosol cloud is drawn through the impactor by means of a **vacuum pump** connected to the outlet of the impactor by a suitable length of tubing.



Typical Data Analysis from a Cascade Impactor

CASCADE IMPACTORS

PRINCIPLES OF OPERATION

Cascade impactors operate on the principle of **inertial impaction**. Each stage of the impactor comprises a single or series of nozzles or jets through which the sample laden air is drawn, directing any airborne particles towards the surface of the collection plate for that particular stage.

Whether a particular particle impacts on that stage is dependent on its aerodynamic diameter. Particles having sufficient inertia will impact on that particular stage collection plate, whilst smaller particles with insufficient inertia will remain entrained in the air stream and pass to the next stage where the process is repeated.

The stages are normally assembled in a stack in order of decreasing particle size. As the jets get smaller, the air velocity increases and finer particles are collected. Any remaining particles are collected on an after-filter (or by a Micro-Orifice Collector).

At the end of the test, the particle mass relating to each stage collection plate is recovered using a suitable solvent and then analysed, usually using HPLC to determine the amount of drug actually present.

By analysing the amount of drug deposited on the various stages in this manner, it is then possible to calculate the Fine Particle Dose (FPD) and Fine Particle Fraction (FPF) and, following further manipulation, the Mass Median Aerodynamic Distribution (MMAD) and Geometric Standard Deviation (GSD).

Factors affecting impaction

- Bounce/Re-entrainment

In some instances, particles may bounce as opposed to impact when they contact the collection plate, in which case they are normally re-entrained into the air stream and carried to a lower stage, ultimately collecting on the wrong stage further downstream. This can be a particular problem with DPIs and certain MDIs (where measurements are based on a limited number of actuations from the inhaler or a surfactant is not present).

This tendency may be avoided by coating the collection plates with a suitable surface coating, e.g. glycerol or silicone oil.

- Inter-Stage Losses

Particle deposition on impactor parts other than the designated collection plates or cups.

Terminology

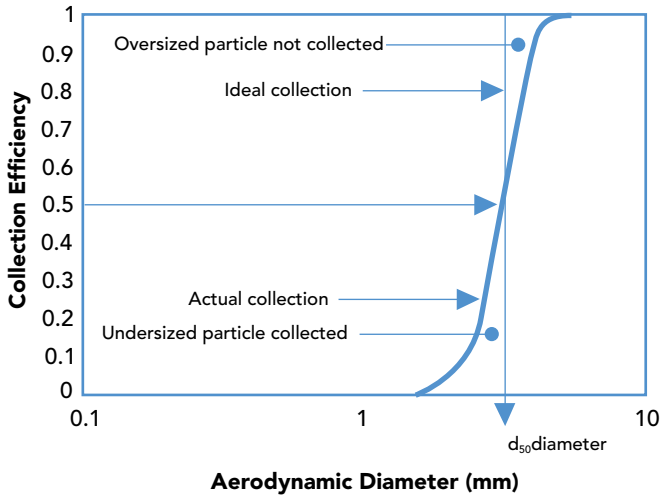
The ***Fine Particle Dose (FPD)*** may be defined as the quantity of drug in the precribed dose that is generally considered to be of a size capable of penetrating the lung during inhalation i.e. respirable. This is usually considered to be 5 microns or less.

The *Fine Particle Dose (FPD)* should not be confused with ***Fine Particle Mass (FPM)*** which is the quantity of drug to be found in one actuation of the device, since the prescribed dose may comprise more than one actuation.

The ***Fine Particle Fraction (FPF)*** is the FPD expressed as a percentage of the delivered dose (the dose that leaves the inhaler device and is available to the patient).

The term **"impactor"** is generally used for an instrument where the particles "impact" on a dry impaction plate or cup. If the collection surface is liquid, as in the case of the Multi-Stage Liquid Impinger (MSLI), then the term **"impinger"** is used. The general principles of inertial impaction apply to both "impactors" and "impingers".

Each stage of the impactor is designed to collect particles greater than a certain size as shown in this graph of aerodynamic diameter vs. collection efficiency. The stage cut-off diameter is defined as the midway point on the curve (D_{50}).



Andersen Cascade Impactor (ACI) (Aluminium, 316 Stainless Steel and Titanium)

Glass Impinger

CHOOSING YOUR IMPACTOR OR IMPINGER

INTRODUCTION

Between them the European and US Pharmacopoeias list no less than five different cascade impactors/ impingers suitable for the aerodynamic assessment of fine particles.

However, only the Andersen Cascade Impactor (ACI), the Next Generation Impactor (NGI) and the Multi-Stage Liquid Impinger (MSLI) appear in both Pharmacopoeias.

When selecting an impactor, much will depend on the product to be tested, the data that is required, the geographical location where the product is to be marketed and whether the unit is to be used for product development or quality control.

In research applications, *in vitro - in vivo* correlation and bioequivalence may be important and so detailed particle size data may be required.

In routine quality control, where the concern is batch-to-batch variation, a coarser test may be acceptable.

The two stage **Glass Impinger,** for example, has been retained as Apparatus A in the European Pharmacopoeia, because of its value as a simple and inexpensive quality control tool.

In general however, it is accepted that an impactor/impinger should have a minimum of five stages and preferably more, if it is to provide detailed particle size distribution data.

Andersen Cascade Impactor (ACI)

The Andersen Cascade Impactor is arguably the most commonly used impactor within the pharmaceutical industry for the testing of inhaled products.

The 8-stage ACI was originally developed as a bacteriological air sampler and then adopted by the pharmaceutical industry for inhaler testing. Many drug applications are based on data collected from the ACI due to its longevity within the industry.

A number of papers published in the late 1990s highlighted concerns relating to the manufacture and performance of the Andersen Cascade Impactor manufactured by Graseby-Andersen between 1992 and 1998.

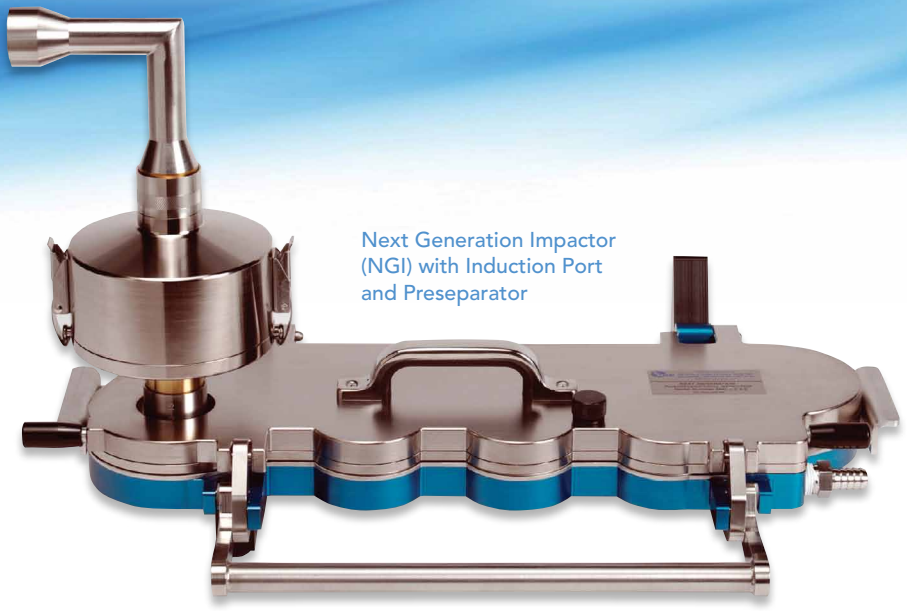
These focused on the choice of material used in their construction, ease of use, accuracy, calibration and the ability to suitably qualify the impactors prior to use.

Because of these criticisms, **Copley Scientific** commenced manufacturing their own Andersen Cascade Impactor using the latest state-of-the-art production techniques.

The combination of improved manufacturing techniques and QC test procedures has resolved the manufacturing variability previously associated with the ACI, restoring full confidence in its use.

The advantages of the ACI may be summarised as follows:

- Well established and readily accepted by the regulatory authorities
- A total of 8 individual stages between 0.4 and 9 microns
- Choice of aluminum, 316 stainless steel or titanium
- 60 and 90 L/min Conversion Kits available for high flow rate testing, whilst retaining the 28.3 L/min cut-off diameters
- Low flow resistance at high flow rates when Stages 6 & 7 are removed
- Small footprint where laboratory space is limited
- Reduced stack option for work with nasal aerosols and sprays
- Easy removal and replacement of damaged and non-conforming stages
- Low cost



Next Generation Impactor (NGI) with Induction Port and Preseparator

CHOOSING YOUR IMPACTOR OR IMPINGER

Next Generation Impactor (NGI)

In 1997, a group of prominent pharmaceutical companies involved in the development and manufacture of inhalers formed a consortium to develop a new impactor specifically designed for testing pharmaceutical inhalers using the latest design theory.

The result, the Next Generation Impactor (NGI), was launched in 2000. Both design and subsequent archival calibration are documented to pharmaceutical standards.

The NGI is a high performance, precision, particle classifying cascade impactor having seven stages plus a micro-orifice collector (MOC).

In practice, its flexibility of use and high productivity are making the NGI the new "workhorse" within many inhaler research laboratories.

This trend will no doubt continue as reproducibility and productivity are improved with the addition of new accessories designed to automate the particle sizing process (see Page 105).

Correlation studies between ACI and NGI show good agreement between particle size distributions although this does not necessarily mean they are interchangeable for all DPIs.

Main features of the Next Generation Impactor (NGI) include:

- Designed by the pharmaceutical industry for the pharmaceutical industry
- Operates between 15 and 100 L/min
- 7 stages (5 out of the 7 always between 0.54 and 6.12 microns)
- Easy drug recovery with low inter-stage losses
- High stage efficiency: all stages: 500 < Re < 3000
- 3-part construction lends itself to semi and full automation
- Documented and published design and archival calibration

Multi-Stage Liquid Impinger (MSLI)

The Multi-Stage Liquid Impinger (MSLI) was the first cascade impactor/impinger specifically designed for inhaler testing.

Whilst the 4-Stage MSLI does not offer the number of stages of the ACI or NGI, it does, by definition, have no inter-stage losses and is suitable throughout the range 30-100 L/min.

Unlike the ACI and NGI, the collection stages of the MSLI are kept moist which eliminates the problem of particle bounce associated with conventional impactors.

Advantages include:

- 4 Stages between 1.7 and 13 microns
- Operates between 30 and 100 L/min
- Virtually no inter-stage losses
- Eliminates particle bounce and hence re-entrainment problems
- Choice of aluminum, 316 stainless or titanium construction
- Easy and quick drug recovery

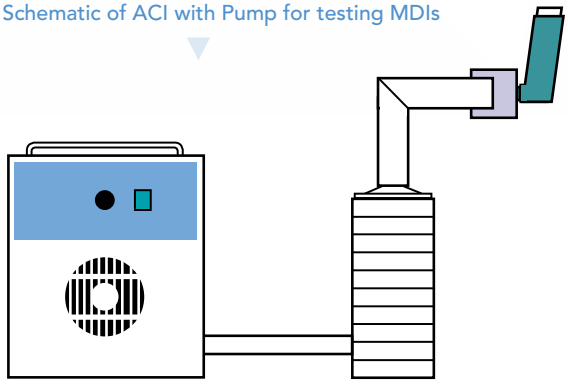
Other Impactors

The following impactors are also worthy of mention and are described in more detail later in the brochure:

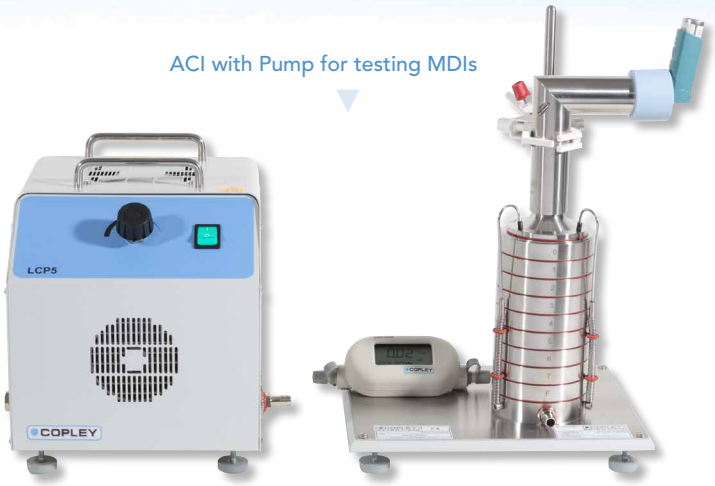
- **Glass Impinger**
- **Marple-Miller Cascade Impactor (MMI)**

Multi-Stage Liquid Impinger (MSLI) in Aluminium, 316 Stainless Steel and Titanium

Schematic of ACI with Pump for testing MDIs



ACI with Pump for testing MDIs



ANDERSEN CASCADE IMPACTOR (ACI)

The Andersen Cascade Impactor (ACI) **manufactured by Copley Scientific** is an 8-stage cascade impactor that has been designed for measuring the aerodynamic particle size distribution (APSD) generated by MDIs and DPIs.

It complies with the specifications laid down in USP Chapter <601>, Ph.Eur. 2.9.18 and the latest proposals aimed at harmonising the respective Pharmacopoeias.

IMPACTOR USE (METERED-DOSE INHALERS)

The standard Andersen Cascade Impactor is designed for use at 28.3 L/min (which is equivalent to 1 cubic foot/min).

The 8 stages have the following particle size collection bands:

- Stage 0 9.0 + microns
- Stage 1 5.8 – 9.0 microns
- Stage 2 4.7 – 5.8 microns
- Stage 3 3.3 – 4.7 microns
- Stage 4 2.1 – 3.3 microns
- Stage 5 1.1 – 2.1 microns
- Stage 6 0.7 – 1.1 microns
- Stage 7 0.4 – 0.7 microns

The Andersen Cascade Impactor, like other cascade impactors, is designed such that as the aerosol stream passes through each stage, particles having sufficient inertia will impact upon that particular stage collection plate, whilst smaller particles with insufficient inertia will remain entrained in the air stream and pass to the next impaction stage.

By analysing the amount of drug deposited on the various stages, it is then possible to calculate the Fine Particle Dose (FPD) and Fine Particle Fraction (FPF) and following further manipulation, the Mass Median Aerodynamic Distribution (MMAD) and Geometric Standard Deviation (GSD) of the active drug particles collected.

IMPACTOR USE (DRY POWDER INHALERS)

The same impactor can be used for determining the particle size of Dry Powder Inhalers (DPIs).

In this instance, however, a **preseparator** is interposed between the induction port and stage 0 of the impactor in order to collect the large mass of non-inhalable powder boluses typically emitted from a DPI prior to their entry into the impactor.

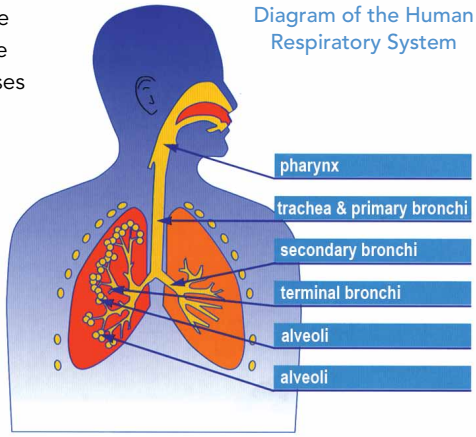
In the case of Dry Powder Inhalers (DPIs), a number of additional factors must be taken into account when testing:

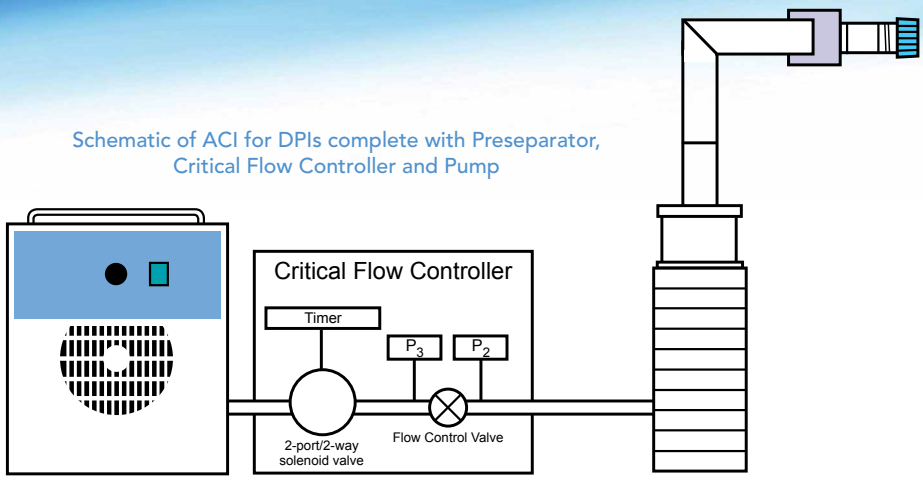
- The pressure drop generated by the air drawn through the inhaler during inspiration
- The appropriate flow rate, Q, to give a pressure drop of 4 kPa
- The duration of simulated inspiration to give a volume of 4 litres
- Flow rate stability in terms of critical (sonic) flow

These factors require the use of the "General Control Equipment" for DPIs specified in USP <601> and "Experimental Set Up" for testing DPIs in Ph.Eur. 2.9.18 which take all of these factors into account.

These specifications form the basis of the **Critical Flow Controllers (see Page 78)** which incorporate all of the equipment required into a single integrated system.

Diagram of the Human Respiratory System





Schematic of ACI for DPIs complete with Preseparator, Critical Flow Controller and Pump

Andersen Cascade Impactor for DPIs (with Preseparator)

ANDERSEN CASCADE IMPACTOR (ACI)

MODIFIED CONFIGURATIONS FOR USE AT 60 AND 90 L/MIN

In many cases (particularly with low resistance DPIs), it is necessary to operate at flow rates greater than 28.3 L/min, if a pressure drop over the inhaler of 4 kPa is to be achieved.

Whilst the ACI can be operated at flow rates greater than 28.3 L/min, it is important to consider the change in cut-points that will occur for each stage. An empirical equation can be used to calculate these cut-point changes over the range of 28.3 – 100 L/min. However, the user should be aware that reduced discrimination between the cut-points will occur as the flow rate is increased. Furthermore, the validity of the empirical equation becomes questionable, the further the test flow rate deviates from 28.3 L/min.

In order to help address these problems, two modified configurations of ACI are available for operating at flow rates of 60 and 90 L/min. These are described in USP Pharmacopoeial Forum Volume 28, Number 2, 2002, p. 601-603 and are now enshrined in USP 38.

In the 60 L/min version, stages 0 and 7 are removed and replaced with two additional stages, -0 and -1. Similarly, in the 90 L/min version, stages 0, 6 and 7 are removed and replaced with three additional stages, -0, -1 and -2. Changes are also made to the configuration of the collection plates (with and without centre holes).

This results in a **new** set of cut-points as per the table below.

Cut-off Diameters at	28.3	60	90	L/min
• Stage -2	----	----	8.0	microns
• Stage -1	----	8.6	6.5	microns
• Stage -0	----	6.5	5.2	microns
• Stage 0	9.0	----	----	microns
• Stage 1	5.8	4.4	3.5	microns
• Stage 2	4.7	3.2	2.6	microns
• Stage 3	3.3	1.9	1.7	microns
• Stage 4	2.1	1.2	1.0	microns
• Stage 5	1.1	0.55	0.22	microns
• Stage 6	0.7	0.26	----	microns
• Stage 7	0.4	----	----	microns

QUALITY

A number of papers published in the late 1990s highlighted concerns relating to the manufacture and performance of the Andersen Cascade Impactor manufactured by Graseby-Andersen between 1992 and 1998.

These focused on the choice of material used in their design, their construction, ease of use, accuracy, calibration and the ability to suitably qualify the impactors prior to use.

Because of these criticisms, Copley Scientific commenced manufacturing the Andersen Cascade Impactor using the latest state-of-the-art production techniques .

These techniques ensure that 100% of the jets **of every stage of every Copley impactor** conform to the published critical dimensions for the ACI stated in USP Chapter <601> and Ph.Eur. Chapter 2.9.18.

The validity of this data is guaranteed by dimensional verification using the very latest vision inspection technology having a demonstrated optical reproducibility of 1 micron (to a 99% confidence interval).

ACI System for testing DPIs

ANDERSEN CASCADE IMPACTOR (ACI)

MATERIALS OF CONSTRUCTION

The Andersen Cascade Impactor was originally designed for environmental air sampling and is traditionally constructed from aluminium. However its adoption by the pharmaceutical industry has placed far harsher demands on the material because of the use of organic solvents in the drug recovery process.

Recent advances in automated, high precision machining techniques now mean that the ACI can be manufactured from **316 stainless steel** (the pharmaceutical industry's preferred material) and also **titanium.**

The main advantage of 316 stainless steel is that of superior corrosion resistance and durability, meaning that 316 stainless steel impactors manufactured by Copley Scientific are not only very competitively priced but also highly cost effective, helping to maintain accuracy and extend impactor life by reducing mechanical and chemical wear. Electrically conductive, stainless steel can also help reduce the unwanted effects of electrostatics in the impactor.

Where the weight of 316 stainless steel is a concern, Copley Scientific can also offer titanium, which has the durability of 316 stainless steel but with a 40% reduction in weight.

Copley Scientific continues to offer aluminium ACIs for those users who prefer a lower cost option or for those cases where their methods are such that corrosion resistance and durability are not an issue. Leak-free inter-stage sealing is achieved through the use of high quality **FDA approved silicone rubber O-rings.**

Preseparators feature a one-piece seamless construction and, together with the induction ports, come with mensuration certificates as standard.

All collection plates are manufactured from 316 stainless steel. They are individually inspected for surface roughness and laser etched on the underside with batch number for traceability.

Also available as options are a one-piece (join-free) 316 stainless steel induction port and specially modified 'O-ring free' 316 stainless steel universal induction port for accepting the NGI style induction port.

EASE OF USE

The "**Quick Clamp**" is an optional accessory for use with the Andersen Cascade Impactor which can also be retrofitted to existing impactors.

Constructed from stainless steel, the "Quick Clamp" provides a quick and easy means of assembling, clamping and dis-assembling all **or part of the impactor stack** (for example, less stages 6 and 7) during routine operation.

Once the assembled stack is in position, the clamping action is achieved very simply by turning a small knob through 90 degrees.

Andersen Cascade Impactor (ACI) - Standard 28.3 L/min Configuration

Stage Number	Nozzles	Ph.Eur. Nozzle Diameter (mm)
0	96	2.55 ± 0.025
1	96	1.89 ± 0.025
2	400	0.914 ± 0.0127*
3	400	0.711 ± 0.0127*
4	400	0.533 ± 0.0127*
5	400	0.343 ± 0.0127*
6	400	0.254 ± 0.0127*
7	201	0.254 ± 0.0127*

* Rounded to 0.013 in the case of USP

ACI Carrying / Wash Rack

Andersen Cascade Impactor
(Aluminium, 316 Stainless Steel and Titanium)

ANDERSEN CASCADE IMPACTOR (ACI)

MENSURATION, QUALIFICATION AND SYSTEM SUITABILITY

Every impactor manufactured by Copley Scientific is machined to the same precision tolerances in order to guarantee reproducibility between impactors and to ensure stage mensuration.

Stage mensuration replaces the need for repetitive calibration using standardised aerosols and ensures that only impactors conforming to specification are used in testing.

In practice, this means that every jet on every stage of every impactor must be individually inspected to ensure compliance.

For this reason, all cascade impactors (including induction ports and preseparators) manufactured by Copley Scientific are checked at every stage of manufacture using the very latest in **metrology equipment** and are provided with a **mensuration certificate** and **leak test certificate** prior to release.

SUMMARY

Andersen Cascade Impactors manufactured by Copley Scientific are:

- Available in aluminium, 316 stainless steel or titanium
- Capable of operation at 28.3, 60 or 90 L/min
- Manufactured to USP and Ph.Eur. critical dimensions
- Supplied with full stage mensuration certificate, certificate of conformity to USP/Ph.Eur. and leak test certificate

The following ancillaries are required in addition to the ACI to complete a fully operating test system for determining the aerodynamic particle size distribution of MDIs:

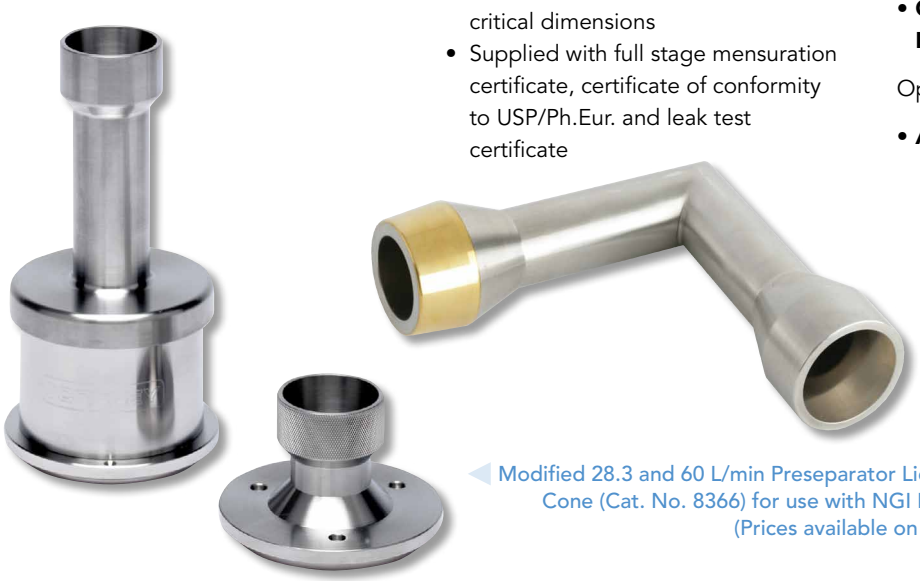
- **Mouthpiece Adapter (see Page 92)**
- **Induction Port (see Page 47)**
- **Vacuum Pump (see Page 93)**
- **Flow Meter (see Page 90)**
- **Data Analysis Software (see Page 86)**

plus the following in order to test DPIs:

- **Preseparator (see Page 47)**
- **Critical Flow Controller (see Page 78)**

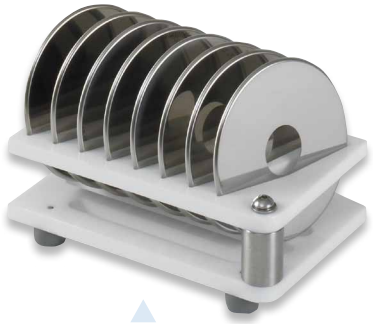
Options:

- **Automation (see Page 105)**



Modified 28.3 and 60 L/min Preseparator Lids (Cat. No. 8421/8422) and Inlet Cone (Cat. No. 8366) for use with NGI Induction Port Cat. No. 8366
(Prices available on request)

'Quick Clamp'



ACI Collection Plate Rack

ACI Collection Plates (featuring batch numbering)

Preseparator, 60 L/min Conversion Kit and Collection Plates

Cat. No.	Description
Impactors	
8301	28.3 L/Min Andersen Cascade Impactor*
8301-60	60 L/Min Andersen Cascade Impactor*
8301-90	90 L/Min Andersen Cascade Impactor*
Induction Ports	
8501	Universal Induction Port (Standard)*
8510	Universal Induction Port (One-piece 316 Stainless Steel)
Preseparators for testing DPIs	
8401	28.3 L/min Preseparator*
8420	60 L/min Preseparator*
8420-90	90 L/min Preseparator*
Conversion Kits for the standard 28.3 L/min ACI	
8318	Conversion Kit for 60 L/min operation*
8319	Conversion Kit for 90 L/min operation*
Options	
8111	Stand (incl. Base Plate, Boss Head and Clamp)
5212	'Quick Clamp' for Andersen Cascade Impactor
5401	ACI Carrying/Wash Rack
5441	ACI Collection Plate Rack
Spare Parts	
8307	Complete Set of 13 ACI Silicone Rubber O-Rings
8314	Set of 8 Stainless Steel Collection Plates (28.3 L/min)
8314-60	Set of 8 Stainless Steel Collection Plates (60 L/min)
8314-90	Set of 8 Stainless Steel Collection Plates (90 L/min)
8316	Box of 100 Glass Fibre Filters (81 mm)
8306	Set of 6 O-Rings for Spring Clamp
8308	Set of 3 Spring Clamps
8309	Set of 3 PVC End Caps for Spring Clamps
8403	Set of 4 O-Rings for Preseparator
8395	ACI Carrying Case
8351	Inlet Cone*
8352	Stage -2A*
8353	Stage -1A (for 90 L/min operation)*
8354	Stage -1 (for 60 L/min operation)*
8355	Stage -0*
8356	Stage 0*
8357	Stage 1*
8358	Stage 2*
8359	Stage 3*
8360	Stage 4*
8361	Stage 5*
8362	Stage 6*
8363	Stage 7*
8364	Stage F (Filter)*
8365	Base (including Hose Fitting)*

* Please specify **Aluminium (A)**, **316 Stainless Steel (S)** or **Titanium (T)** when placing your order.

NGI for MDIs (with Induction Port, but without Preseparator)

NEXT GENERATION IMPACTOR (NGI)

INTRODUCTION

Before the introduction of the NGI, the Andersen Cascade Impactor was the main impactor used by the pharmaceutical industry.

Although originally designed for microbial sampling, the ACI is a well-established instrument that has served the industry well. It remains in widespread use and is expected to do so in the foreseeable future. Because of its air sampling origins however, the ACI does suffer from certain drawbacks and it is not easy to automate.

In developing the **Next Generation Impactor,** the consortium involved drew on their extensive experience to come up with a list of "musts" and "wants" for the new impactor.

The result, the NGI, was an impactor having the following features:

- Designed by the pharmaceutical industry for inhaler testing
- Meets and exceeds all Ph.Eur. and USP specifications
- Particle size range: 0.24 – 11.7 microns (dependent on flow rate)
- Seven stages; five with cut-offs between 0.54 and 6.12 microns at flow rates from 30 to 100 L/min
- Excellent stage efficiency, accuracy and reproducibility
- Archivally calibrated flow rate range: 30 – 100 L/min
- Additional calibration at 15 L/min for nebuliser applications
- Supplied with full stage mensuration report (system suitability)
- Low inter-stage wall losses ensure good drug recovery (mass balance)
- User friendly design for maximum throughput and easy automation
- Electrically conductive; unaffected by static
- Design and archival calibration formally documented and published

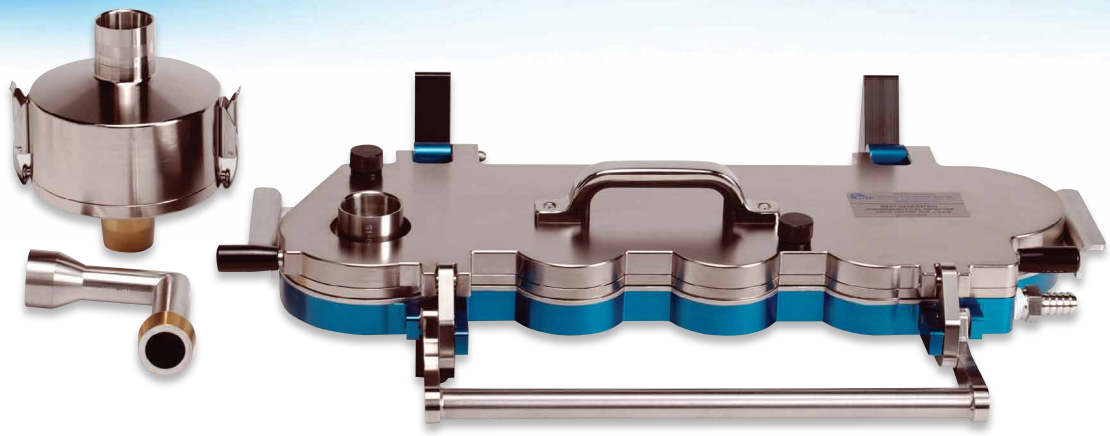
Cut-off diameters at	15	30	60	100	L/min
• Stage 1	14.10	11.76	8.06	6.12	microns
• Stage 2	8.61	6.40	4.46	3.42	microns
• Stage 3	5.39	3.99	2.82	2.18	microns
• Stage 4	3.30	2.30	1.66	1.31	microns
• Stage 5	2.08	1.36	0.94	0.72	microns
• Stage 6	1.36	0.83	0.55	0.40	microns
• Stage 7	0.98	0.54	0.34	0.24	microns
• MOC	0.70	0.36	0.14	0.07	microns

DESCRIPTION

The initial design considerations concentrated on the number of stages and basic layout. Seven stages were finally specified to give five with cut-off diameters in the 0.5 - 5 micron range and a horizontal planar layout adopted for ease of operation and automation.

The cut-off diameters for the relevant stages at volumetric flow rates of 15, 30, 60 and 100 L/min are given below.

The air flow passes through the impactor in a saw tooth pattern. Particle separation and sizing is achieved by successively increasing the velocity of the airstream as it passes through each by forcing it through a series of nozzles containing progressively reducing jet diameters.



NGI for DPIs (with Induction Port and Preseparator removed)

The impactor itself comprises just **three main parts:**

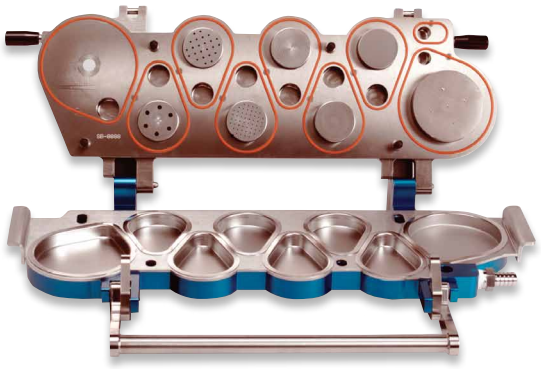
1. The cup tray containing the eight collection cups used to collect the samples prior to analysis.
2. The bottom frame used to support the cup tray.
3. The lid containing the inter-stage passageways and the seal body which holds the nozzles in place.

In routine operation, the three parts are held together using the handle clamping mechanism. Each circular nozzle assembly (stage) is held above a tear-shaped cup in a single seal body.

The feasibility of incorporating **removable nozzles** was considered at some length by the consortium but it was decided that this was not possible without compromising impactor integrity. The current fixed design gives confidence in the jet-to-plate distance – a major determinant of capture efficiency. Perhaps more importantly, it completely eliminates the high levels of risk associated with removable nozzles being replaced in the wrong position.

A removable tray holds all the sample cups such that all of the cups can be removed and/or replaced in one single operation. Low inter-stage losses and minimal particle carryover mean that only the cups and tray need changing between tests. Most NGI users benefit from multiple sets of cups with a single impactor in order to maximise productivity.

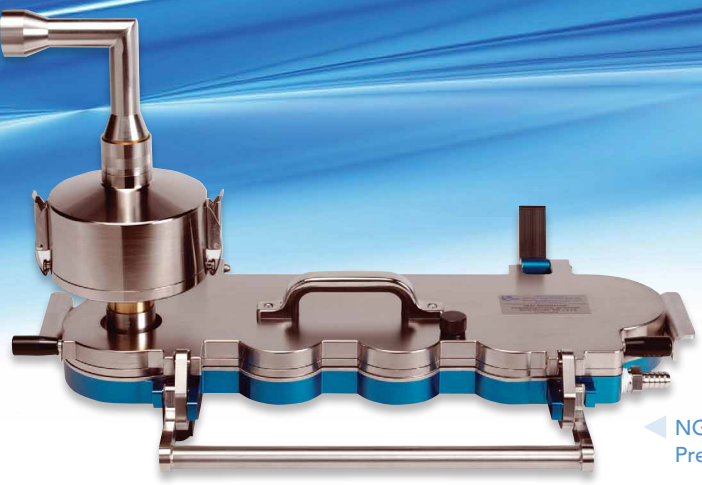
At either end, the NGI has two larger cups that collect from Stage 1 Cup and the **Micro-Orifice Collector (MOC)** respectively.



NGI (Open View) Showing Nozzles and Collection Cups

NGI (Open View) Showing Cup Tray Removed

Collection Cups and Cup Tray



NGI for DPIs (with Preseparator)

Preseparator (internal view)

NEXT GENERATION IMPACTOR (NGI)

The large cup used in Stage 1 minimises large particle impaction on the walls of that particular stage.

Whilst not a particle classifying stage in its own right, the Micro Orifice Collector has 4032 jets each approx. 70 microns in diameter and is capable of 80% collection efficiency of 0.3 micron particles (at 30 L/min) thus, in most cases, eliminating the need for a final filter paper.

However, if ultra-fine particles are present, as for example in solution MDIs, then an **Internal** or **External Filter Holder** can be used to collect these particles in the conventional manner.

The **NGI Induction Port** is manufactured from 316 stainless steel. The tapered and hardened outlet provides an airtight seal with the inlet to Stage 1 without the use of O-Rings whilst retaining the critical internal dimensions stated in Ph.Eur. and USP.

As with other impactors, the NGI requires the use of a preseparator when used with DPIs in order to catch any powder boluses and large non-inhalable particles. The **NGI Preseparator** is a high capacity, high efficiency, two-stage preseparator with a sharp and reproducible cut-point of between 10 and 15 microns depending on flow rate.

Four special types of sample collection cup are available in addition to those supplied as standard with the NGI:

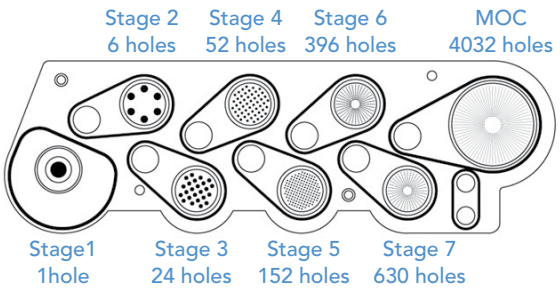
- Gravimetric Cup (for PSD determinations based on weight)
- Sintered Glass Disc Cup (for liquid impingement tests)
- Exhaust Cup (to bypass downstream portion of impactor)
- Glass Disc Cup (for Malvern Morphologi G3-ID system tests)

The NGI measures approx. 500 mm (L) x 160 mm (W) x 300 mm (H) (including induction port and preseparator) and weighs approx. 10 kg.

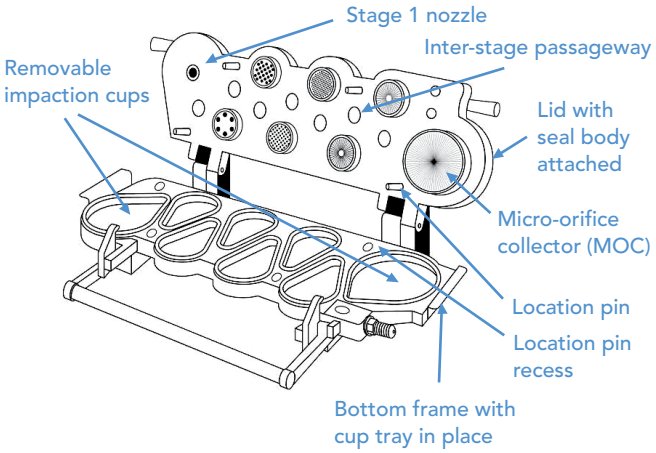
Further details regarding the design and archival calibration of the NGI can be found in the Journal of Aerosol Medicine Volume 16(3), 2003 and Volume 17(4), 2004.

PROCEDURE

1. Open the hinged lid of the NGI using the quick-release handle.
2. Place a fresh set of collection cups (coated as required) into a cup tray and locate the tray in the bottom frame of the impactor.
3. Close the impactor and perform a leak test (if necessary).
4. Attach the preseparator (if required) and the induction port to the inlet of the NGI and a suitable vacuum pump to the outlet.
5. Connect the inhaler to the inlet of the induction port using a suitable mouthpiece adapter and actuate the dose.
6. Remove the inhaler, the throat and the preseparator (if used) and recover the sample from these components using a suitable solvent.
7. Open the impactor, remove the cup tray and add 10 ml of solvent to each of the cups. Agitate gently before assaying the contents using a suitable solvent.
8. The impactor is now ready for another test.



Schematic of Seal Body showing orientation of the various stages



NGI Cup Rack

NGI Carrying/Wash Rack

Internal (left) & External (right) Filter Holders

Malvern Glass Disc Cup

The following ancillaries are required in addition to the NGI to complete a fully operating test system for determining the aerodynamic particle size distribution of MDIs:

- **Mouthpiece Adapter (see Page 92)**
- **Induction Port (Page 51)**
- **Vacuum Pump (see Page 93)**
- **Flow Meter (see Page 90)**
- **Data Analysis Software (see Page 86)**

plus the following in order to test DPIs:

- **Preseparator (Page 51)**
- **Critical Flow Controller (see Page 78)**

Options:

- **Automation (see Page 105)**

Small Gravimetric Cup

Cat. No.	Description
Impactors	
5201	Next Generation Impactor (NGI)
Induction Ports	
5203	NGI Induction Port
Preseparators for testing DPIs	
5204	NGI Preseparator
Accessories	
5205	NGI Carrying/Wash Rack
5206	Internal Filter Holder
5210	External Filter Holder
5222	NGI Collection Cup Rack
5240	Box of 100 Filters (for Internal/External Filter Holder above)
5241	Small Gravimetric Cup (for APSD determinations based on weight)
5244	Large Gravimetric Cup (for APSD determinations based on weight)
5242	Sintered Glass Disc Cup (for liquid impingement tests)
5242A	Malvern Glass Disc Cup (for Morphologi G3-ID system tests)
5243	Exhaust Cup (to bypass downstream stages of impactor)
5254	NGI Transportation Case
Spare Parts	
5208	Collection Cup Tray
5209	Set of 8 Collection Cups (2 Large, 6 Small)
5245	Welded Cup Tray Manifold
5211	Set of 18 Seals for the Next Generation Impactor
5246	Set of 10 Seals for the NGI Preseparator
5247	Set of 10 Seals for the NGI Internal Filter Holder
5248	Set of 10 Seals for the NGI External Filter Holder
5249	NGI Outlet Diameter Reducing Adapter

MULTI-STAGE LIQUID IMPINGER (MSLI)

The Multi-Stage Liquid Impinger (MSLI) is a versatile **four–stage** liquid impinger which can be used for determining the particle size (aerodynamic size distribution) of DPIs in the case of USP Chapter <601> and for MDIs and DPIs in the case of Ph.Eur. Chapter 2.9.18.

The MSLI is available in a range of materials: **aluminium, 316 stainless steel** or **titanium.** This choice allows flexibility in terms of corrosion resistance, weight and cost. The MSLI is fitted with PTFE seals as standard.

The design is such that at a flow rate of 60 L/min, the cut-off diameters of Stages 1, 2, 3 and 4 are 13, 6.8, 3.1 and 1.7 microns respectively. Stage 5 comprises an integral paper filter to capture the remaining fraction of particles less than 1.7 microns.

The MSLI has, by definition, no inter-stage losses and is suitable for use throughout the range **30 - 100 L/min.**

Unlike the ACI, NGI and MMI, the collection stages of the MSLI are kept moist which helps to reduce the problem of re-entrainment sometimes experienced when using more conventional impactors. It employs the same induction port as the other cascade impactors.

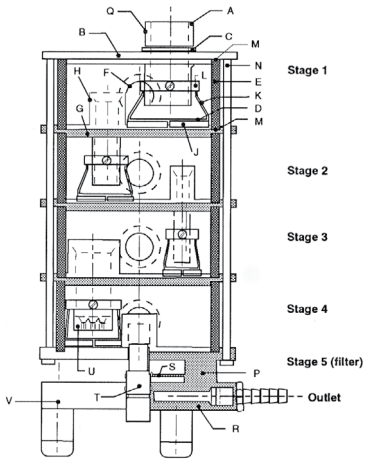
When testing Dry Powder Inhalers, a flow rate, Q, should be used where Q is the flow rate required to produce a drop of 4.0 kPa over the inhaler as determined during testing with the Sampling Apparatus for DPIs (Delivered Dose), provided that the value of Q falls in the range of 30-100 L/min. For a value of Q > 100, a flow rate of 100 L/min should be used.

A **stage mensuration certificate** and **leak test certificate** are included with each MSLI as standard. Stage mensuration replaces the need for repetitive particle calibration using standardised aerosols and ensures that only impactors conforming to specification are used in testing.

During the mensuration, the sintered glass impingement stages are positioned using calibrated gauge blocks to ensure that the correct jet-to-plate distance is maintained.

The MSLI uses the same system components as that of the Andersen Cascade Impactor (see Page 47) with the exception of the preseparator which is not required since Stage 1 of the MSLI performs this function.

Multi-Stage Liquid Impinger



Cat. No.	Description
8801	Multi-Stage Liquid Impinger (MSLI)*
8501	Universal Induction Port*

* Please specify **Aluminium (A), 316 Stainless Steel (S)** or **Titanium (T)** when placing your order.

Options

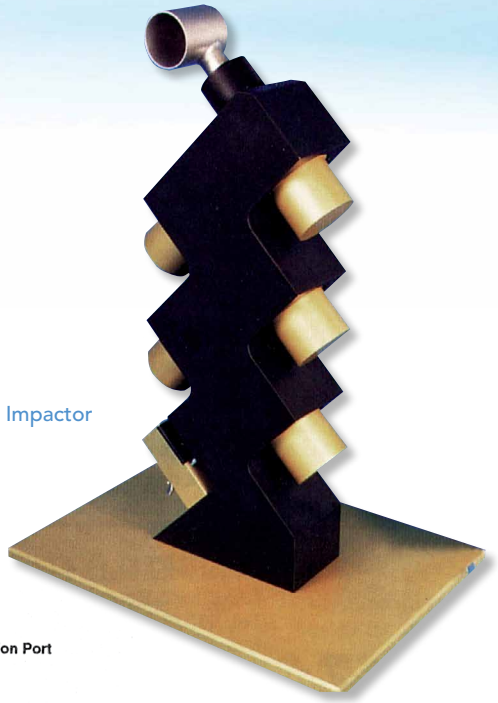
8111	Stand (incl. Base Plate, Boss Head and Clamp)
8851	Torque Adjuster for MSLI

Spare Parts

8805	Set of 3 O-Rings
8807	Set of 8 Inter-Stage PTFE Gaskets (Code M on schematic)
8814	Filter Support Plate (Code S on schematic)
8834	Pack of 10 Silicone Rubber Stoppers
8839	Pack of 100 Glass Fibre Filters 76 mm
8840	Ground Glass Cylinder (Code E on schematic)
8844	Set of 4 Sintered Glass Discs (Code D on schematic)

MARPLE-MILLER CASCADE IMPACTOR (MMI)

Marple-Miller Cascade Impactor



The Marple-Miller Impactor Model 160 is specified as Apparatus 2 in the USP and is a five-stage cascade impactor which has been designed for determining the particle size (aerodynamic size distribution) of Dry Powder Inhalers (DPIs).

The **Model 160** has five impaction stages and is calibrated for operation between **60 and 90 L/min**. Each stage has a removable collection cup to assist in the quick and simple recovery of the drug particles with low inter-stage losses.

A paper filter is also incorporated after Stage 5 to ensure total mass balance. At a volumetric flow rate of 60 L/min, the cut-off diameters of Stages 1 to 5 are as follows:

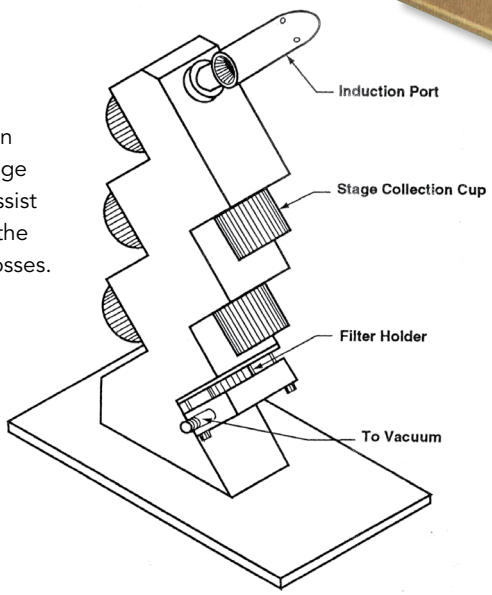
- Stage 1: 10 microns
- Stage 2: 5.0 microns
- Stage 3: 2.5 microns
- Stage 4: 1.25 microns
- Stage 5: 0.63 microns

and at 90 L/min:

- Stage 1: 8.1 microns
- Stage 2: 4.0 microns
- Stage 3: 2.0 microns
- Stage 4: 1.0 microns
- Stage 5: 0.5 microns

Two other versions of the impactor are available, such that between the three impactors, a **flow rate range of 4.9 to 90 L/min** is covered.

When testing DPIs according to USP, a flow rate, Q, should be used where Q is the flow rate required to produce a pressure drop of 4.0 kPa over the inhaler when tested on the Dosage Unit Sampling Apparatus (DUSA) for DPIs (see Page 20). This is provided that the value of Q falls in the range of 30-100 L/min (for a value of Q > 100, a flow rate of 100 L/min should be used).



The actual cut-off diameters of each of the individual stages of the impactor at the flow rate, Q, may be calculated as follows:

$D50'Q = D50'Qn\ (Qn/Q)1/2$

where D50'Q is the cut-off diameter at the flow rate, Q, and the subscript, n, refers to the nominal values determined when Qn equals 60 L/min. Thus when Q equals 40 L/min, the cut-off diameter of Stage 2 is given by the formula:

D50'40 L/min = 5 microns x (60/40)1/2 = 6.1 microns

In this impactor, particles are deposited directly onto the bottom of the stage collection cups which can then be easily removed after each test without dismantling the impactor.

Because the impactor is designed to have very low inter-stage losses, it is not necessary to frequently clean the inter-stage passageways between tests.

The Marple-Miller Impactor **Model 150** has half the number of jets per stage compared with Model 160, such that the same cut-points apply at 30 L/min as opposed to 60 L/min. This version is calibrated for use through the flow rate range **30 to 60 L/min**.

A low flow rate version for paediatric applications, the **Model 150P**, is also available for operation between **4.9 L/min and 12 L/min**.

The MMI uses the same system components as the Andersen Cascade Impactor (see Page 35) with the exception of the preseparator which is not required since Stage 1 of the MMI performs the same function.

Cat. No.	Description
6901	Marple-Miller Cascade Impactor Model 160 (60 - 90 L/min)
6902	Marple-Miller Cascade Impactor Model 150 (30 - 60 L/min)
6903	Marple-Miller Cascade Impactor Model 150P (4.9 - 12 L/Min)

Glass Twin Impinger

Modification for Nasal Sprays

Spare Set of Glassware

GLASS TWIN IMPINGER

The value of the Glass Twin Impinger, particularly with respect to routine quality control applications, is recognised by its retention as Apparatus A in Ph.Eur. 2.9.18.

Its usage is restricted to the assessment of nebulisers, MDIs and such DPIs where it can be demonstrated that a flow rate of 60 (+/- 5) L/min is suitable.

Developed at GSK's laboratories in Ware, UK, the Glass Twin Impinger is relatively simple and easy to use, and assemble.

The major advantage is that it is manufactured solely from glass so that it is not prone to corrosion in the same way as conventional metallic impactors.

The Glass Twin Impinger comes complete with stainless steel base plate, stand, clamp and boss head in addition to plastic clips to retain the glass parts in position and is supplied with a mensuration certificate confirming that the critical dimensions conform to those stated in Ph.Eur.

It operates on the principle of liquid impingement to divide the dose emitted from the inhaler into respirable and non-respirable portions.

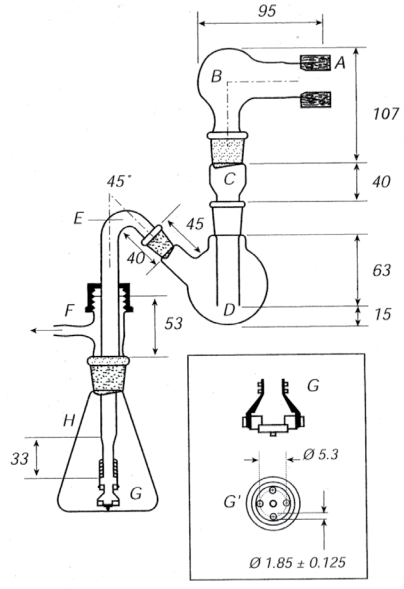
The non-respirable dose impacts on the oropharynx and is subsequently swallowed. This is considered as the back of the glass throat and the upper impingement chamber (collectively described as **Stage 1**). The remaining respirable dose penetrating the lungs is collected in the lower impingement chamber (**Stage 2**).

The upper impingement chamber is designed such that at a flow rate of 60 L/min through the impinger, the particle cut-off is **6.4 microns**. Particles smaller than 6.4 microns pass into the lower impingement chamber.

Prior to testing, 7 mL of solvent is typically dispensed into the upper impingement chamber and 30 mL to the lower impingement chamber. After the test is complete, the active drug collected in the lower impingement chamber is assayed and expressed as a respirable fraction (or percentage) of the delivered dose.

The Glass Impinger requires a special mouthpiece adapter, a vacuum pump and a flow meter to complete the system.

A special modification for the measurement of the particle size of nasal sprays according to Aaiche and Beyssac is also available as an option.

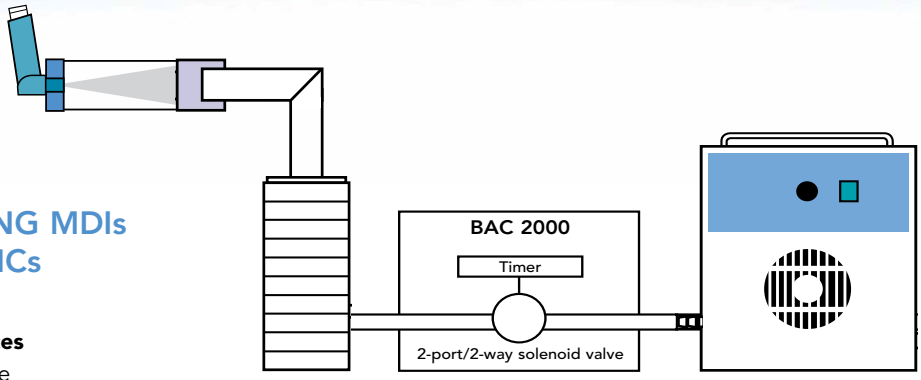


Schematic of Glass Twin Impinger

Cat. No.	Description
8901	Glass Twin Impinger
8999	Modification for Nasal Sprays (acc. to Aaiche & Beyssac)

Spare Parts

8903	Throat (Ph.Eur. Code B)
8904	Neck (Ph.Eur. Code C)
8905	Upper Impingement Chamber (Ph.Eur. Code D)
8906	Coupling Tube (Ph.Eur. Code E)
8907	Screwthread Side-Arm Adapter (Ph.Eur. Code F)
8912	Lower Jet Assembly (Ph.Eur. Code G)
8908	Lower Impingement Chamber (Ph.Eur. Code H)
8909	Throat Flow Meter Adapter (Ph.Eur. Code I)
8910	Vacuum Pump Adapter (Ph.Eur. Code J)
8913	Set of 2 Conical Joint Clips (Yellow)
8914	Set of 4 Conical Joint Clips (Green)
8916	Spare Set of Glassware (incl. clips and Lower Jet Assembly)



ACI based System (with Pump and Breath Actuation Controller Model BAC 2000)

IMPACTORS FOR TESTING MDIs WITH SPACERS AND VHCs

Spacers and **Valved Holding Devices (VHCs)** are add-on devices which are used in conjunction with pressurised metered dose inhalers (pMDIs) to overcome the problems of poor inhalation technique, e.g. the patient delays inhalation after actuating the inhaler.

A full description of these add-on devices and their use can be found on Pages 34 and 35.

The new draft chapter <1602> for testing **Spacers and Valved Holding Chambers used with Inhalation Aerosols** recently released by USP specifies two tests relating to the Aerodynamic Particle Size Distribution (APSD) of the accessories concerned.

In both cases, the spacer/VHC is tested with the mouthpiece or facemask removed.

Test Part 1A is designed to measure the APSD from the spacer/VHC when used in optimal conditions, that is to say, with no delay following actuation of the inhaler.

Direct comparisons can then be made between the APSD produced by the pMDI both with and without the add-on device.

If the spacer/VHC is intended for adults, then the standard ACI or NGI (without preseparators) should be used in conjunction with a suitable pump capable of producing 28.3 or 30 L/min respectively and appropriate mouthpiece adapter.

If the add-on is intended for neonates, infants or small children, then use the NGI at 15 L/min or the MMI 150 or 150 P described on Page 54.

Test Part 1B is used for testing VHCs only and is designed to measure the APSD from the VHC when used in "worst case" conditions, that is to say, with **a delay of 2 or more seconds** between inhaler actuation and sampling onset.

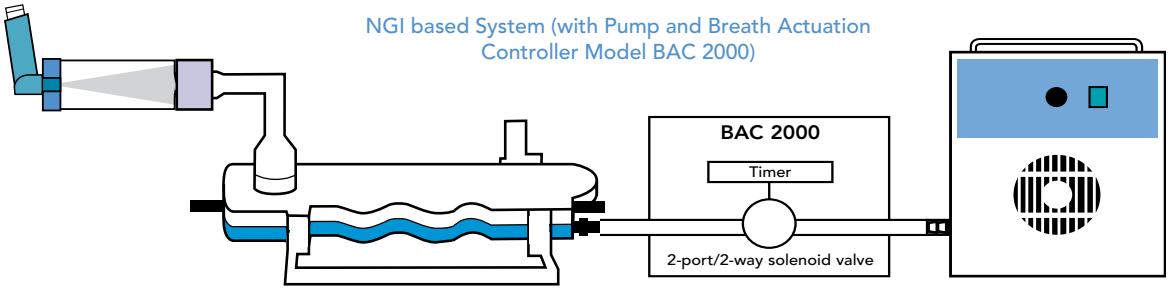
The delay can be simulated by placing a timer controlled two way solenoid valve such as the Breath Actuation Controller Model BAC 2000 between the impactor and the pump (see illustrations).

This provides near instantaneous starting and stopping of the air flow during testing and has both delay and inhaled time functions without compromising the integrity of the induction port and/or test setup.

The following equipment is required to provide a fully operating test system for determining the APSD of spacers/VHCs:

- **Mouthpiece Adapter (see Page 92)**
- **ACI (Page 47), NGI (Page 51) or MMI (see Page 54)**
- **Induction Port (see above)**
- **Breath Actuation Controller (see Page 84)**
- **Vacuum Pump (see Page 93)**
- **Flow Meter (see Page 90)**

NGI based System (with Pump and Breath Actuation Controller Model BAC 2000)



IMPACTORS FOR TESTING NASAL DELIVERY SYSTEMS

Traditionally, nasal preparations have been used for the local administration of anti-histamines, decongestants, and steroids in order to alleviate cold or allergy symptoms and nasal congestion.

More recently, attention has focused on two other areas:

a) The potential rapid drug absorption into the systemic circulation provided by the turbinates and lymphoid tissues located at the back of the nasal cavity. This is already in use in a number of areas, e.g. migraine and pain relief, osteoporosis, vaccines, etc., and

b) The potential of the "Nose to Brain" entry to the central nervous system presented by the olfactory region at the top of the nasal cavity for the treatment, for example, of diseases of aging such as Alzheimers Disease, etc.

Conventional nasal technologies fall into three main categories:

- Metered Spray Pumps (Aqueous based)
- Propellant based Nasal Aerosols (MDIs)
- Powder based Nasal Devices

Nasal sprays typically produce droplets in the range 20-200 microns which is outside the effective range of inertial impactors. For this reason, the droplet size distribution of nasal sprays and aerosols is normally determined by means of laser diffraction.

At the same time however, most sprays deliver a proportion (typically <5%) of fine droplets in the <10 micron range.

It is important to quantify this **"fine particle dose"** since it can penetrate beyond the nasal tract and into the lower respiratory tract or lungs, which may prove undesirable.

In its Draft Guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" of April 2003, the FDA recognises the nature of this problem and recommends the use of a cascade impactor in conjunction with a high volume expansion chamber to measure the amount of drug in small particles or droplets in respect of nasal sprays and the particle/droplet size distribution in the case of nasal aerosols.

The purpose of this exercise is to quantify the amount of drug present in the form of particles or droplets that are less than 10 microns, with a view to predicting their possible deposition in the lungs.

In accordance with the draft guidance, Copley Scientific now offers a range of glass expansion chambers to meet these requirements.

In the case of **nasal sprays**, a 2 litre or larger (5 litre) expansion chamber is preferred. In the case of **nasal aerosols**, a 1 litre chamber is used to maximise drug deposition below the top stage of the impactor.

Each of the chambers contains an entry port at approx. 30 degrees to the outlet port for insertion of the nasal spray or aerosol. Special nosepiece adapters are available for the entry port to accommodate powder, spray and aerosol based devices.

Adapters are also available to connect the outlet port of the expansion chamber to the inlet cone of the Andersen Cascade Impactor (ACI).

The adapters are available in aluminium, 316 stainless steel or titanium and have internal dimensions similar to those at the outlet of the Universal Induction Port typically used for orally administered inhaled products.

Each adapter is supplied with a clamping device which allows the glass expansion chamber to be easily removed from the impactor for assay.

Reduced Stack ACI

IMPACTORS FOR TESTING NASAL DELIVERY SYSTEMS

During use, the clamp provides an airtight seal between the expansion chamber and the adapter through the use of an FDA approved silicone rubber O-ring incorporated into the neck of the adapter.

A special adapter and clamp are also available for the Next Generation Impactor.

The majority of nasal products are designed to generate droplets/particles having a mass median aerodynamic diameter (MMAD) of greater than 10 to 20 microns. This is to increase nasal deposition and minimise deposition in the lungs.

Cascade Impactors, on the other hand, are designed to capture particles in the range 0 to 10 microns. It follows that the majority of particles discharged from a nasal product will be deposited on the upper stages of the impactor concerned.

As a general rule, the **potential areas of interest** may be divided into three groups:

1. Those particles >10 microns and hence retained in the intranasal passageways.
2. Those particles between 5 and 10 microns destined for the gastrointestinal tract.
3. Those particles <5 microns potentially capable of depositing in the lungs.

After validation, it may therefore be appropriate to use a reduced impactor stack (e.g. Stage 0 = >9 microns, Stage 2 = 4.7 to 9 microns, Stage F = 0.4 – 4.7 microns of an Andersen Cascade Impactor at 28.3 L/min).

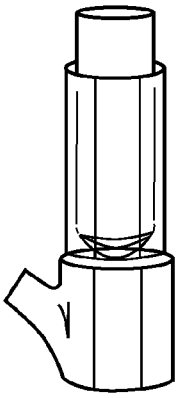
In these cases, we would recommend the use of the "Quick Clamp" (see Page 47) which is designed to allow clamping of the ACI with a reduced number of stages, or the special versions of the ACI and NGI such as the FSA or FSI classified under AIM (see Page 62).

The following ancillaries are required in addition to the items below to complete a fully operating test system for determining the aerodynamic particle size distribution of nasal sprays and aerosols:

- **Cascade Impactor (see Page 43 for ACI, Page 48 for NGI)**
- **Vacuum Pump (see Page 93)**
- **Flow Meter (see Page 90)**

Expansion Chamber to Flow Meter Adapter

Metered Nasal Spray Pump



Propellent based Nasal Aerosol

Cat. No.	Description
Expansion Chambers	
8950	1000 mL Glass Expansion Chamber
8951	2000 mL Glass Expansion Chamber
8952	5000 mL Glass Expansion Chamber
8953	Volume Verification Certificate for Expansion Chamber
8954	Adapter & Clamp for Andersen Cascade Impactor (ACI)*
5217	Adapter & Clamp for Next Generation Impactor (NGI)*
8961	Set of 10 O-Rings for Expansion Chamber Adapter
5212	'Quick Clamp' for ACI
Nasal Adapters	
8957	Nasal Aerosol Nosepiece Adapter for Expansion Chamber Inlet
8958	Tooling Charge for above (per nasal aerosol device)
8959	Nasal Spray Nosepiece Adapter for Expansion Chamber Inlet
8960	Tooling Charge for above (per nasal spray device)
8956	Expansion Chamber to Flow Meter Adapter

* Please specify **Aluminium (A)**, **316 Stainless Steel (S)** or **Titanium (T)** when placing your order.

NGI Cooler

IMPACTORS FOR TESTING NEBULISERS

INTRODUCTION

In 2006, the European Medicines Agency (EMA) issued a new "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" in which they included regulatory guidance on the drug aspects of nebulisers on the grounds that the safety and efficacy of nebulisers was dependent on the nebuliser/drug combination and not just on the nebuliser alone.

As a result of the EMA initiative and recognising the lack of suitable test methods for nebulisers, the Pharmacopoeias have in turn introduced a new Chapter on "**Preparations for Nebulisation: Characterisation**" (see Ph.Eur. Chapter 2.9.44 and USP Chapter <1601>).

It is these proposals that form the basis for the tests specified in Annex C of the new **ISO 27427:2013** requirements (based on the European Standard EN 13544-1:2007) for the "safety, performance and testing for general purpose nebulising systems intended for continuous or breath-actuated delivery of liquids in an aerosol form, to humans through the respiratory system", and the tests and equipment outlined below.

NGI COOLER

The recommended **flow rate of 15 L/min** employed in the APSD testing of nebulisers is lower than that of other OINDPs in order to better simulate the normal tidal breathing conditions employed in their *in vivo* use.

For this reason, an EPAG (European Pharmaceutical Aerosol Group) led initiative was launched in 2002 to provide an extension to the archival calibration of the Next Generation Impactor (NGI) to 15 L/min.

The results published in 2004 indicated that the NGI could be used to meet the requirements of the future standard, albeit without the preseparator and by using the internal filter holder to collect any fine droplets less than 0.98 microns. Cup coating is not normally required.

This produces an impactor with seven stages having cut-off diameters at 14.1, 8.61, 5.39, 3.30, 2.08, 1.36 and 0.98 microns respectively at 15 L/min.

Internal Filter Holder

It is believed that for devices such as nebulisers, which deliver the active as an aerosolised solution, evaporation caused by heat from the impactor can be a problem.

The ensuing loss of solvent reduces droplet size, producing artificially low particle size measurements and thus compromising the integrity of the resulting data. Cooling the impactor to approximately 5 degrees Celsius is the recommended method for overcoming this problem.

The **NGI Cooler** comfortably accommodates the NGI, either closed or open, allowing testing in a temperature controlled environment. Rapid cooling ensures that test temperatures, user adjustable as low as 5 degrees C, are reached in less than 5 minutes; temperature stability is to within +/- 1.5 degrees C. Large front and rear opening doors allow for easy access with special access ports to accommodate the nebuliser and vacuum pump connections.

3-Way Valve

NGI System for Testing Nebulisers (with Breath Actuation Controller Model BAC 2000)

PROCEDURE

Determine the sampling time (T_o) by balancing stage overload against analytical sensitivity. The time chosen should be sufficient to ensure adequate sample is collected for analysis without overloading the collection cups concerned.

Set the flow rate to 15 L/min by proceeding as follows:

1. Assemble the test system as instructed.
2. Attach a suitable flow meter to the inlet of the induction port.
3. Switch on the vacuum pump.
4. Open the 3-way valve** connecting the vacuum pump to the impactor.
5. Adjust the flow control valve on the vacuum pump until the flow rate through the system is steady at 15 L/min +/- 5%.
6. Switch off the pump, close the 3-way valve** and remove the flow meter and adapter.

* *Note: If method development indicates that the nebulised aerosol is significantly affected by evaporation then use the NGI Cooler to cool the impactor before and during testing.*

** *Alternatively, use a timer controlled two way solenoid valve such as the Breath Actuation Controller Model BAC 2000 between the impactor and the pump (see description on Page 84).*

This provides near instantaneous starting and stopping of the air flow during testing and has both delay and inhaled time functions without compromising the integrity of the induction port and/or test set-up.

Proceed as follows:

1. Prepare the nebuliser for operation in the normal manner.
2. Switch on the vacuum pump, the nebuliser and the cooler (if required) and allow to stabilise.
3. Ensure that the environmental conditions are as stated.
4. Open the 3-way valve** so that the flow passes through the impactor.
5. Sample for the predetermined time (T_o).
6. Close the 3-way valve and switch off the nebuliser and vacuum pump.
7. Dismantle the impactor and, using a suitable method, determine the mass of active collected in the induction port, on each stage and on the final filter.
8. Collect and present the data as described in the monograph.

The following ancillaries are required in addition to the items below to complete a fully operating test system for determining the aerodynamic particle size distribution of nebulisers:

- **Vacuum Pump (see Page 93)**
- **Breath Actuation Controller (see Page 84)****
- **Flow Meter (see Page 90)**
- **Data Analysis Software (see Page 86)**

Cat. No.	Description
Impactor	
5201	Next Generation Impactor (NGI)
5203	NGI Induction Port
5206	Internal Filter Holder
5240	Box of 100 Filters (for Internal/External Filter Holder above)
5003	Mouthpiece Adapter
5004	Tooling Charge for above
5006	3-Way Valve**
NGI Cooler	
5009	NGI Cooler (option)
5011	NGI Cooler Qualification Documentation
5012	NGI Cooler Qualificaton Tools
5013	Re-calibration of NGI Cooler Qualification Tools

ABBREVIATED IMPACTOR MEASUREMENT (AIM)

INTRODUCTION

In 2002, the FDA launched a new initiative "Pharmaceutical cGMPs for the 21st Century" in which it proposed a new approach to pharmaceutical manufacturing. This initiative gave birth to **Process Analytical Technology (PAT)**, a framework for understanding and improving the processes involved in pharmaceutical development, manufacturing and quality assurance described in FDA's Guidance of September 2004.

PAT operates on the premise that quality cannot be tested into a product; rather, it should be built-in or should be by design. The goal is to ensure final product quality by understanding and controlling the processes involved in the manufacturing process.

The **Quality by Design (QbD)** approach agreed and recently recommended for adoption by the EMA, FDA and the Japanese MWHL in the form of the five quality related guidelines, ICH Q8, Q9, Q10, Q11 and Q12 published by the International Conference on Harmonisation (ICH), extends this philosophy to all parts of the product cycle from product development, transfer through to manufacturing, manufacturing and finally product end.

Unfortunately, because of their unique nature of part device/ part formulation, the practical implementation of QbD principles to orally inhaled products (OIPs) is not easy.

Aerodynamic Particle Size Distribution (APSD) is widely recognised as a Critical Quality Attribute (CQA) in the *in vitro* characterisation of an OINDP. This is because it is the APSD of an aerosol cloud that influences where the particles in that cloud are deposited in the respiratory tract following inhalation and hence is a major determinant in its therapeutic efficacy.

The preferred instrument of choice for measuring the APSD of inhaled products for both regulators and pharmacopoeias alike is the cascade impactor. This is because it has three unique features which currently no other technique can replicate:

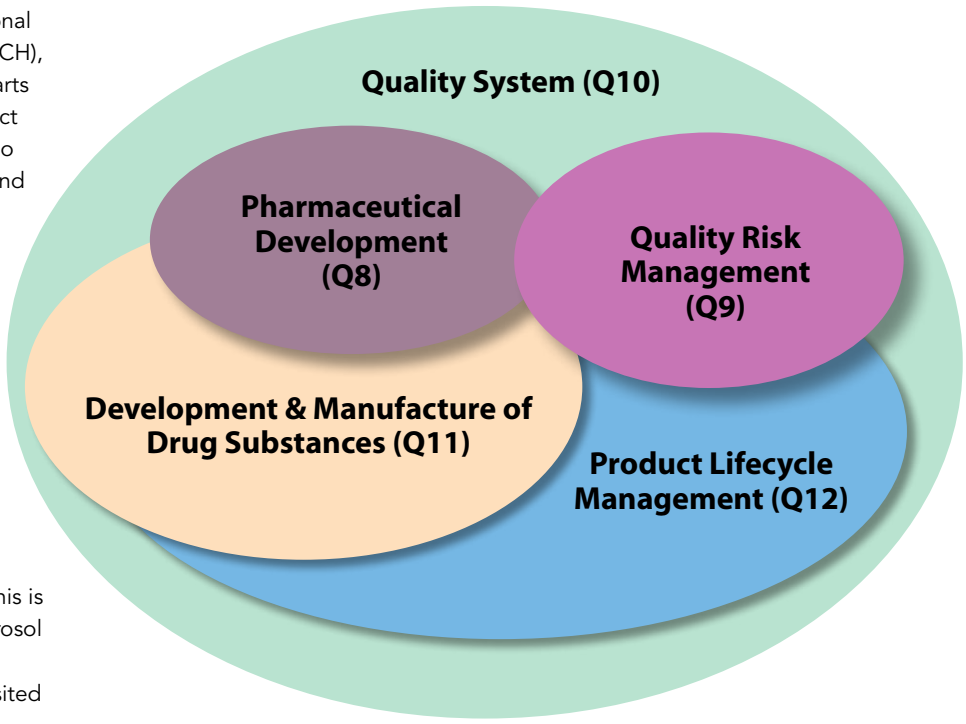
1. Cascade impactors measure **aerodynamic particle size**.
2. Cascade impactors measure the **active pharmaceutical ingredient.**
3. Cascade impactors measure the **entire dose**.

However, while cascade impaction provides the measure of particle size that is most relevant to deposition in the human respiratory tract, the physical characteristics of the human respiratory tract means that cascade impaction can never be directly analogous to the lungs.

Further, whilst providing a detailed size classification of the aerosol cloud concerned, recent QbD initiatives have drawn attention to the fact that the full resolution multi-stage cascade impaction methods commonly used to determine the APSD of OIPs can not only be laborious and time consuming but also require a high degree of skill and consistency on the part of the analyst if error is to be avoided.

The analytical and instrumental factors underlying these errors have been systematically reviewed by the Product Quality Research Institute (PQRI) in an article entitled "Considerations for the Development and Practice of Cascade Impaction Testing including a Mass Balance Failure Investigation Tree", J.Aerosol.Med., 2003; 16(3): 235-247.

For these reasons, attention has once again turned to the concept of **Abbreviated Impactor Measurement**.



ABBREVIATED IMPACTOR MEASUREMENT (AIM)

AIM IN THE QC ENVIRONMENT

The concept of **Abbreviated Impactor Measurement (AIM),** as typified by the Glass Impinger on Page 54 (still available as Apparatus A in Ph.Eur.) and the Fisons Single Stage Metal Impactor described in earlier versions of the European Pharmacopoeia (until 2002) is not new. However, the initiative in recent years started with abbreviated versions of the Andersen Cascade Impactor (ACI).

The concept is founded on the basis that once the full Aerodynamic Particle Size Distribution (APSD) profile of the product has been established in development using a full-resolution cascade impactor (and the process validated) then for product batch release testing and QC applications, it is possible to use simpler but highly sensitive metrics, solely to determine if the product is fit for purpose. This is known as **Efficient Data Analysis (EDA).**

Typically the APSDs of inhaled products are in the form of a Normal (or Gaussian) Distribution centred around the Mass Median Aerodynamic Diameter (MMAD). It is therefore possible to determine even subtle changes in the APSD by measuring the following:

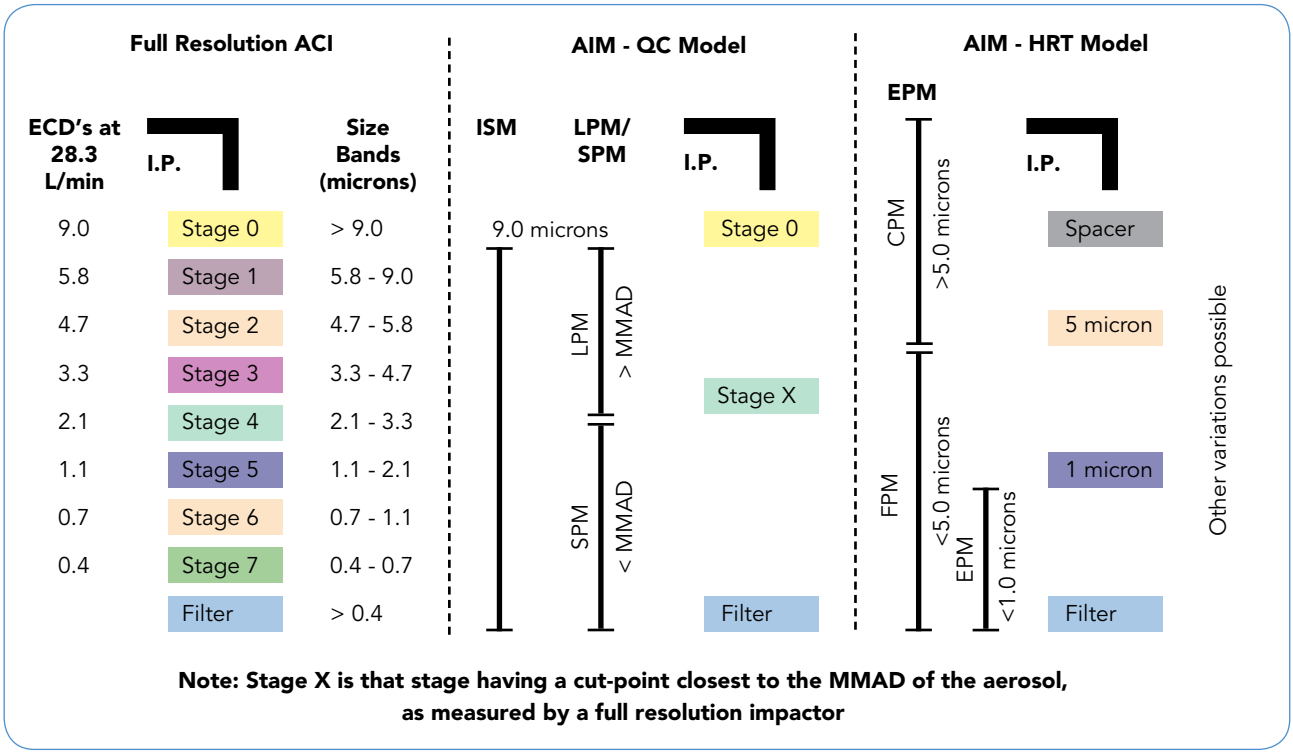
1. Impactor Sized Mass (ISM) which is considered the sum of the drug mass deposited on the filter and all impactor stages except the uppermost. This metric indicates any shift in the amplitude of the APSD.

2. Ratio of Large Particle Mass to Small Particle Mass (LPM/SPM) which is considered to be the ISM split into two fractions on either side of the MMAD: LPM greater than the MMAD and SPM smaller than the MMAD. This ratio indicates any shift in the central tendency of the APSD.

Although EDA can be applied to full-resolution impactor testing, its true value comes from combining it with AIM, since only a reduced number of impactor stages are required, speeding up throughput and further reducing analytical error. Full-resolution impactor testing is then reserved for Out-of-Specification (OOS) investigations.

In the diagram below, the **AIM-QC** model shows how abbreviating the ACI to just 2 stages and a filter, with the central stage (Stage X) selected to have a cut-off diameter close to the product MMAD, allows the EDA metrics of ISM and LPM/SPM to be easily determined.

The table on Page 44 indicates which ACI stage can be used for "Stage X' depending on the test flow rate and product MMAD (as determined from full-resolution impactor testing).



Note: Stage X is that stage having a cut-point closest to the MMAD of the aerosol, as measured by a full resolution impactor

Adapted from: Mitchell, J.P. *et al.* Relative Precision of Inhaler Aerodynamic Particle Size Distributon (APSD) Metrics by Full Resolution and Abbreviated Andersen Cascade Impactors (ACIs): Part 1., AAPS PharmSciTechnol., 2010, 11(2): 843-851

ABBREVIATED IMPACTOR MEASUREMENT (AIM)

AIM IN THE R&D ENVIRONMENT

Abbreviated Impactor Measurement (AIM) has also been suggested as a possible useful tool in R&D for the fast screening of new formulations in product development.

Abbreviated impactors have three main advantages over their more conventional multi-stage counterparts:

a) speed of throughput (this allows more samples to be measured in a given time frame)
b) less complicated so less prone to method and analyst error and
c) far easier to automate.

As far as R&D is concerned, the main aim is to find a link between *in vitro* and *in vivo* performance so as to reduce the dependence on time-consuming and expensive clinical trials.

This is not easy; as has been mentioned before, a cascade impactor is not analogous to the lung. The lung is a complex organ, with high humidity, decreasing velocity with each bifurcation and complex deposition mechanisms (diffusion and sedimentation, as well as impaction). This makes correlation between *in vitro* cascade impactor measurements and deposition in the **Human Respiratory Tract (HRT)** highly complex.

Nevertheless, there is some evidence to suggest that abbreviated versions of full stack cascade impactors can be used to broadly indicate *in vivo* lung deposition based on two or three size bands (or fractions):

1. **Coarse Particle Mass (CPM)** – That portion of the aerosol considered to be too large to be inhaled (usually considered to be >5 microns).

2. **Fine Particle Mass (FPM)** – That portion between 5 and 1 micron, usually considered likely to deposit deep into the lung and hence be therapeutically effective.

3. **Extra-fine Particle Mass (EPM)** – That portion below 1 micron, usually considered to be too small to deposit in the lung and therefore exhaled.

FSA-HRT with AIT (see Page 68) in Aluminium

In this case, the **AIM-HRT** model shown in the diagram on Page 61 shows how abbreviating the ACI to 2 stages, plus a filter and a spacer can be used to determine the CPM, FPM and EPM.

The selected stages have **cut-off diameters** equal or close to 5 and 1 microns. The Spacer provides additional dead space prior to the first impaction stage, equivalent to a full resolution impactor. This has been shown to be significant for improving the equivalence between AIM and full-resolution measurements for ethanol based MDIs.

Other stages can be used if their cut-off diameters are considered more applicable to the HRT correlation that is trying to be achieved.

AIM - THE FUTURE

In order to meet these various demands and to provide a basis for the proof-of-concept work necessary to validate them, Copley Scientific has introduced a number of different versions of abbreviated impactor for use in both **Quality Control (QC Models)** and **R&D (HRT Models) environments** based on reduced stage versions of the popular Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI). Full details may be found on Pages 63 to 65.

If validated and implemented, such impactors would effectively help to speed up the process of screening formulations in the early development phases, prior to full-resolution impactor studies being performed on the most promising candidates.

FSA-QC (in 316 Stainless Steel)

FSA-HRT with AIT (see Page 68) in Aluminium

ABBREVIATED IMPACTOR MEASUREMENT (AIM)

FAST SCREENING ANDERSEN (FSA)

The Fast Screening Andersen (FSA) is an AIM version of the standard Andersen Cascade Impactor (ACI) suitably modified to provide a reduced stack plus filter (F) suitable for either:

a) Quality Control (**FSA-QC**) or
b) Product Development (**FSA-HRT**).

The principles of each type are described on Pages 61 and 62.

In the **FSA-QC**, Stages 0 (or -1, or -2A) and F are used in conjunction with a **Stage X**, having a cut-off diameter as close as possible to the **Mass Median Aerodynamic Diameter (MMAD)** of the aerosol, as determined during full resolution cascade impactor testing.

In the **FSA-HRT** stages with cut-off diameters are available at **5.0 and 1.0 microns** for MDI applications at 28.3 L/min. Also, for this flow rate and higher flow rates (60 and 90 L/min) stages having traditional ACI cut-points of **4.7 and 1.1 microns** are available, primarily for DPI applications.

Preseparators can be used, where appropriate, to remove large powder boluses, as in the case of most DPIs.

Cat. No.	Description
FSA-QC with Stage X cut-off diameter close to product MMAD	
8341	FSA-QC - 28.3 L/min (Stages 0, X and F)*
8342	FSA-QC - 60.0 L/min (Stages -1, X and F)*
8343	FSA-QC - 90.0 L/min (Stages -2A, X and F)*
FSA-HRT with cut-off diameters of 5.0 and 1.0 or 4.7 and 1.1 microns	
8344	FSA-HRT - 28.3 L/min (Spacer, Stages 5.0 and 1.0 micron, and F)*
8345	FSA-HRT - 28.3 L/min (Spacer, Stages 2, 5 and F)*
8346	FSA-HRT - 60.0 L/min (Spacer, Stages 1, 4 and F)*
8347	FSA-HRT - 90.0 L/min (Spacer, Stages -0, 3 and F)*
Induction Ports	
8501	Universal Induction Port (Standard)*
8510	Universal Induction Port (One-piece 316 Stainless Steel)
Preseparators for testing DPIs	
8401	28.3 L/min Preseparator*
8420	60 L/min Preseparator*
8420-90	90 L/min Preseparator*
Spare Parts	
8367-I	Stage 5.0 micron cut-off @ 28.3 L/min*
8368	Stage 1.0 micron cut-off @ 28.3 L/min*
8371	FSA Spacer Stage*
8334	Complete Set of 7 FSA Silicone Rubber O-Rings
8335	Set of 2 Stainless Steel Collection Plates (28.3 L/min)
8336	Set of 2 Stainless Steel Collection Plates (60 or 90 L/min)
8316	Box of 100 Glass Fibre Filters (81 mm)
8308A	Set of 3 Shortened Spring Clamps - 4 Stage
8308B	Set of 3 Shortened Spring Clamps - 3 Stage

* Please specify **Aluminium (A), 316 Stainless Steel (S)** or **Titanium (T)** when placing your order.

Stage Cut-off Diameters for the Next Generation Impactor at Different Flow Rates

	Flow Rate (L/min)								
Stage	**15**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
1	14.10	11.72	10.03	8.89	8.06	7.42	6.90	6.48	6.12
2	8.61	6.40	5.51	4.90	4.46	4.12	3.84	3.61	3.42
3	5.39	3.99	3.45	3.09	2.82	2.61	2.44	2.30	2.18
4	3.30	2.30	2.01	1.81	1.66	1.54	1.45	1.37	1.31
5	2.08	1.36	1.17	1.04	0.94	0.87	0.81	0.76	0.72
6	1.36	0.83	0.70	0.61	0.55	0.50	0.46	0.43	0.40
7	0.98	0.54	0.45	0.38	0.34	0.31	0.28	0.26	0.24

Determined from: Virgil A. Marple et al. Next Generation Impactor (A New Impactor for Pharmaceutical Inhaler Testing).
Part II: Archival Calibration: Journal of Aerosol Medicine; Volume 16, Number 3, 2003; 301-324 and
Part III: Extension of Archival Calibration to 15 L/min: Journal of Aerosol Medicine; Volume 17, Number 4, 2004; 335-343

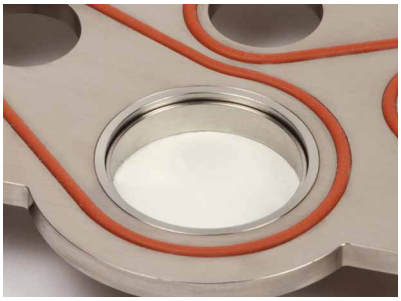
ABBREVIATED IMPACTOR MEASUREMENT (AIM)

REDUCED NGI (rNGI)

As described on the previous pages, the drive for greater efficiency is stimulating debate as to whether full-resolution, multiple-stage cascade impaction still needs to be applied to the extent that it is currently.

The **Reduced Next Generation Impactor (rNGI)** is an abbreviated method for utilising the NGI for both AIM-QC or AIM-HRT applications. In the case of the NGI, the individual stages are fixed within the seal body, such that they cannot be removed. In order to use the NGI in an abbreviated form, it is possible to use the Exhaust Cup to bypass certain stages (see Page 51). Alternatively the **rNGI Filter Holder Assembly** can be used.

In the same way as with the FSA, depending on the flow rate to be used, a stage of the NGI can be selected having a cut-off diameter close to the product MMAD (in the case of an **rNGI-QC** application) or close to 5 microns (in the case of an **rNGI-HRT** application). The cut-off diameters for the NGI at a range of flow rates are shown in the table above.



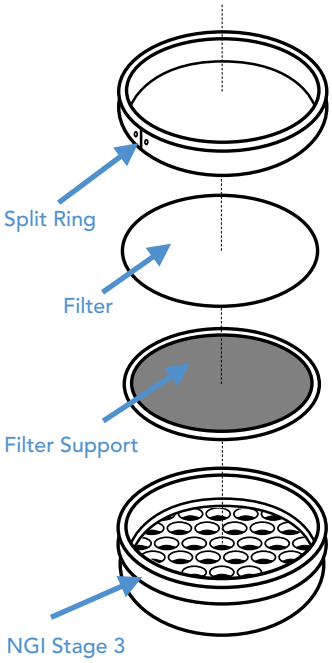
The rNGI Fiter Holder Assembly is placed in the stage immediately after the cut-off stage selected.

The rNGI Filter Holder Assembly consists of a filter support mesh which is placed on top of the stage nozzles and a split ring used to hold the filter in position on top of the filter support mesh.

On operating the rNGI, particles smaller than the cut-off diameter of the stage preceding the rNGI Filter Holder Assembly will be captured on the paper filter of the rNGI, whilst particles larger than the cut-off diameter of the stage preceding the rNGI Filter Holder Assembly will impact as normal in the collection cups of those stages upstream.

Note that when using the rNGI Filter Holder Assembly it is not possible to have a second stage representing the Extra-fine Particle Mass (EPM).

The flow resistance and the total volume of the NGI are not appreciably affected by the presence of the rNGI Filter Holder Assembly and therefore with careful selection of a suitable filter, makes this approach useful for



AIM studies of DPIs, when equivalence between NGI and rNGI data is desirable, but where start-up kinetics issues may otherwise be significant.

When the NGI is being used in the rNGI configuration, no modifications to the collection cups or method of assay are required.

Cat. No.	Description
5259	rNGI Filter Holder Assembly
5259A	Pack of 100 Filters for above

◀ rNGI Filter Holder Assembly

Interchangeable Inserts

Fast Screening Impactor

Filter Holder

ABBREVIATED IMPACTOR MEASUREMENT (AIM)

FAST SCREENING IMPACTOR (FSI)

Based on proven NGI Preseparator technology, the **Fast Screening Impactor (FSI)** represents a purpose-made approach to AIM that segregates the dose into Coarse Particle Mass (CPM) and Fine Particle Mass (FPM) making it suitable for **AIM-HRT** application (i.e. **FSI-HRT**) for MDIs, DPIs and nasal sprays.

A range of inserts is available, generating a 5 micron cut-off diameter within the flow rate range of 30-100 L/min at 5 L/min intervals, making it ideal for DPIs tested at a flow rate that equates to a 4 kPa pressure drop over the inhaler.

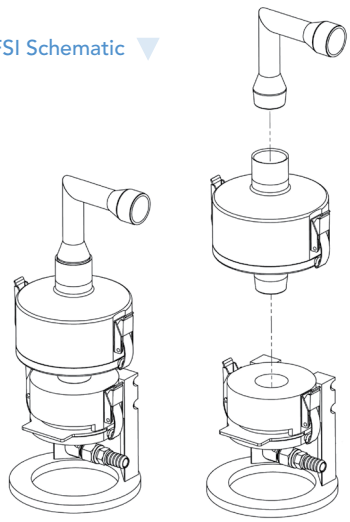
The FSI uses the same Induction Port as the NGI. It employs a two-stage separation process in which first large non-inhalable boluses are captured in a liquid trap followed by a fine-cut impaction stage at 5 microns. This gives unparalleled accuracy, high capacity, low internal losses and low carryover. The fine particle dose is collected on a glass fibre filter located in an external filter holder with quick-release catches for easy access.

A preseparator may be used, if required, to remove large non-inhalable particles, as with a conventional impactor. This also adds volume and has been shown to improve correlation with the NGI, when testing DPIs.

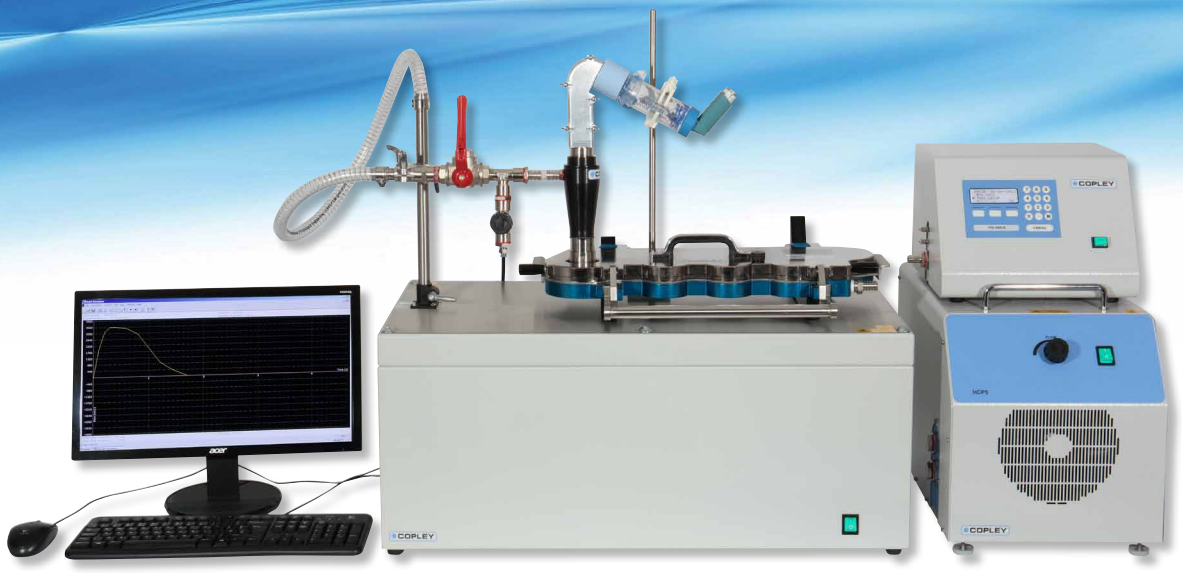
An additional insert is available for generating a 10 micron cut-off diameter at 30 L/min which when used with a glass expansion chamber (see Page 56) makes it ideal for the fast screening of nasal aerosols and sprays.

Bespoke inserts are also available on request with a range of cut-off diameter/flow rate combinations, allowing for an **FSI-QC** version, with a cut-off diameter selected close to the product MMAD.

FSI Schematic



Cat. No.	Description
Fast Screening Impactor (FSI) complete	
5260	FSI complete with one insert (please specify flow rate – see below)
5261	Additional Inserts – 5 microns @ 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 L/min for MDIs or DPIs (please specify flow rate)
5240	Box of 100 Filters (for Fine Fraction Collector)
Fine Fraction Collector for users that already have NGI Preseparator	
5262	Fine Fraction Collector only
Note: For a complete system, prospective users must also purchase an insert (see 5261) to replace the existing insert in their preseparator	
Accessories for MDIs and DPIs	
5203	NGI Induction Port
5204	NGI Preseparator
Accessories for Nasal Sprays	
5263	Additional Insert – 10 microns @ 30 L/min for Nasal Sprays
5217S	Adapter & Clamp for Next Generation Impactor (NGI)
8950	1000 mL Glass Expansion Chamber
8951	2000 mL Glass Expansion Chamber
8952	5000 mL Glass Expansion Chamber
8953	Volume Verification Certificate for Expansion Chamber



IVIVC System for MDIs with VHC with Alberta Idealised Throat (Child Version), Mixing Inlet, NGI and Breathing Simulator BRS 3000

IMPROVED *IN VITRO - IN VIVO* CORRELATION

INTRODUCTION

Accelerating time to market and adopting better practice in the development, manufacture and quality assurance of medicines are ongoing goals for the pharmaceutical industry.

Better *in vitro - in vivo* correlation (IVIVC) has long been an industry aim, but the current climate clearly adds impetus to the desire for progress.

Inhaled product development in particular presents some unique challenges in this respect.

The difficulty of precisely correlating drug deposition behaviour with clinical efficacy, the impact of patient-to-patient variability and the complex interaction between formulation and device, all complicate the development process.

In the case of most dry powder inhalers (DPIs) for example, the actuation and operation of the device relies solely on the breathing profile of the individual concerned using the inhaler.

A child for example with chronic asthma will exhibit a vastly different breathing profile from an otherwise healthy adult using the device for systemic purposes.

One strategy for improving the significance of cascade impaction data is to modify the test set-up in order to mimic the *in vivo* drug delivery process more closely.

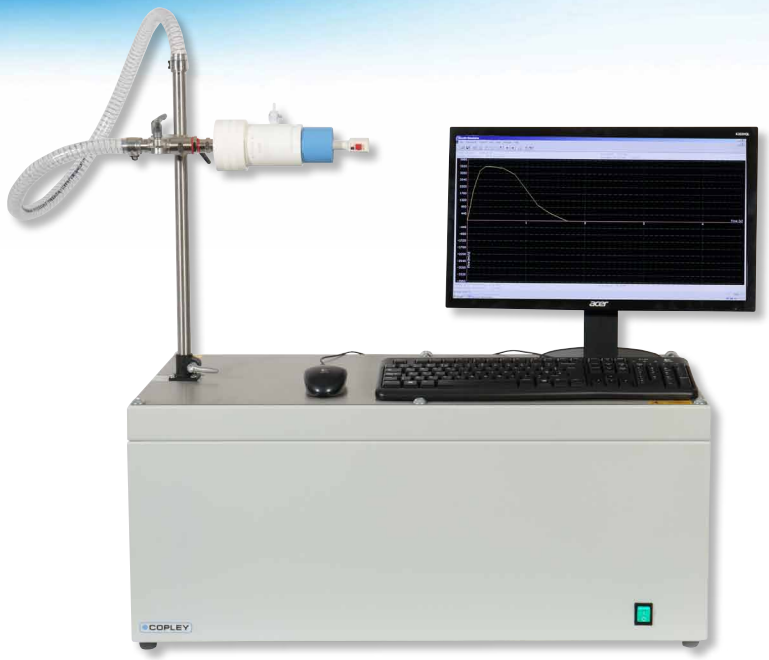
Two factors that have been identified as being critical to the improvement process are:

NGI with Alberta Idealised Throat (Child Version) and MDI with Valved Holding Chamber (VHC)

1. Replacing the existing Ph.Eur./USP Induction Port with an age-appropriate mouth/throat model having a more realistic human-like geometry.

The Ph.Eur./USP Induction Port (Throat) normally used to interface the device with the impactor has a simple, well defined geometry developed with testing standardisation in mind.

It is easy to manufacture and gives consistent performance, essential for QC testing. However, it is widely accepted that this port does not provide an accurate representation of what happens in the upper respiratory tract *in vivo* in that it consistently under-predicts the amount of active captured in this area.



Dose Unit Sampling Apparatus (DUSA) for DPIs with Breathing Simulator BRS 3000 for Delivered Dose Uniformity IVIVC Studies

Indeed, several studies have indicated that replacing the pharmacopoeial throat with one more anatomically correct in terms of oropharyngeal geometry gives more clinically accurate results.

The **Alberta Idealised Throat (AIT)** (see Page 68) is a new impactor/device interface designed specifically to replace the compendial inlet in providing a more realistic representation of the human mouth/throat.

The AIT was developed as a result of extensive research into typical patient populations including visual observations combined with a review of CT scans and anatomical texts.

2. Replacing the existing constant flow rate conditions employed in testing with breathing profiles more representative of conditions *in vivo*.

Human beings do not breathe at a constant flow rate. It makes sense therefore that if more realistic test conditions are to be attained, that flow rates that simulate breathing conditions more representative of those found *in vivo* should be applied.

For MDIs with spacers/VHCs and nebulisers, tidal breathing (at rest) is the normal mode of respiration. In the case of MDIs and DPIs, these usually require a single, forced inhalation manoeuvre designed to draw the dose deep into the lungs.

Various breathing patterns should be employed covering the age and condition of the patients to be treated (paediatric to geriatric, mild to severe impairment to the lungs).

In practice, this means replacing the fixed flow rate vacuum pump normally employed for regulatory testing with a **Breathing Simulator** (see Page 73) capable of providing breath profiles.

This in itself can lead to other problems during subsequent analysis. Applying more representative breathing profiles during testing is complicated by the fact that the impactors used to measure aerodynamic particle size distribution (APSD) operate at constant flow rates.

This problem can be resolved by interposing a "Mixing Inlet" between the induction port/throat and the Cascade Impactor concerned.

The **Mixing Inlet** (see Page 70) decouples the flow rate through the device from the air flow drawn through the impactor, thereby enabling more representative testing.

Utilising geometry that encourages gentle mixing, it allows the introduction of a secondary air stream that creates a sheath flow to supplement the flow through the device, thereby entraining the sample aerosol before entry into the impactor.

This makes it possible to use a breathing simulator in conjunction with a compressed air supply and the mixing inlet to provide a breathing pattern to the device to simulate tidal breathing or just inhalation (for DPIs) whilst simultaneously measuring the APSD in the conventional manner at a constant flow rate.

It also makes it possible, for example, to operate the product under test at a very low flow rate but boost air flow through the impactor to achieve the calibrated steady-state flow required.

Mixing Inlet mounted on ACI

Alberta Idealised Throat

Alberta Idealised Throat (open)

IMPROVED *IN VITRO - IN VIVO* CORRELATION

ALBERTA IDEALISED THROAT (AIT)

One way to accurately simulate the deposition of orally inhaled drug products (OIDPs) in the throat is to use an anatomically correct human throat cast.

The major drawback is that the geometry represented by such a cast is that of a single human subject.

Experimental work has shown significant differences in deposition behaviour between various throat casts, attributable to inter-subject variability in the geometry of the mouth and throat.

Arguably, the Ph.Eur./USP induction port routinely used in testing represents the opposite approach in inlet design to that of the cast.

Alberta Idealised Throat, Leak Test Inlet Cap and Outlet Adapter

Developed with testing standardisation in mind, it has a simple well defined geometry that lends itself to high precision manufacture and the consistent performance demanded in product QC testing.

Unfortunately, these benefits come at the cost of *in vivo* correlation. Indeed, whilst the induction port is ideal for QC applications, in practice, it has been found to significantly underestimate the actual amount of active found in the throat *in vivo*.

One method of improving *in vitro - in vivo* correlation is to replace the standard Ph.Eur./USP Induction Port (Throat) normally used in the testing of inhalers with a throat having more human-like characteristics.

For more than a decade, researchers at the Aerosol Research Laboratory at the University of Alberta, Canada, have been working to develop a more suitable representation of the mouth-throat for routine cascade impactor testing.

The aim was to produce an interface that is both easy to manufacture and reflective of *in vivo* behaviour, a solution that lies part way between the human throat cast and the pharmacopoeial induction port.

The **Alberta Idealised Throat (AIT)** was developed as a result of extensive research into typical patient populations including information provided by CT and MRI scans, direct visual observation of living subjects and data in the archival literature. The throat has a standardised, highly reproducible, human like geometry offering robust performance independent of flow rate.

Its smooth, more uniform internal geometry has been specifically designed to make drug recovery quick and simple in comparison with a human throat cast. Quick release clips make for easy internal access.

Two versions are available corresponding to adult and child (6-14 years old range) geometries respectively.

IVIVC System for DPIs with Alberta Idealised Throat, Mixing Inlet, NGI and Breathing Simulator BRS 3000

OPTIMISATION

The test set-up shown above illustrates how new equipment for *in vitro* testing is being exploited to optimise data gathering for demonstrating bioequivalence in a DPI.

There are three pieces of equipment present that are routinely absent from the standard set-up: a **breathing simulator**; an **Alberta Idealised Throat (AIT)** (in place of the standard USP induction port) and a **Mixing Inlet**.

It is worth looking in detail at exactly what each element contributes.

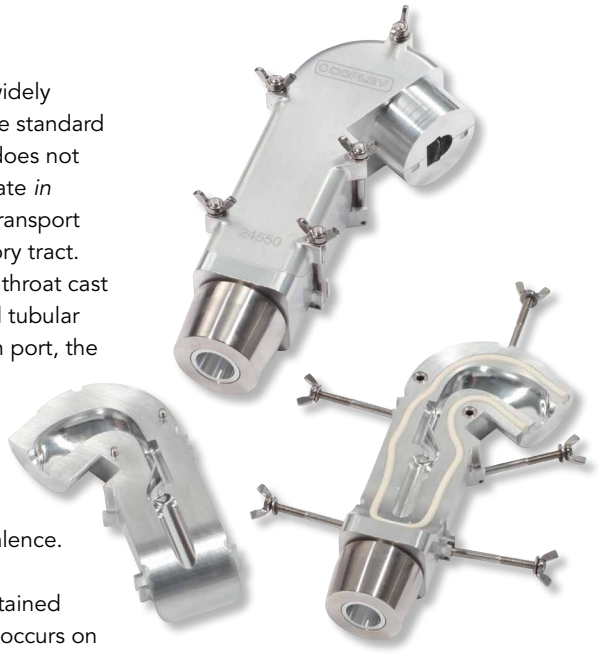
The **Mixing Inlet** decouples the flow profile applied across the device from the flow conditions applied in the cascade impactor.

It allows the application of a patient-relevant breathing profile across the DPI while at the same time enabling the cascade impactor to work at the constant flow rate required for accurate APSD measurement.

The **Breathing Simulator** enables exploration of the impact of different breathing profiles. In bioequivalance testing it therefore allows the robust demonstration of equivalent drug delivery performance across a range of conditions that represent the variability associated with a target user group.

The flexibility to fully scope variability is far greater than with the standard pharmacopoeial test set-up.

Finally, the **AIT** addresses widely recognised limitations of the standard USP induction port, which does not provide a particularly accurate *in vitro* realisation of aerosol transport through the upper respiratory tract. Part way between a human throat cast and the simple right angled tubular design of the USP induction port, the AIT produces data that are more representative of measured *in vivo* behaviour, thereby supporting the robust demonstration of bioequivalence. Furthermore it ensures that the APSD measurement obtained via cascade impaction only occurs on the portion of the aerosol that would likely enter the lungs.



Alberta Idealised Throat (Child Version)

Cat. No.	Description
8511	Alberta Idealised Throat (AIT) in Aluminium (Adult Version)
8514	Flow Meter To Alberta Idealised Throat Adapter (Adult Version)
8515	Mouthpiece Adapter for Alberta Idealised Throat (Adult Version)
5004	Tooling Charge for above (Adult Version)
8516	Spare Silicone Seal for Alberta Idealised Throat (Adult Version)
8518	Leak Test Inlet Cap and Outlet Adapter (Adult Version)
8530	Alberta Idealised Throat (AIT) in Aluminium (Child Version)
8531	Flow Meter to Alberta Idealised Throat Adapter (Child Version)
5003	Mouthpiece Adapter for Alberta Idealised Throat (Child Version)
5004	Tooling Charge for above (Child Version)
8532	Spare Silicone Seal for AIT (Child Version)
8533	Leak Test Inlet Cap and Outlet Adapter (Child Version)
8512	Alberta Idealised Throat to ACI/FSA Adapter (Adult & Child)
8513	Alberta Idealised Throat to NGI/FSI Adapter (Adult & Child)

NGI Mixing Inlet

IMPROVED *IN VITRO - IN VIVO* CORRELATION

MIXING INLET

The cut-off diameters generated by each stage of any cascade impactor are dependent on a steady, fixed flow of air passing through it.

In contrast, the *in vivo* inhalation profiles of breathing cycles generated by patients produce a continually varying flow rate far removed from the fixed, steady-state flow rates employed in *in vitro* testing.

For this reason, over the years, there have been various attempts to link cascade impactors directly to **breathing simulators** in order to reproduce the actual clinical condition more closely.

Any such system must be capable of varying the flow rate through the inhaler whilst ensuring that the aerosol generated is sampled at a fixed rate through the impactor.

Another problem can be when the test flow rate applied to the inhaler is lower than the minimum calibrated flow rate of the impactor.

This is common, for example, in paediatric studies where the user wishes to simulate the flow rate typical *in vivo* of a minor, say 10 L/min, whereas the impactor requires a flow rate of 28.3 L/min in order to operate within its calibrated range.

Next Generation Impactor (NGI) fitted with Mixing Inlet

DESCRIPTION

The **Mixing Inlet** fits between the USP Induction Port (or Alberta Idealised Throat) and the inlet of the impactor used to carry out the test.

It is designed to permit the cascade impactor to be operated at a constant flow rate (e.g. 100 L/min), whilst allowing a lower fixed or variable rate, such as a breathing pattern generated by a breath simulator, to pass through the inhaler itself.

Supplementary (or "make-up") air is provided from a compressed air source to the inlet port on the side of the Mixing Inlet using a Flow Control Manifold with 6 mm or 1/4" compressed air fittings. A flow control valve contained within the manifold is used to match the steady-state flow rate exiting the impactor. This balances the flow and ensures that the flow rate at the inlet to the Induction Port is zero.

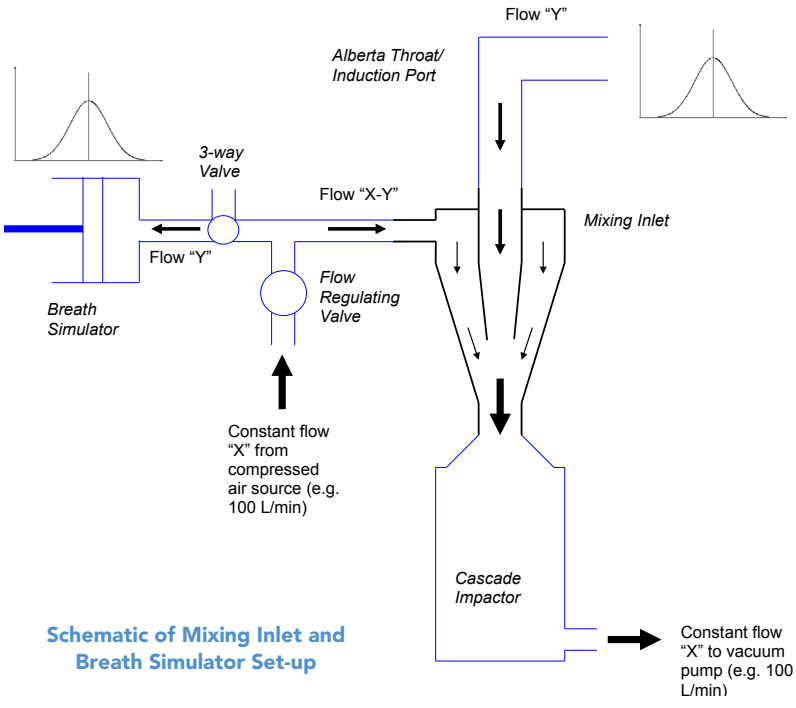
IVIVC System with Real Time Breath Profile Verification Chamber

In a case where low flow rates are required (e.g. paediatric studies) the supplementary air can be reduced using the flow control valve, such that the difference between this and the air flow leaving the impactor is made up at the induction port, allowing for low flow rate testing of the inhaler.

In cases when the inhaler is to be tested using patient representative breath profiles, a breath simulator is introduced using a "T-piece" connected to the supplementary air line. In a balanced flow condition (where the supplementary flow equals that leaving the impactor) the breath simulator withdraws flow according to the desired breathing pattern from the supplementary air line, causing the breathing pattern to be replicated at the Induction Port and hence the inhaler under test.

The gentle mixing action between the sample-laden air flow through the Induction Port and the supplementary air ensures low internal losses within the Mixing Inlet itself.

Suitable **breathing simulators** can be found on Pages 73-77.



Schematic of Mixing Inlet and Breath Simulator Set-up

Cat. No.	Description
8328	Mixing Inlet for ACI, FSA and MSLI
8329	Mixing Inlet for NGI and FSI
8323	Set of 5 O-Rings for Mixing Inlet
8338	Flow Control Manifold for Mixing Inlet (6 mm)
8339	Flow Control Manifold for Mixing Inlet (1/4")

Ancillaries

INTRODUCTION

This section describes the ancillaries required in addition to the Dosage Unit Sampling Apparatus (DUSA) and Cascade Impactor to make up a fully operating test system for determining the Delivered Dose Uniformity and Aerodynamic Particle Size Distribution of orally inhaled and nasal drug products (OINDPs).

Breathing simulators are increasingly used in testing OINDPs to replace existing constant flow rate conditions with breathing profiles more representative of conditions *in vivo*.

Copley Scientific offer a choice of three Breath Simulators covering the range of breathing patterns to be found in neonatal, infant, child and adult physiologies.

The **Critical Flow Controller** is designed to generate a standardised square-wave breath profile suitable for the routine testing of "passive" breath activated devices such as Dry Powder Inhalers, where the delivered and fine particle dose of the device is dependent on the strength and duration of the patient's inspiration.

The **Breath Actuation Controller** is an electrically operated timer controlled two-way valve specifically designed for testing Breath Actuated (or Breath Operated) MDIs, Spacers and VHCs used with MDIs and Nebulisers to USP <1601> and Ph.Eur. 2.9.44.

The **Data Analysis** function is provided by CITDAS (Copley Inhaler Testing Data Analysis Software), a proven third generation software program designed specifically for the simple and rapid processing of impactor drug deposition data according to pharmacopoeial requirements. It has an existing database of more than 200 users.

Based on over 12 years of experience, CITDAS can be installed and up and running in minutes – it requires no specialist IT knowledge to install and does not require 21 CFR 11 because the data output is in hard copy format. It will accept data from the ACI, NGI, MSLI and/or MMI. Provision is made to customise the data options to individual needs.

Flow rate is a critical parameter in the *in vitro* testing of OINDPs. Copley Scientific offers two **Flow Meters** with the required range and accuracy to perform this task, one based on *differential pressure* and the other on *thermal mass* measurement methods. Both units will give the same results providing they are calibrated and operated correctly.

No inhaler testing system would be complete without the **Mouthpiece Adapters, Tubing and Quick Release Connectors** designed to link the various components of the system together.

Finally, at the heart of every inhaler testing system is the **Pump**. The Pharmacopoeias are careful to point out that "a vacuum pump with excess capacity must be selected in order to draw air, at the designated volumetric flow rate" through the system and, in the case of Dry Powder Inhalers to generate sonic flow.

Copley Scientific offers a choice of three pumps dependent on the set-up concerned and the capacity required.

Breathing Simulators
BRS 2000 and 3000

BREATHING SIMULATORS

Breathing Simulators, instruments that generate an inhalation and/or exhalation profile that micmics that of a human subject, have become a routine feature of orally inhaled product (OIP) testing. Their use is two fold:

1. Regulatory

To measure the delivered dose of drug (DDU) from:

a) Nebulisers as per USP <1601> and Ph.Eur. 2.9.44 and

b) Pressurised metered dose inhalers (pMDIs) when used in conjunction with spacers and valved holding chambers as per the proposed USP Chapter <1602>

in accordance with the appropriate regulations.

2. Better *in vitro - in vivo* correlation (IVIVC)

To replace the fixed flow rate vacuum pump normally employed for regulatory testing with a unit capable of producing breath profiles more representative of conditions *in vivo*.

A pMDI, when used without a spacer or VHC, actively delivers the drug directly to the patient using a propellant. With these devices, inhalation must be coordinated with the actuation to ensure success, but the shape and characteristics of the breathing profile employed by the patient in their use are unlikely to have much effect on the aerodynamic particle size distribution (APSD) of the delivered aerosol and/or the effectiveness of delivery.

This is not the case for dry powder inhalers (DPIs), nebulisers or pMDIs used with spacers / valve holding chambers. Here the breathing profile of the patient directly influences the efficiency of drug delivery.

For this reason, more laboratories are turning to the use of breathing simulators to measure the effects of different profiles, flow rates and breathing techniques during their development.

Such an approach is supported by the QbD (Quality by Design) strategy outlined in ICH Q8 which relies on scoping the potential impact of any variability that may arise from, for example, differences in patient physiology or technique.

Copley Scientific produce a range of breathing simulators from the BRS 1100, an inexpensive unit producing sinusoidal wave forms and designed specifically to meet the regulatory requirements of USP and Ph.Eur., to the BRS 3000, a versatile, fully computer controlled Breathing Simulator designed for both regulatory and research and development applications, using more varied, patient derived, breathing profiles.

BRS 1100	BRS 2000	BRS 3000
Volume (manually adjust): 0 to 800 mL	Volume (computer controlled): 0 to 900 mL	Volume (computer controlled): 0 to 5000 mL
Frequency: 12 - 40 bpm	Frequency: 0+ (upper defined by acceleration limit)	Frequency: 0+ (upper defined by acceleration limit)
I:E Ratio: 1:1, 1:2 or 1:3	I:E Ratio: variable	I:E Ratio: variable
Waveforms: Sinusoidal	Waveforms: Sinusoidal, Square, Triangular, User defined (flow vs time)	Waveforms: Sinusoidal, Square, Triangular, User defined (flow vs time)
Tidal breathing: inhalation & exhalation	Tidal breathing profiles: inhalation and exhalation	Tidal breathing profiles: Inhalation and exhalation
Select start on inhalation or exhalation stroke	Inhalation only profiles User defined profiles (flow vs time)	Inhalation only profiles User defined profiles (flow vs time)
User Interface: Keypad & 4-line display	User Interface: Embedded computer (Windows XP)	User Interface: Embedded computer (Windows XP)
Uses: Testing Nebulisers (Ph.Eur. 2.9.44 and USP <1601>) Testing MDIs with Spacers/VHCs (USP <1602>)	**Uses:** Testing Nebulisers (Ph.Eur. 2.9.44 and USP <1601>) Testing MDIs with Spacers/VHCs (USP <1602>)	**Uses:** Limited testing of Nebulisers (Ph.Eur. 2.9.44 and USP <1601>) and MDIs with Spacers/VHCs- (USP <1602>) Improving IVIVCs for MDIs and DPIs: - With DUSA for MDI/DPI (Dose Uniformity) - With Impactor and Mixing Inlet (APSD)

Volume Adjustment Hatch

BREATHING SIMULATOR MODEL BRS 1100 (0 - 800 mL VERSION)

The **Breathing Simulator Model BRS 1100** is a microprocessor controlled instrument which was designed specifically for generating the neonatal, infant, child and adult breathing patterns required for the dose uniformity testing of nebulisers, in accordance with "ISO 27427:2010 Anaesthetic & Respiratory Equipment - Nebulising Systems and components, European Pharmacopoeia Chapter 2.9.44 Preparations for Nebulisation: Characterisation and USP <1601> Products for Nebulization: Characterization."

It can also be used to generate the profiles required in the new USP proposed Chapter <1602> for testing "Spacers and Valve Holding Chambers used with Inhalation Aerosols".

The BRS 1100 has the following features:

- Piston/cylinder arrangement, driven by motor with accurate speed and position control
- Inlet/outlet port for direct connection to the dose filter holder and nebuliser, spacer or VHC
- Tidal volume of 0 - 800 mL (155 to 770 mL certified)
- Frequency adjustable between 12 and 40 breaths per minute
- Sinusoidal waveform
- Inhalation/Exhalation Ratio (I:E Ratio) of 1:1, 1:2 or 1:3
- Selectable start position (inhalation or exhalation) for testing spacers/ VHCs
- Cycle number: 1-9999 breaths
- Cycle time: 0 to 8 hours
- Emergency cut-out facility in the event of a blocked inlet/outlet

User interface with the BRS 1000 is menu driven by means of a membrane keypad fitted with a 4-line LCD.

The volume required is set by means of an adjustable linkage accessed by opening the hatch on the right hand side of the casing. The scale is graduated directly in mL.

Delivered Dose Sampling Apparatus for Nebulisers

Qualification KIt

Volume is adjusted by means of a calibrated scale

BREATHING SIMULATOR MODEL BRS 1100 (0 - 800 mL VERSION)

Thereafter, all that is required to run a test is to specify:

a) the number of breaths required **or** the duration of the test in terms of hours, minutes and seconds and

b) the operating speed in terms of breaths-per-minute (bpm) and

c) the I/E Ratio, and

d) the start position (inhalation or exhalation) and then select *Run Method* and *OK*.

The BRS 1100 measures 410 x 480 x 275 mm (wxdxh) and weighs 18 kg.

Breathing Pattern						
Parameter	**Adult 1**	**Adult 2**	**Adult**	**Child**	**Infant**	**Neonate**
Volume (mL)	770	500	500	155	50	25
Freq. (bpm)	12	13	15	25	30	40
I:E Ratio	1:2	1:2	1:1	1:2	1:3	1:3
USP <1601>	-	-	✓	✓	✓	✓
Ph.Eur. 2.9.44	-	-	✓	✓	✓	✓
USP <1602>	✓	✓	-	✓	✓	✓

Delivered Dose Sampling Apparatus for Spacers and Valved Holding Chambers (VHCs)

Cat. No.	Description
9131	Breath Simulator Model BRS 1100
9106A	IQ/OQ/PQ Documentation for BRS 1100/2000/3000
9105	BRS 1100/2000/3000 Qualification Kit
9107	Re-calibration of BRS 1100/2000/3000 Qualification Kit
9108	BRS 1100 Re-calibration Certificate
9133	BRS 1100 Inlet to Mixing Inlet Flow Control Manifold Adapter

Accessories - Delivered Dose Sampling of Nebulisers & Spacers/VHCs
See Pages 32-33 and 34-37 respectively

BRS 2000 Set-up for the testing of Nebulisers

BREATHING SIMULATOR MODEL BRS 2000 (0 - 900 mL VERSION)

The Breathing Simulator Model BRS 2000 is an advanced computer controlled breathing simulator, with up to **900 mL** volume, suitable for the testing of Nebulisers and Spacers and Valved Holding Chambers (VHCs) used with Metered-Dose Inhalers (MDIs)

The BRS 2000 has been specifically designed to generate all of the breathing profiles used in measuring the *drug delivery rate* and *total drug delivered* of **Nebulisers** according to Ph.Eur. 2.9.44 and USP <1601> (see Page 24), namely **neonate, infant, child and adult.**

It will also generate the neonate, infant, child, adult 1 and adult 2 breath profiles proposed in the new USP Chapter <1602> for the *in vitro* assessment of **Spacers and Valved Holding Chambers** used with MDIs.

The BRS 2000 is also suitable for generating other wave forms used in developmental studies of nebulisers and other inhaled products requiring an inhalation volume of < 900 mL.

The control function is provided in the form of an embedded computer running Windows XP used in conjunction with a colour monitor, keyboard and mouse. An ethernet connection socket is provided for network printing.

Standard breathing patterns can be defined by editing the following parameters:

- Selected Pattern: square, sinusoidal or triangular
- Tidal Volume: 0 - 900 mL (155 to 770 mL certified)
- Duration of inhalation (in seconds)
- Delay after inhalation (in seconds)
- Duration of exhalation (in seconds)
- Delay after exhalation (in seconds)
- Number of Breathing Cycles

The in-built software automatically calculates the:

- Duration of the test
- Breathing Frequency (bpm)
- Inhalation / Exhalation (I:E) Ratio (%) and displays all of the parameters on screen together with a graphic display of the pattern generated

Alternatively, the user can generate their own ***Flow versus Time*** profiles in the form of text files containing tabulated data points. Up to **1000 data points** can be entered, with time intervals as small as **20 milliseconds**, allowing the creation of high-resolution breathing profiles, (e.g. as measured in clinic).

Breathing patterns, which can consist of single or multiple breaths, with or without exhalation phases, can be saved and loaded into the software, as required.

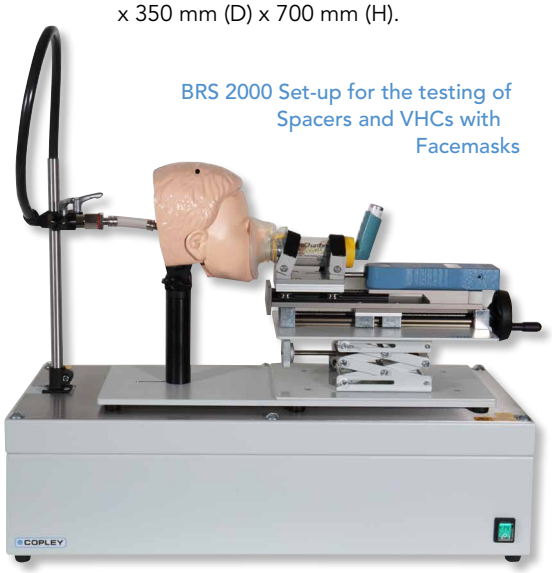
Selecting *Start* activates the breathing cycle programme. During operation, the current position within the cycle is indicated on screen by a moving red dot located on the inhalation/ exhalation curve.

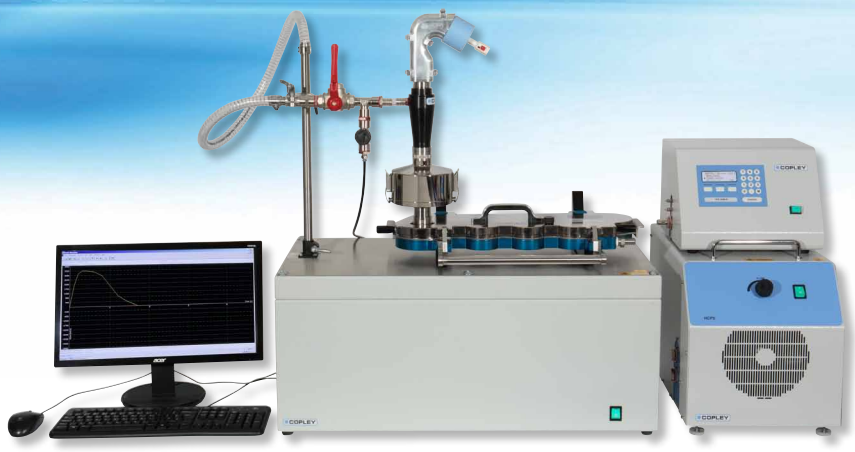
The BRS 2000 compensates for test equipment induced flow resistance experienced at the inlet, by adjusting power to the motor controlling the piston/cylinder arrangement. If the flow line becomes blocked, the BRS 2000 will automatically abort the test.

The inlet for connection to the test apparatus concerned is fully adjustable in terms of height and angle.

The BRS 2000 measures 750 mm (W) x 350 mm (D) x 700 mm (H).

BRS 2000 Set-up for the testing of Spacers and VHCs with Facemasks





IVIVC System for DPIs with Alberta Idealised Throat, Mixing Inlet, NGI, Breathing Simulator BRS 3000, Pump and Flow Controller

BREATHING SIMULATOR MODEL BRS 3000 (500 mL - 5 LITRE VERSION)

The Breathing Simulator Model BRS 3000 is similar in design and operation to the BRS 2000 except that it has a volume of **500 mL - 5 Litres** (certified).

It also features a maximum flow rate of **240 L/min** (free flow) and a maximum acceleration of **25 L/s²** (free flow) making it the ideal unit for the testing of **MDIs and DPIs for improved IVIVCs.**

Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD) continue to be subjects of close scrutiny as the concept of Quality by Design (QbD) becomes more widespread. The emphasis is now on method development that uses **design of experiments (DoE)** to identify the most significant factors, the **critical quality attributes (CQAs)**, relevant to the product concerned.

For this reason, laboratories are devoting more resources to method development in an attempt to try to establish *in vitro - in vivo* relationships at an early stage in the product design.

As already mentioned in the section on *in vitro - in vivo correlation* (see Pages 66-71), two of the main factors that have been identified as critical to IVIVC are:

1. Replacing the conventional Induction Port with a mouth/ throat model having a more realistic human geometry (such as the **Alberta Idealised Throat** described on Page 68).
2. Replacing the existing flow rate conditions employed in testing with breathing profiles more typical of conditions *in vivo* (see the **Mixing Inlet** described on Page 70).

The Breathing Simulator Model BRS 3000 has been specifically designed to provide the latter.

In the case of **DDU**, the BRS 3000 (and BRS 2000) can be connected directly to the Dose Unit Sampling Apparatus using a suitable adapter (see Pages 24-30, 67 and ordering information below).

In the case of **APSD** measurements, a Mixing Inlet (See Page 70) is required to decouple the variable flow through the inhaler (generated by the Breath Simulator) from the steady-state flow rate through the cascade impactor.

Therefore in order to generate a test system for the measurement of APSD, using realistic patient profiles, the following items are required:

1. The conventional Ph.Eur. / USP Induction Port **or** Alberta Idealised Throat (Adult or Child).
2. Mixing Inlet with BRS 2000/3000 Flow Control Valve and Adapter for connection to a compressed air supply (see ordering information below).
3. Cascade Impactor (ACI, NGI, MSLI, FSA or FSI).

The BRS 3000 measures 800 mm (W) x 400 mm (D) x 850 mm (H).

Cat. No.	Description
9111	Breath Simulator Model BRS 2000
9121	Breath Simulator Model BRS 3000
9105	BRS 1100/2000/3000 Qualification Kit
9106A	IQ/OQ/PQ Documentation for BRS 1100/2000/3000
9107	Re-calibration of BRS 1100/2000/3000 Qualification Kit
9109	Real-Time Breath Profile Verification Chamber (see Page 71)
9110	Accessory Support Stand for BRS 2000/3000
Accessories - Delivered Dose Sampling of Nebulisers & Spacers/VHCs	
See Pages 32-33 and 34-37 respectively	
Accessories - Dose Uniformity of MDIs and DPIs (IVIVCs)	
9122	Adapter for use with DUSAs for MDIs and DPIs
Accessories for use with Mixing Inlet and Cascade Impactors (IVIVCs)	
9123	BRS 2000/3000 Flow Control Manifold for Mixing Inlet (6 mm)
9124	BRS 2000/3000 Flow Control Manifold for Mixing Inlet (1/4")

BRS 1100/2000/3000 Qualification Kit

CRITICAL FLOW CONTROL

INTRODUCTION

The vast majority of Dry Powder Inhalers (DPIs) are classified as "passive" breath activated devices; that is to say, they rely solely on the patient's inspiration to operate.

There is no necessity to co-ordinate breathing with the activation – the patient simply inhales deeply to access the drug.

It follows that both the delivered and fine particle dose of DPIs are dependent on the strength and duration of the patient's inspiration, a critical quality attribute (CQA) which must be simulated during the course of *in vitro* testing.

The testing of DPIs is further complicated by the fact that different inhalers provide varying degrees of **resistance to flow** i.e. some require more effort to inhale than others **(see graph below).**

TESTING *IN VITRO*

In the case of the *in vitro* testing of DPIs, the pharmacopoeias specify that the duration of a single inhalation cycle (equivalent to that of a typical user when inhaling the drug) be achieved through the use of a 2-way switching valve connected to a vacuum pump.

The operation of the switching valve, and hence the duration of the breathing cycle, is controlled by means of a timer.

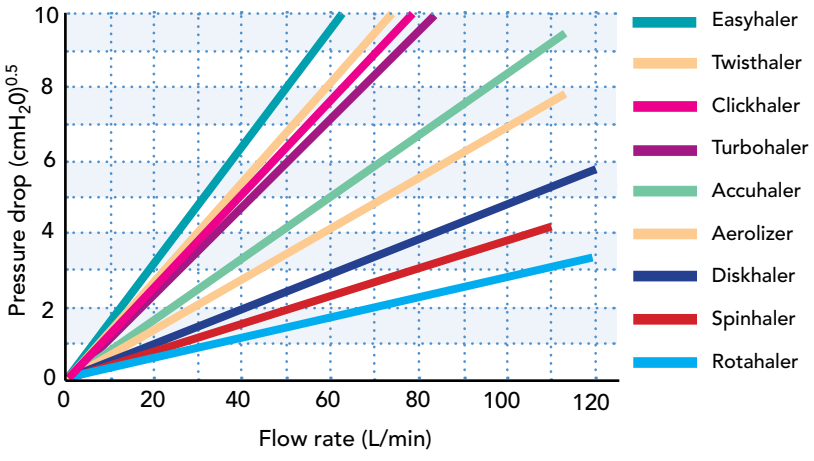
One side of the valve is connected to either the sampling apparatus (in the case of delivered dose) or a cascade impactor (in the case of particle size determination) and the other to a vacuum pump.

In pre-test mode, the switching valve is in the closed position such that no flow passes through the test apparatus.

On initiation of the test, the 2-way valve switches such that flow now passes through the test apparatus and hence the inhaler under test. On expiration of the pre-set time, the solenoid closes again and the "inhalation" cycle is complete.

The relationship between pressure drop and flow rate for a range of commercially available DPIs

Assi, K.H. and Chrystyn, H, et al. The device resistance of recently introduced dry-powder inhalers. Journal of Pharmacy and Pharmacology, 52 (Suppl): 58, 2000.



FLOW RATE

In the *in vitro* case, the *in vivo* strength and duration of the user's inspiration is replicated by the flow rate used and the time for which the solenoid valve concerned remains open.

To establish the correct flow rate to be used, it is first necessary to establish the flow rate required to produce a pressure drop comparable with that found at the mouth of the user *in vivo* when using the particular inhaler being studied.

Both European and US Pharmacopoeias suggest a pressure drop over the inhaler of 4 kPa as being broadly representative of the pressure drop generated during inhalation by patients using DPIs.

The pressure drop created by the air drawn through an inhaler can be measured directly by measuring the absolute pressure downstream of the inhaler mouthpiece and comparing this directly with atmospheric pressure.

Using a flow control valve, it is then a simple matter to adjust the flow rate from the vacuum pump to produce the required pressure drop of 4 kPa and then, by replacing the inhaler with a suitable flow meter, to measure the flow rate, Q, required to produce this pressure drop.

It is this flow rate, Q, that the Pharmacopoeias state should be used for the determination of both delivered dose and particle size.

The only exception to this criterion is that if the flow required to produce a 4 kPa pressure drop is >100 L/min, as for example in the case of particularly low resistance inhalers, whereupon 100 L/min should be used.

CRITICAL FLOW CONTROL

INSPIRATION VOLUMES

Once the flow rate, Q, has been established, it is now necessary to control the volume of air drawn through the inhaler during testing to the 4 litres per simulated inhalation specified in the Pharmacopoeias (2 litres in the case of the FDA guidelines and USP).

This is in order to simulate, as far as possible, the *in vivo* inspiration volume of the patient and is achieved by introducing a timer-controlled fast acting solenoid valve between the test device and the vacuum pump, as described on the preceding page.

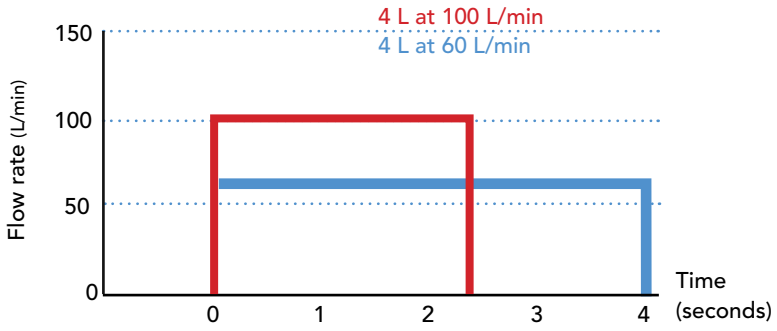
4 litres is considered to be the normal forced inhalation capacity of an average sized male weighing approx. 70 kg. (In practice, it is not uncommon to widen the scope of the test parameters to cover a broader target patient population, such as geriatrics and paediatrics, as well as those already suffering from pulmonary problems, including typical use and unintentional misuse conditions).

The solenoid valves used in the Critical Flow Controllers manufactured by Copley Scientific open and close in <25 milliseconds (the Pharmacopoeias state <100 milliseconds).

By using the timer to control the time that the solenoid valve is open, it is possible to control the volume of air drawn through the inhaler to achieve the volume specified (see diagram above).

For example, if the volume specified is 4 litres and the flow rate, Q, is 100 L/min then the timer should be set to 2.4 seconds. It follows that if Q is 60 L/min, then the timer should be set for 4 seconds, if Q is 30 L/min then the timer should be set at 8 seconds, etc.

The relationship between flow rate and test time for DPI testing.



CRITICAL (SONIC) FLOW

Having set the required parameters to control the strength and duration of the simulated breathing cycle, there is one final variable which needs to be considered, namely that of flow rate stability.

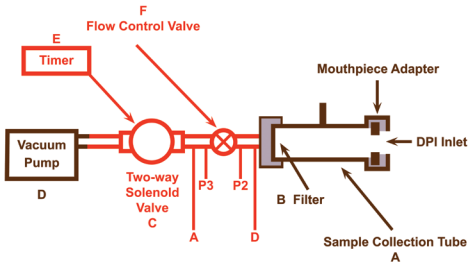
Stable flow control is critical to good impactor measurement practice. This is because the aerodynamic sizing ability of inertial impactors is dependent on the velocity of the air flow passing through each stage. That velocity is directly related to the volumetric air flow rate.

A number of factors can influence flow rate stability particularly if the vacuum pump used is worn or working at the limits of its capacity.

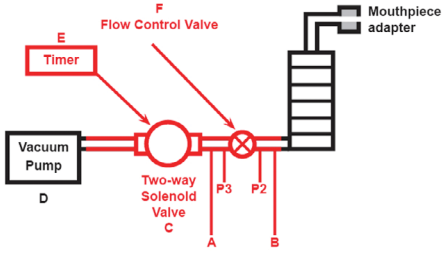
An easy way to validate flow rate stability is to ensure that critical (sonic) flow occurs in the flow control valve concerned. This can be confirmed by simply measuring the absolute pressure at a point on either side of the flow control valve (see schematics below).

Providing that the pressure downstream of the valve is less than half of the upstream pressure i.e. that the ratio P3/P2 ≤ 0.5 then critical (sonic) flow is assured and the flow rate can be assumed to be stable.

If this criterion cannot be achieved, it is likely that the vacuum pump is worn or is of insufficient capacity and should be repaired or replaced.



Schematic of Sampling System for DPIs



Schematic of Particle Size System for DPIs

Critical Flow Controller Model TPK and TPK-R (Inlet/Outlet Reversed)

CRITICAL FLOW CONTROL

CRITICAL FLOW CONTROLLER MODEL TPK

In summary, a number of factors can have a significant effect on the testing of Dry Powder Inhalers:

- The resistance to flow posed by the inhaler under test
- The appropriate flow rate, Q, required to generate a 4 kPa pressure drop over the inhaler concerned
- The duration of inspiration required to give the specified test volume
- The stability of the flow rate in terms of critical (sonic) flow

The "Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers" and the "Experimental set-up for testing powder inhalers" described in Ph.Eur. in Chapters 0671 and 2.9.18 respectively and "Apparatus B: Sampling apparatus for dry powder inhalers" and the "Apparatus 2,3, 4 or 5: General control equipment" described in USP Chapter 601 take all of these factors into account.

These specifications form the basis of the Critical Flow Controller Model TPK which incorporates all of the equipment required into a single integrated system.

The main features of the TPK are as follows:

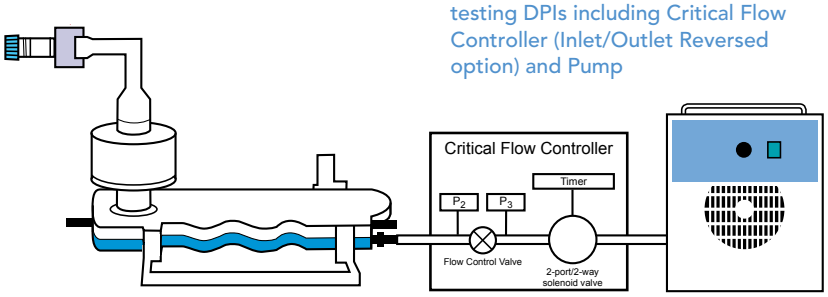
- Differential pressure meter for measuring pressure drop, P1 (Range: 0 to 100 kPa Resolution: 0.1 kPa)
- Flow control valve to adjust flow rate
- Timer-controlled solenoid valve to adjust duration of flow (Range: 0 to 999.9 seconds, Resolution: 0.1 seconds)
- Absolute pressure meter for measuring sonic flow, P2 and P3 (Range: 0 to 100 kPa, Resolution 0.1 kPa)
- Membrane keypad control
- LED display of differential and absolute pressure values
- LCD back-lit display of set and elapsed actuation times

PROCEDURE

1. Delivered Dose Uniformity

Follow the procedure described under Delivered Dose Uniformity – Dosage Unit Sampling Apparatus (DUSA) for DPIs (see Page 30).

Schematic of NGI System for testing DPIs including Critical Flow Controller (Inlet/Outlet Reversed option) and Pump



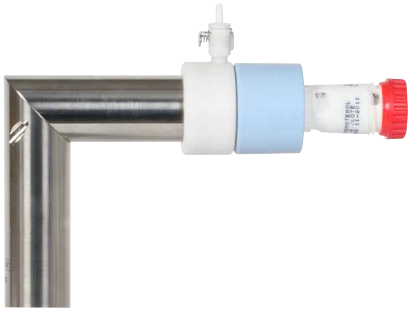
2. Aerodynamic Particle Size Distribution

Use a Cascade Impactor (ACI, NGI or MSLI) together with the system components relevant to that particular impactor to perform this test.

Proceed as follows:

1. Assemble the appropriate system as shown in the schematic for testing the APSD of DPIs (see below).
2. Attach a suitable flow meter (see Page 90) to the inlet of the induction port 3. Switch on the pump and open the two-way solenoid valve.
3. Adjust the flow control valve until the flow rate, as measured by the flow meter, is equal to Q (as measured **either** during DDU – see 1 above **or** by employing the Induction Port P1 Measurement Adapter depicted below and described on Page 96).

Induction Port P1 Measurement Adapter for measuring Device Flow Resistance in absence of DUSA for DPIs



CRITICAL FLOW CONTROL

4. Check that sonic flow is being achieved by pressing the keys relating to P2 and P3 and reading the results from the LED display. Close the solenoid valve and remove the flow meter.
5. Using the TPK timer, adjust the test flow duration to give the inspiration volume required, for example, 4 litres.
6. Insert the mouthpiece of the primed/loaded inhaler into the inlet of the induction port using a suitable mouthpiece adapter (Page 92).
7. Discharge the powder into the impactor/impinger by activating the timer, thus opening the solenoid valve.
8. Now conduct the assay as appropriate to the apparatus concerned.

Flow Time Verification Kit

Cat. No.	Description
8701	Critical Flow Controller Model TPK
8701-R	Critical Flow Controller Model TPK-R (Inlet/Outlet Reversed)
8750	TPK Re-calibration Certificate
8752	Flow Time Verification Kit
8753	Re-calibration of Flow Time Verification Kit
8502	Induction Port P1 Measurement Adapter

Critical Flow Controller TPK	Critical Flow Controller TPK 2000
Flow control valve for flow rate control	Flow control valve for flow rate control
P3 measurement (electrical control)	P3 measurement (electronic control)
P2 measurement (electrical control)	P2 measurement (electronic control)
P1 measurement (electrical control)	P1 measurement (electronic control)
Digital timer for control of solenoid valve	Electronic timer for control of solenoid valve
2-way/2-port solenoid valve	2-way/2-port solenoid valve
LED display of pressure only	4-line LCD display of all parameters
Membrane timer, P1, P2 and P3 buttons with LEDs	Illuminated mechanical start button and keypad
P1 range 0-100 kPa, resolution 0.1 kPa	P1 range 0-15 kPa, resolution 0.01 kPa
P2 & P3 range 0-100 kPa, resolution 0.1 kPa	P2 & P3 range 0-120 kPa, resolution 0.1 kPa
Timer range 0-999.9s, resolution 0.1s	Timer range 0-999.9s, resolution 0.1s
Solenoid valve opening/closing time 25/25 ms	Solenoid valve opening/closing time 25/25 ms
	Automatic test set-up function
	Automatic calculation of P3/P2 ratio
	Actuation setting/counting function
	External temperature/humidity sensor module
	Flow meter DFM 2000/DFM 3 interface
	USB printer port interface for data output
	Foot switch (or TTL input) interface for remote actuation
	RS232 (serial) interface for data output and remote actuation
	Impactor leak test function
	User calibration function
	Storage of calibration time/date
	Total impactor Delta-P function
	Spacer/VHC testing delay function

Critical Flow Controller Model TPK 2000-R (Inlet/Outlet Reversed)

TPK 2000 with External Temperature/Humidity Sensor

CRITICAL FLOW CONTROL

CRITICAL FLOW CONTROLLER MODEL TPK 2000

The Critical Flow Controller Model TPK 2000 is designed to control and document all the critical parameters associated with the delivered dose testing and aerodynamic particle size distribution measurement of Dry Powder Inhalers (DPIs).

Its predecessor, the Critical Flow Controller Model TPK has already become an international standard in the field of DPI testing.

The more advanced **Critical Flow Controller Model TPK 2000** retains the same critical specifications laid down in Ph.Eur. and USP as the earlier model but incorporates a number of additional features namely:

- 4-Line menu-driven LCD display of all parameters
- Improved differential pressure meter for measuring pressure drop, P1 (range: 0 to 15 kPa, resolution: 0.01 kPa)
- Automatic calculation and display of sonic (critical) flow
- Automatic test set-up function
- Setting and counting of number of test actuations
- Illuminated test actuation button indicates readiness to actuate
- Foot switch or external TTL trigger facility for remote actuation
- RS232 connection for flow meter (for recording flow rate during set-up)
- USB printer port and RS232 port for data output
- External temperature/humidity sensor (option)

* For measuring environmental test conditions as recommended by FDA

It also includes a series of extra functions including those for:

- Auto print-out or download of relevant calibration and test parameters
- Facility to measure impactor leak rates and "total pressure drop"
- User calibration function (with optional calibration kit)
- Storage of calibration time/date
- Spacer testing delay function

A series of menus guide the user through the operation of the instrument. Interaction with the unit is via a touch sensitive membrane keypad.

A highly durable, illuminated test button independent from the keypad allows high speed, repeat actuations for multiple actuation testing. The facility for TTL trigger inputs is also provided to allow actuations to be performed remotely.

Multiple ports/sockets allow connection to external devices such as a PC, a printer, a foot switch, a flow meter, and a temperature/relative humidity sensor for the monitoring of environmental conditions.

The TPK 2000 is fitted with two external pressure ports. These can be used singularly or together to perform a variety of functions.

The first port can be connected to the Dose Unit Sampling Apparatus (DUSA) for DPIs **or** to the Induction Port P1 Measurement Adapter depicted on Page 80 and is used to determine **device resistance** by measuring the **pressure drop** over the inhaler (P1).

The second of the two ports is used for the measurement of **atmospheric pressure** during the test set-up process.

In combination, the two pressure ports can also be used for determining impactor leak rates and for ACI and NGI Delta-P measurements.

Delta-P measurements can be extremely useful in monitoring day-to-day performance of the impactor nozzles and can be used as an "early warning" of any critical nozzle wear or occlusion (see Page 124).

TPK 2000 Firmware Version 4.04+ now provides for the **Leak Testing** of cascade impactors as part of the routine test set-up, **without** the need for additional leak test equipment.

This encourages leak testing prior to each and every analysis, thereby safeguarding data quality.

Typical System for Testing DPIs

CRITICAL FLOW CONTROL

PROCEDURE

The TPK 2000 menu system automatically guides the user through the correct test set-up procedure.

During initial delivered dose uniformity testing, the user is instructed to set the pressure drop over the inhaler (P1) to the desired value (typically 4 kPa) using the flow control valve located on the left side of the unit.

If the flow rate (as measured by a flow meter positioned in place of the inhaler) required to generate the pressure drop is more than 100 L/min, then provision is made to skip the P1 setting and re-adjust the control valve to achieve a flow rate of exactly 100 L/min. This also applies during impactor particle sizing when the test flow rate has already been predetermined during the DDU phase.

The TPK 2000 now automatically measures and calculates the test set-up parameters: P1, P2, P3, P3/2 ratio, flow rate, temperature, relative humidity, atmospheric pressure together with test set-up time, TPK 2000 and flow meter serial numbers and calibration data.

All of this data can be printed out or output to an external PC immediately after the test set-up process is complete.

Prior to running the actual test, the TPK 2000 prompts the user to enter the duration of the test (the inspiration time) along with the number of actuations for the test phase.

Provision is also made to programme a time delay before commencing the flow (i.e. opening of the solenoid valve).

This has a number of advantages since the user can reproducibly control the time between priming the inhaler and starting the flow. This facility can be used to control both inspiration delay times and effective inspiratory volume, essential when testing the effectiveness of **spacers and valved holding chambers (VHCs)**.

During the test, the current actuation number (e.g. 3 of 20) is indicated on the display together with the test duration, time delay (if used) and elapsed time.

Actuations are normally triggered by depressing the illuminated 'RUN' button on the TPK 2000 front panel. This button is illuminated once the test parameters have been entered, indicating that the unit is ready for the first actuation and repeated for each further actuation.

If desired, test actuations can be triggered remotely using the optional foot switch, RS232 input or external TTL trigger (for automation) via sockets located on the rear panel.

Cat. No.	Description
8760	Critical Flow Controller Model TPK 2000
8760-R	Critical Flow Controller Model TPK 2000-R (Inlet/Outlet Reversed)
8769	Temperature and Relative Humidity Sensor (option)
8761	Foot Switch (option)
8766	Printer (option)
8763	TPK 2000 Re-calibration Certificate
8752	Flow Time Verification Kit
8753	Re-calibration of Flow Time Verification Kit
8502	Induction Port P1 Measurement Adapter

Note: See Page 90 for details of Flow Meters suitable for connection to the TPK 2000

Breath Actuation Controller BAC 2000

BREATH ACTUATION CONTROL

BREATH ACTUATION CONTROLLER MODEL BAC 2000

A cut-down version of the TPK 2000, the Breath Actuation Controller is an electrically operated, timer controlled two-way solenoid valve.

In practice, it is positioned in the line between the DUSA collection tube/ cascade impactor and the vacuum pump in order to control the air flow supply to the inhaler under test.

The solenoid valve employed provides near instantaneous starting and stopping of the air flow during testing and has both delay and inhaled time functions.

User interface is via a membrane keypad with a 4-line LCD and menu driven operation.

An independent illuminated test button allows high speed, repeat actuation and recording for multi-shot testing.

Facility for TTL trigger inputs (via a DIN socket) and RS232 communication are also provided to allow actuations to be performed remotely, e.g. via an optional footswitch or external triggering system.

The BAC 2000 is a microprocessor controlled instrument designed specifically for three test applications:

1) Breath Actuated (or Breath Operated) Metered Dose inhalers (MDIs)

As the name implies, the Breath Actuation Controller Model BAC 2000 is a key element in determining the "Delivered Dose Uniformity" and "Particle Size Distribution" of Breath Actuated or Breath Operated MDIs.

In this instance, the initiation of the flow triggers the inhaler such that sampling from the MDI occurs only at the predetermined flow rate.

The volume of air sampled (the breath) is the product of the flow rate (typically 28.3 or 30 L/min) and the time that the valve is open.

The BAC 2000 can also be used to restrict the volume of air sampled to the 2 litres or less as recommended by the FDA and specified in USP 38 when carrying out "Delivered Dose Uniformity" testing on conventional MDIs.

See Pages 25-26 for further details.

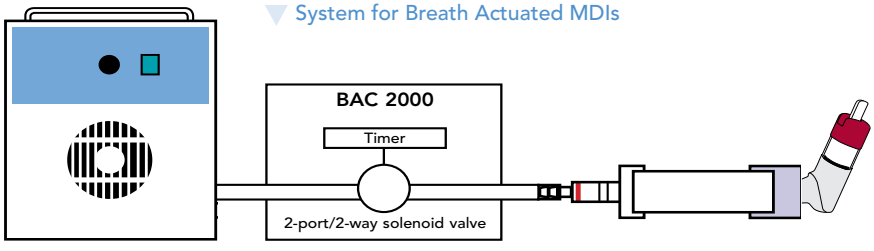
2) Spacers and Valved Holding Chambers (VHCs) used with MDIs

For the testing of the Spacers and Valved Holding Chambers (VHCs) commonly employed with MDIs in accordance with the specifications as laid down in the new USP draft Chapter <1602>.

Spacers and VHCs are add-on devices which are used in conjunction with pMDIs to overcome the problems associated with poor uncoordinated inhalation technique on the part of the user. This usually occurs when the patient delays inhalation rather than breathing in on actuation.

The draft chapter specifies two tests to determine aerodynamic particle size, Test Part 1A to measure the APSD under "optimal" conditions i.e., on actuation and Test Part 1B under "worst case" conditions that is to say with a delay of 2 or more seconds between inhaler actuation and sampling onset.

System for Breath Actuated MDIs



System for Nebulisers

The BAC 2000 has both delay and inhaled time functions.

In the case of Test Part 1B, the flow is set at the usual test flow rate for MDIs (28.3 or 30L/min). When called upon, the delay function is used to introduce the MDI aerosol into the spacer or VHC by starting the timer at the same time as actuating the MDI. Once the delay period has elapsed, the solenoid valve automatically opens to draw the aerosol into the the cascade impactor.

See Page 55 for further details.

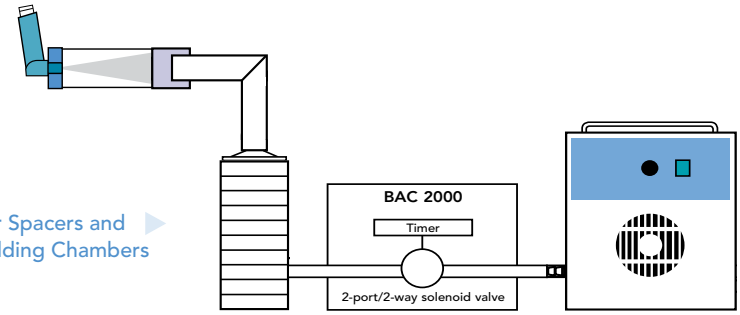
3) Nebulisers to USP <1601> and Ph.Eur. 2.9.44

For the testing of Nebulisers according to USP <1601> and Ph.Eur. 2.9.44.

In this case, the BAC 2000 is used as a substitute for the manually operated 3-way valve to set a test operating time (typically 60 seconds) for which the nebulised aerosol is drawn into the Next Generation Impactor (NGI).

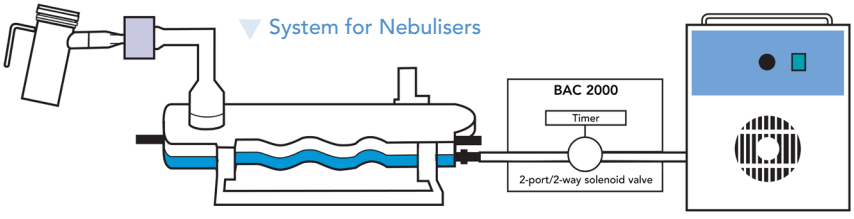
See Pages 58-59 for further details.

Note: The same functions can be provided by the TPK 2000 (described on Pages 82-83) and in the case of the Breath Actuated/Operated MDIs and Nebulisers by both TPK 2000 and TPK (described on Pages 80-81).



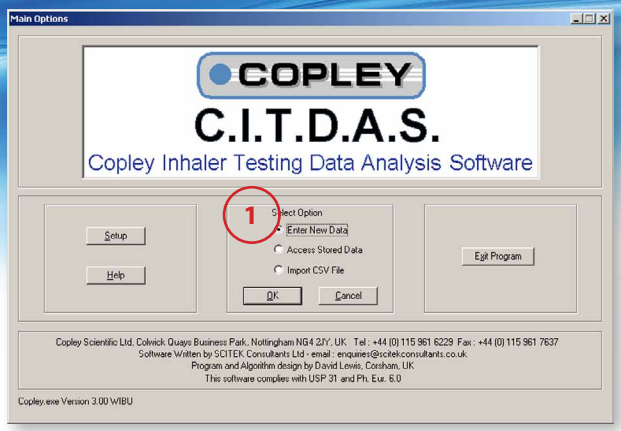
System for Spacers and Valved Holding Chambers

Breath Actuation Controller Model BAC 2000
Electronic timer for control of solenoid valve
2-way/2-port solenoid valve
4-line LCD display of all parameters
Illuminated mechanical start button and keypad
Timer range 0-999.9s, resolution 0.1s
Solenoid valve opening/closing time 25/25 ms
Actuation setting/counting function
Foot switch (or TTL input) interface for remote actuation
RS232 (serial) interface for and remote actuation
Spacer/VHC testing delay function

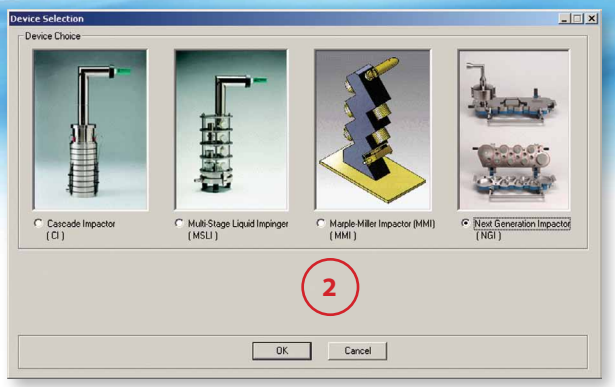


System for Nebulisers

Cat. No.	Description
8780	Breath Actuation Controller Model BAC 2000
8761	Foot Switch (option)
8781	BAC 2000 Re-test Certificate
8752	Flow Time Verification Kit
8753	Re-calibration of Flow Time Verification Kit



1: Opening Screen



2: Selecting the Impactor

COPLEY INHALER TESTING DATA ANALYSIS SOFTWARE (CITDAS)

INTRODUCTION

USP Chapter <601> and Ph.Eur. Chapter 2.9.18 specify various types of multi-stage cascade impactor that can be used for measuring the particle size distribution of inhalers together with suggestions as to how the resulting data should be analysed. Hitherto, this data analysis has largely been performed using a variety of techniques with little attention being paid to standardisation and validation.

Copley Inhaler Testing Data Analysis Software (CITDAS) Version 3.10 is a standardised approach to the entry, analysis and reporting of the Aerodynamic Size Distribution of drug output from MDIs, DPIs and Nebulisers in accordance with USP and Ph.Eur.

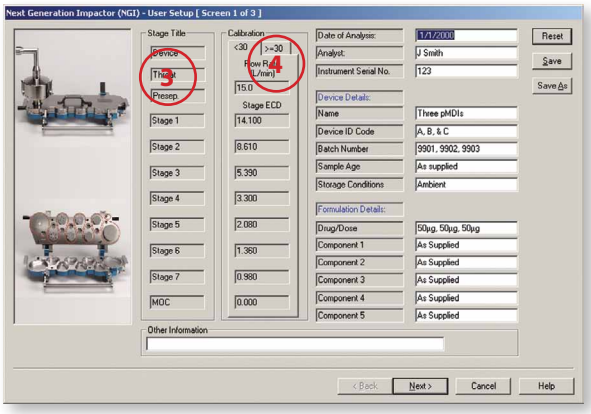
Fully validated, the software will accept data from the Andersen Cascade Impactor, the Multi-Stage Liquid Impinger, the Marple-Miller Impactor and the Next Generation Impactor.

CITDAS Version 3.10 has been designed to run on **Microsoft Windows Vista, XP, 7 and 8** operating systems. Installation is particularly quick and easy and does not require special IT knowledge.

SIMPLE OPERATION

On entering the program, the operator is prompted to select the source of the data to be analysed, whether new, stored or imported (1) and the type of impactor being used (2). One of the powerful new features incorporated into Version 3.10 of the software is the 'Import CSV file' facility which allows 'Comma Separated Variables' data input into CITDAS to be streamlined without the need for manual entry.

The system then defaults to the **User Set-up Screen** where the user is requested to fill in various information fields to identify themselves, the impactor being used and the inhaler(s) under test.



3: User Set-up (NGI)

The majority of the fields are free-form and the field names can be customised in Maintenance Mode (there are two levels of access: operator and maintenance) to meet individual user requirements.

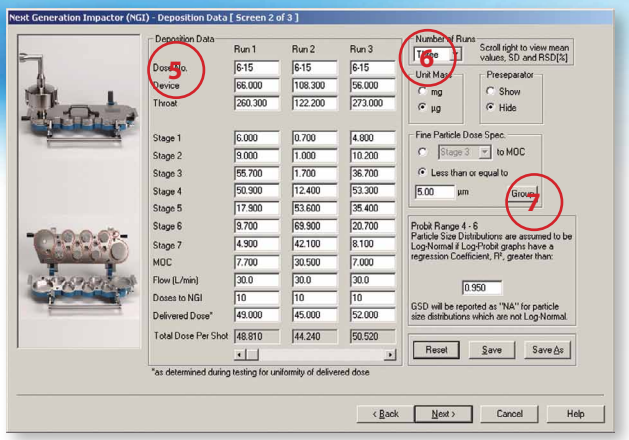
The same screen also contains the stages (3) and calibration data (4) applicable to the impactor being used (i.e. impactor stage ECDs). The software defaults to the stage effective cut-off diameters (ECDs) recommended by the manufacturer of the impactor at that flow rate selected by the operator. This includes NGI calibration data for 15 to 30 L/min such that the software can now be used for nebulisers as well as MDIs and DPIs.

Alternatively, specific calibration data, as for example relating to that particular impactor, can be entered if desired and saved as a template.

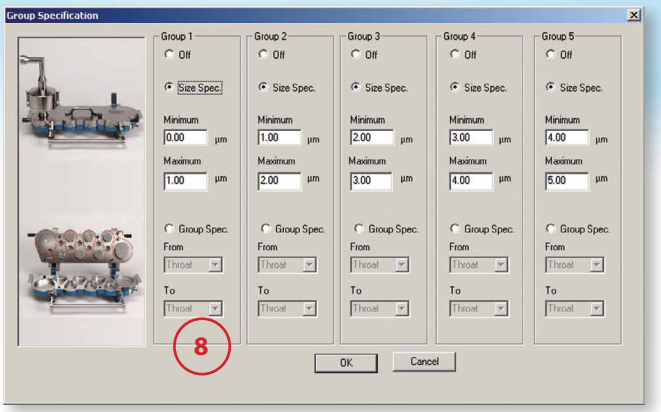
The **Deposition Data Screen** provides fields for the entry of the drug deposition (5) recovered from the impactor stages in addition to:

- Dose No. - The number of the dose sampled from the inhaler
- Device - The drug deposition on the actuator/inhaler
- Flow Rate - The flow rate employed during operation (L/min)
- Doses to Device - The number of doses sampled by the device
- Delivered Dose - As determined during Delivered Dose Uniformity
- Number of Runs - Number of runs to be processed (1-12)

This screen also allows the user to select the number of runs to be processed (1-12) and the units of measurement in terms of µg or mg (6). Provision is also made for omitting the deposition data from the preseparator where it is not deployed and also, Stages 6 and/or 7 when using the ACI at flow rates greater than 60 L/min.



4: Deposition Data (NGI)



5: Group Specification (NGI)

COPLEY INHALER TESTING DATA ANALYSIS SOFTWARE (CITDAS)

The number of runs to be processed can be adjusted between 1 and 12. Three runs are displayed per screen - further runs are accessed by means of the scroll bar.

The same screen allows the user to specify the criteria to be applied when calculating the Fine Particle Dose (FPD) and Geometric Standard Deviation (GSD). In the case of the FPD, this can be expressed in terms of either impactor stage or selected aerodynamic particle size (e.g. 5 microns).

One key feature of Version 3.10 that will be welcomed by users is the ability to define up to five fine particle dose/ fraction groupings (7). Each group being defined by a range of either impactor stage or aerodynamic particle diameter (by interpolation).

This means that in addition to reporting fine particle dose values, it is now possible to routinely subdivide the reported delivered dose into up to five groupings based on stage or particle size. This includes the preseparator.

This facility is accessed through the Group button (7) on the Deposition Data screen which in turn reveals the **Group Specification Screen (8).**

The results of the various tests are calculated automatically and displayed on the **Shot Weight Input & Results Summary Screen** together with graphical representations (9) of the data for each run selected from the following options:

- Log Probability Graphs of Percentage of Mass Less than Stated Aerodynamic Diameter against Log Aerodynamic Diameter
- Histograms of Drug Mass against Drug Distribution
- Cumulative Graphs of Percentage Drug Distribution against particle size

The drug deposition bar chart (10) can be viewed (and subsequently printed) with or without throat deposition. The same screen allows the user to input shot weights expressed in terms of the Mean and Standard Deviation for each particular run (11).

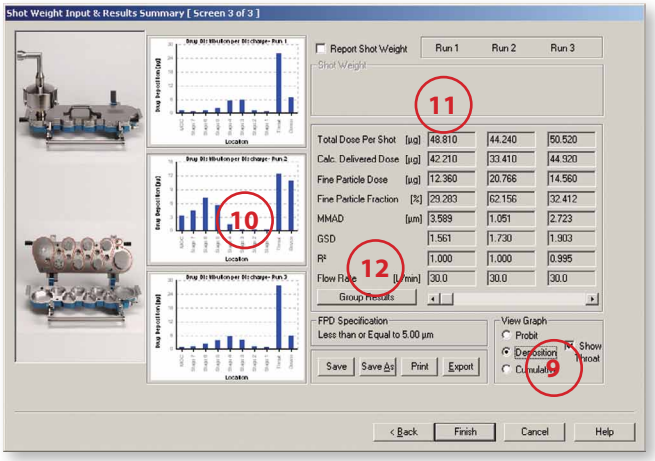
The following summarised data (12) is listed for each run:

- Total Dose per Shot [µg] or [mg]
- Delivered Dose [µg] or [mg]
- Fine Particle Dose [µg] or [mg]
- Fine Particle Fraction [%]
- Mass Medium Aerodynamic Diameter (MMAD) [µm]
- Geometric Standard Deviation (GSD)
- Particle Undersize log-probit graph (probit values 4-6)
- Regression Coefficient (R^2)
- Device Sampling Flow Rate [L/min]

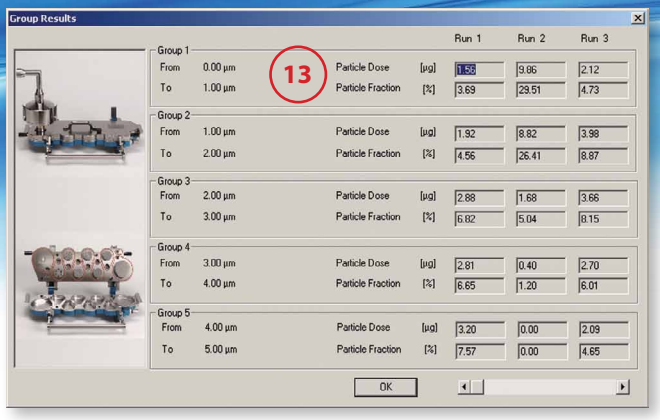
Version 3.10 also provides the facility to display, print or output 'Mean/ dose', 'SD/dose' and '%RSD/dose' data at the end of the 12 runs. This data can be accessed by scrolling right at data entry.

The **Group Results Screen** (overleaf) can be accessed through the Group Results button positioned below the summarised data fields.

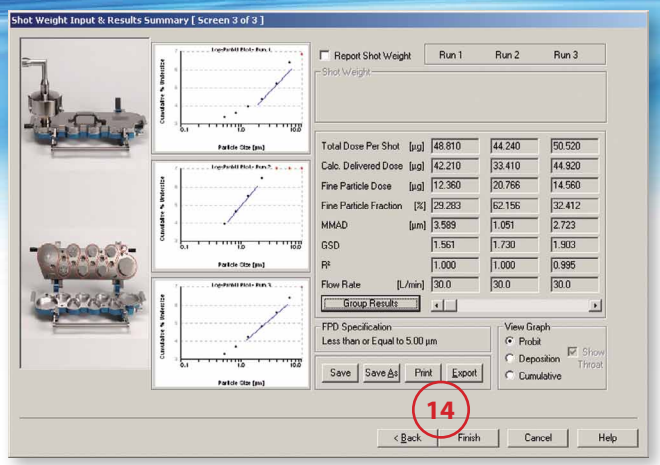
It gives up to 5 stage groupings (13), between two stages or between two particle sizes in each case. The group results can be printed on a separate printout.



6: Short Input and Results Summary



7: Group Results Screen



8: Printing

COPLEY INHALER TESTING DATA ANALYSIS SOFTWARE (CITDAS)

PRINTOUT FORMATS

CITDAS now has five printout types allowing the user to present data in five different formats:

- European Pharmacopoeia format
- United States Pharmacopeia format
- Graphical Summary
- Tabular Summary
- Group Results

All of the printout formats are located on a special **Print Screen** (15) which is accessed by pressing the Print Button (14) on the **Shot Weight Input and Results Summary Screen.**

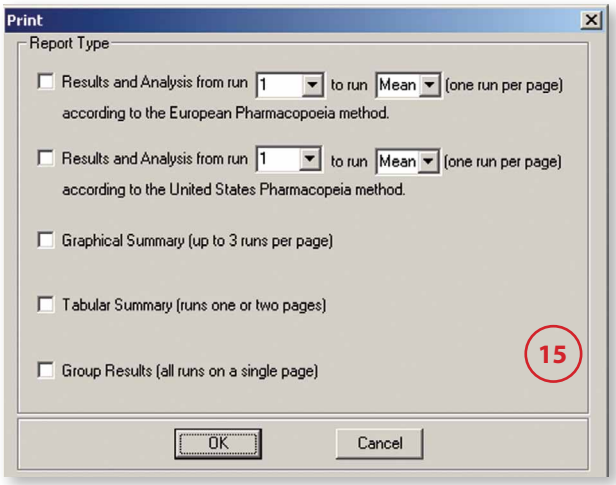
Examples of the various printouts may be found on Page 89. In response to customer feedback, Version 3.10 includes three significant improvements on earlier versions:

- Improved Accuracy (MMAD within +/- 0.003% of actual, GSD within +/- 0.007% of actual and FPD within 0.06% of total drug mass per dose)
- Mass balance calculations on USP and Ph.Eur. printouts expanded from 75-125% to also include 80-120% and 85-115% to meet FDA requirements
- Tabular summary now includes raw data input to allow cross check against output data on the same printout
- Limit of Detection (LOD) introduced to improve robustness and data integrity for narrow particle size distributions

SUMMARY OF KEY FEATURES

- Standardised approach to the analysis of impactor data
- Accepts data from ACI, MSLI, MMI and NGI
- Instant comparison of up to 12 runs
- Auto-correction of results to allow for impactor calibration differences and/or differing flow rates
- Fine Particle Dose (FPD) selection based on either impactor stage or aerodynamic particle size (e.g. 5 µm)
- Shot weight report option
- Automatic calculation of FPD, FPF, MMAD and GSD
- On-screen graphs in either histogram, log probability or cumulative formats
- Full printouts in both Ph.Eur. and USP formats, incl. graphical, tabular and group summaries
- Fully updated to reflect the definitive archival calibrationof the NGI at 15 L/ min so as to include Nebulisers
- Facility to import/export data as CSV files for manipulation in Microsoft Excel or similar software packages
- Stage groupings

CITDAS is supplied as standard with **full supporting validation documentation**, which provides verification of the correct storage of input parameters and details of the algorithms, methods and conclusions employed to calculate the results.

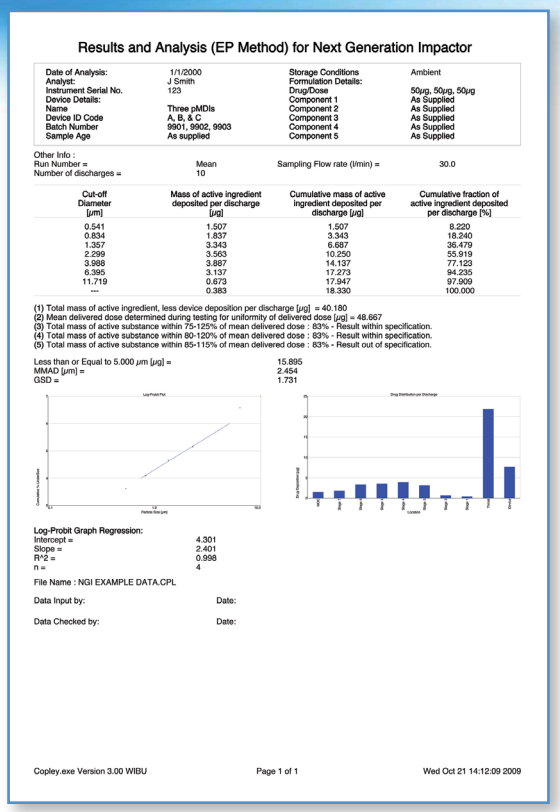


9: Print Screen

A **Waters Empower™** spreadsheet is now available on request to all CITDAS V3.10 users. This automatically converts files generated by Empower into CSV files, suitable for import into CITDAS, thus removing the need for manual data input.

Cat. No.	Description
8250	Copley Inhaler Testing Data Analysis Software (CITDAS) V3.10
8251	Upgrade from CITDAS V2.00 to V3.10

PRINTOUT FORMATS



Results and Analysis (EP Method) for Next Generation Impactor

Date of Analysis:	1/1/2000	**Storage Conditions**	Ambient
Analyst:	J Smith	**Formulation Details:**	
Instrument Serial No.	123	**Drug/Dose**	50µg, 50µg, 50µg
Device Details:		**Component 1**	As Supplied
Name	Three pMDIs	**Component 2**	As Supplied
Device ID Code	A, B, & C	**Component 3**	As Supplied
Batch Number	9901, 9902, 9903	**Component 4**	As Supplied
Sample Age	As supplied	**Component 5**	As Supplied

Other Info :
Run Number = Mean Sampling Flow rate (l/min) = 30.0
Number of discharges = 10

Cut-off Diameter [µm]	Mass of active ingredient deposited per discharge [µg]	Cumulative mass of active ingredient deposited per discharge [µg]	Cumulative fraction of active ingredient deposited per discharge [%]
0.541	1.507	1.507	8.220
0.834	1.837	3.343	18.240
1.357	3.343	6.687	36.479
2.299	3.563	10.250	55.919
3.988	3.887	14.137	77.123
6.395	3.137	17.273	94.235
11.719	0.673	17.947	97.909
---	0.383	18.330	100.000

(1) Total mass of active ingredient, less device deposition per discharge [µg] = 40.180
(2) Mean delivered dose determined during testing for uniformity of delivered dose [µg] = 48.667
(3) Total mass of active substance within 75-125% of mean delivered dose : 83% - Result within specification.
(4) Total mass of active substance within 80-120% of mean delivered dose : 83% - Result within specification.
(5) Total mass of active substance within 85-115% of mean delivered dose : 83% - Result out of specification.

Less than or Equal to 5.000 µm [µg] = 15.895
MMAD [µm] = 2.454
GSD = 1.731

Log-Probit Graph Regression:
Intercept = 4.301
Slope = 2.401
R^2 = 0.998
n = 4

File Name : NGI EXAMPLE DATA.CPL

Data Input by: Date:

Data Checked by: Date:

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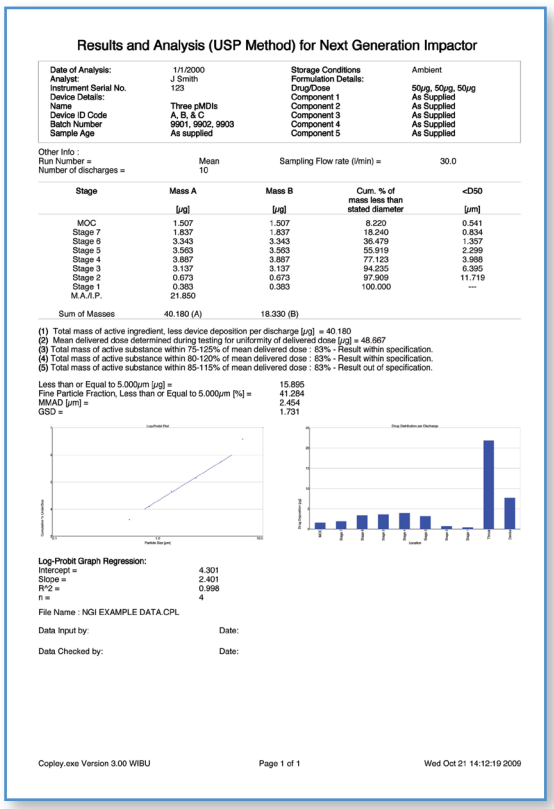
Ph.Eur. Method (1 run per page)



Results and Analysis (USP Method) for Next Generation Impactor

Date of Analysis:	1/1/2000	**Storage Conditions**	Ambient
Analyst:	J Smith	**Formulation Details:**	
Instrument Serial No.	123	**Drug/Dose**	50µg, 50µg, 50µg
Device Details:		**Component 1**	As Supplied
Name	Three pMDIs	**Component 2**	As Supplied
Device ID Code	A, B, & C	**Component 3**	As Supplied
Batch Number	9901, 9902, 9903	**Component 4**	As Supplied
Sample Age	As supplied	**Component 5**	As Supplied

Other Info :
Run Number = Mean Sampling Flow rate (l/min) = 30.0
Number of discharges = 10

Stage	Mass A [µg]	Mass B [µg]	Cum. % of mass less than stated diameter	<D50 [µm]
MOC	1.507	1.507	8.220	0.541
Stage 7	1.837	1.837	18.240	0.834
Stage 6	3.343	3.343	36.479	1.357
Stage 5	3.563	3.563	55.919	2.299
Stage 4	3.887	3.887	77.123	3.988
Stage 3	3.137	3.137	94.235	6.395
Stage 2	0.673	0.673	97.909	11.719
Stage 1	0.383	0.383	100.000	---
M.A./I.P.	21.850			
Sum of Masses	40.180 (A)	18.330 (B)		

(1) Total mass of active ingredient, less device deposition per discharge [µg] = 40.180
(2) Mean delivered dose determined during testing for uniformity of delivered dose [µg] = 48.667
(3) Total mass of active substance within 75-125% of mean delivered dose : 83% - Result within specification.
(4) Total mass of active substance within 80-120% of mean delivered dose : 83% - Result within specification.
(5) Total mass of active substance within 85-115% of mean delivered dose : 83% - Result out of specification.

Less than or Equal to 5.000µm [µg] = 15.895
Fine Particle Fraction, Less than or Equal to 5.000µm [%] = 41.284
MMAD [µm] = 2.454
GSD = 1.731

Log-Probit Graph Regression:
Intercept = 4.301
Slope = 2.401
R^2 = 0.998
n = 4

File Name : NGI EXAMPLE DATA.CPL

Data Input by: Date:

Data Checked by: Date:

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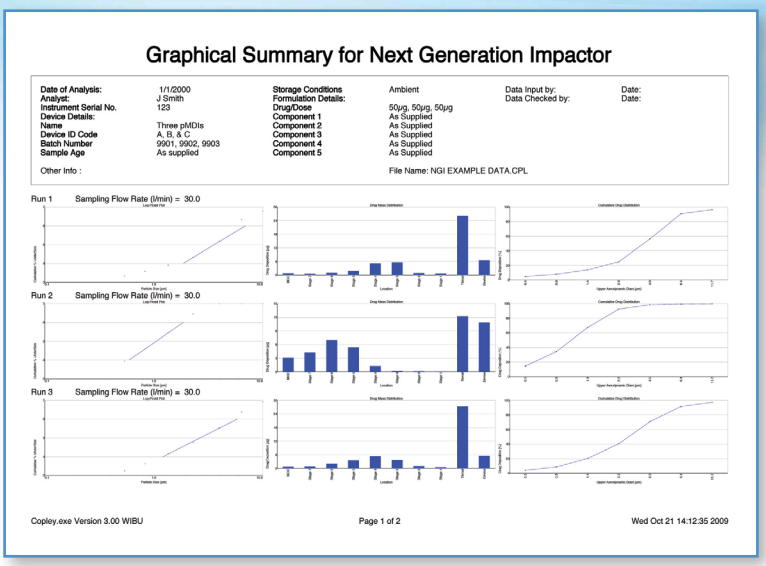
USP Method (1 run per page)



Graphical Summary for Next Generation Impactor

Date of Analysis:	1/1/2000	**Storage Conditions**	Ambient	Data Input by:	Date:
Analyst:	J Smith	**Formulation Details:**		Data Checked by:	Date:
Instrument Serial No.	123	**Drug/Dose**	50µg, 50µg, 50µg		
Device Details:		**Component 1**	As Supplied		
Name	Three pMDIs	**Component 2**	As Supplied		
Device ID Code	A, B, & C	**Component 3**	As Supplied		
Batch Number	9901, 9902, 9903	**Component 4**	As Supplied		
Sample Age	As supplied	**Component 5**	As Supplied		

Other Info : File Name: NGI EXAMPLE DATA.CPL

Run 1 Sampling Flow Rate (l/min) = 30.0

Run 2 Sampling Flow Rate (l/min) = 30.0

Run 3 Sampling Flow Rate (l/min) = 30.0

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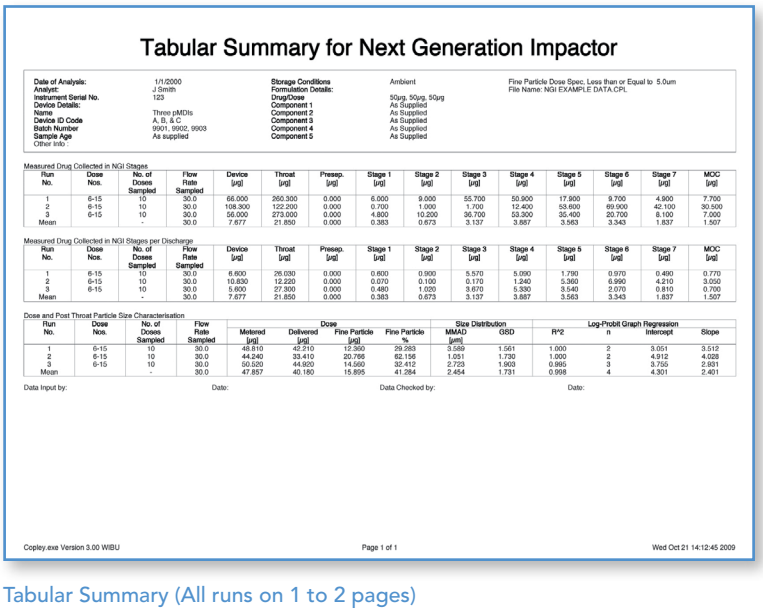
Graphical Summary (3 runs per page)



Tabular Summary for Next Generation Impactor

Date of Analysis:	1/1/2000	**Storage Conditions**	Ambient	Fine Particle Dose Spec, Less than or Equal to 5.0um	
Analyst:	J Smith	**Formulation Details:**		File Name: NGI EXAMPLE DATA.CPL	
Instrument Serial No.	123	**Drug/Dose**	50µg, 50µg, 50µg		
Device Details:		**Component 1**	As Supplied		
Name	Three pMDIs	**Component 2**	As Supplied		
Device ID Code	A, B, & C	**Component 3**	As Supplied		
Batch Number	9901, 9902, 9903	**Component 4**	As Supplied		
Sample Age	As supplied	**Component 5**	As Supplied		

Other Info :

Measured Drug Collected in NGI Stages

Run No.	Dose Nos.	No. of Doses Sampled	Flow Rate Sampled	Device [µg]	Throat [µg]	Presep. [µg]	Stage 1 [µg]	Stage 2 [µg]	Stage 3 [µg]	Stage 4 [µg]	Stage 5 [µg]	Stage 6 [µg]	Stage 7 [µg]	MOC [µg]
1	6-15	10	30.0	66.000	260.300	0.000	6.000	9.000	55.700	50.900	17.900	9.700	4.900	7.700
2	6-15	10	30.0	108.300	122.200	0.000	0.700	1.000	1.700	12.400	53.600	69.900	42.100	30.500
3	6-15	10	30.0	56.000	273.000	0.000	4.800	10.200	36.700	53.300	35.400	20.700	8.100	7.000
Mean		-	30.0	7.677	21.850	0.000	0.383	0.673	3.137	3.887	3.563	3.343	1.837	1.507

Measured Drug Collected in NGI Stages per Discharge

Run No.	Dose Nos.	No. of Doses Sampled	Flow Rate Sampled	Device [µg]	Throat [µg]	Presep. [µg]	Stage 1 [µg]	Stage 2 [µg]	Stage 3 [µg]	Stage 4 [µg]	Stage 5 [µg]	Stage 6 [µg]	Stage 7 [µg]	MOC [µg]
1	6-15	10	30.0	6.600	26.030	0.000	0.600	0.900	5.570	5.090	1.790	0.970	0.490	0.770
2	6-15	10	30.0	10.830	12.220	0.000	0.070	0.100	0.170	1.240	5.360	6.990	4.210	3.050
3	6-15	10	30.0	5.600	27.300	0.000	0.480	1.020	3.670	5.330	3.540	2.070	0.810	0.700
Mean		-	30.0	7.677	21.850	0.000	0.383	0.673	3.137	3.887	3.563	3.343	1.837	1.507

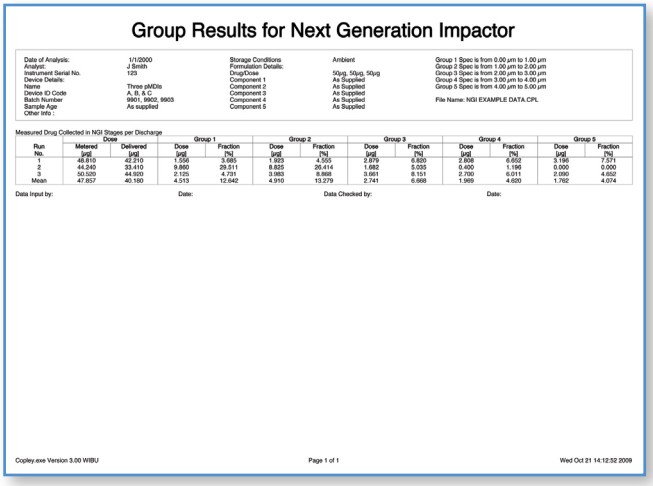
Dose and Post Throat Particle Size Characterisation

Run No.	Dose Nos.	No. of Doses Sampled	Flow Rate Sampled	Dose				Size Distribution		Log-Probit Graph Regression			
				Metered [µg]	Delivered [µg]	Fine Particle [µg]	Fine Particle %	MMAD [µm]	GSD	R^2	n	Intercept	Slope
1	6-15	10	30.0	46.810	42.210	12.360	29.283	3.589	1.561	1.000	2	3.051	3.512
2	6-15	10	30.0	44.240	33.410	20.766	62.156	1.051	1.730	1.000	2	4.912	4.028
3	6-15	10	30.0	50.520	44.920	14.660	32.412	2.723	1.903	0.995	3	3.755	2.931
Mean		-	30.0	47.857	40.180	15.895	41.284	2.454	1.731	0.998	4	4.301	2.401

Data Input by: Date: Data Checked by: Date:

Copley.exe Version 3.00 WIBU Page 1 of 1 Wed Oct 21 14:12:45 2009

Tabular Summary (All runs on 1 to 2 pages)



Group Results for Next Generation Impactor

Date of Analysis:	1/1/2000	**Storage Conditions**	Ambient	Group 1 Spec is from 0.00 µm to 1.00 µm	
Analyst:	J Smith	**Formulation Details:**		Group 2 Spec is from 1.00 µm to 2.00 µm	
Instrument Serial No.	123	**Drug/Dose**	50µg, 50µg, 50µg	Group 3 Spec is from 2.00 µm to 3.00 µm	
Device Details:		**Component 1**	As Supplied	Group 4 Spec is from 3.00 µm to 4.00 µm	
Name	Three pMDIs	**Component 2**	As Supplied	Group 5 Spec is from 4.00 µm to 5.00 µm	
Device ID Code	A, B, & C	**Component 3**	As Supplied		
Batch Number	9901, 9902, 9903	**Component 4**	As Supplied	File Name: NGI EXAMPLE DATA.CPL	
Sample Age	As supplied	**Component 5**	As Supplied		
Other Info :					

Measured Drug Collected in NGI Stages per Discharge

Run No.	Dose		Group 1		Group 2		Group 3		Group 4		Group 5	
	Metered [µg]	Delivered [µg]	Dose [µg]	Fraction [%]	Dose [µg]	Fraction [%]	Dose [µg]	Fraction [%]	Dose [µg]	Fraction [%]	Dose [µg]	Fraction [%]
1	46.810	42.210	1.556	3.686	1.903	4.508	2.879	6.820	2.806	6.652	3.196	7.571
2	44.240	33.410	0.860	29.511	8.825	26.414	1.682	5.035	0.400	1.196	0.000	0.000
3	50.520	44.920	2.125	4.731	3.983	8.868	3.661	8.151	2.700	6.011	2.090	4.652
Mean	47.857	40.180	4.513	12.642	4.910	13.279	2.741	6.668	1.969	4.620	1.762	4.074

Data Input by: Date: Data Checked by: Date:

Copley.exe Version 3.00 WIBU Page 1 of 1 Wed Oct 21 14:12:52 2009

Group Results (all runs on 1 page)

FLOW METERS

Flow Meter Model DFM 2000

INTRODUCTION

The Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD) are two of the main Critical Quality Attributes (CQAs) in measuring the therapeutic efficacy of orally inhaled and nasal drug products (OINDPs).

The data produced by both of these tests can be severely compromised if the inlet flow rate (the flow rate at the entrance to the induction port or DUSA) used during testing is inaccurate and/or inconsistent, generating discrepancies with regard to its effects on both the cascade impactor itself and the inhaler under test.

Cascade impaction, the method used to measure APSD, divides the aerosol cloud into various size fractions on the basis of particle inertia which is a function of aerodynamic particle size and velocity.

In this technique, particle-laden air is drawn through a series of stages, each of which has a predetermined number of nozzles of defined diameter. Providing that the volumetric flow rate of the air stream remains constant, the air velocity increases from stage to stage.

Particles with sufficient inertia impact on the collection surface at a set distance beneath the nozzles while smaller particles are retained in the air stream and carried to the next stage. The result is a series of size fractions, typically between 0 and 10 microns.

The jet-to-plate distances on most commonly used impactors are fixed. Therefore, as long as the nozzle diameters remain within defined tolerances and there are no inherent leaks in the system, it can be seen that the cut-off diameter (the aerodynamic diameter of particles that accumulate on any given collection surface) of any given stage **is directly related to the volumetric flow rate of the inlet air passing through it.** A change in the flow rate results in a change in the aerodynamic particle size characteristics of the stage or stages concerned.

Indeed, a simplified version of Stokes' law, which describes the relationship between stage cut-off diameter, nozzle diameter and air flow rate, demonstrates that a 5% deviation in flow rate changes the stage cut-off diameter by approximately 2.5%. At a flow rate of 60 L/min, Stage 1 of an Andersen Cascade Impactor should give a theoretical cut-off of 4.7 microns – reduce that flow rate to 57 L/min and cut-off is effectively reduced to 4.58 microns.

The volumetric air flow can not only affect the ability of the cascade impactor to function correctly but also compromises the actual performance of the inhaler itself.

For many inhaled products, for example, the air flow drives the aerosolisation of the formulation and can therefore have a marked impact on how the dose disperses and hence on the resulting aerodynamic particle size determination.

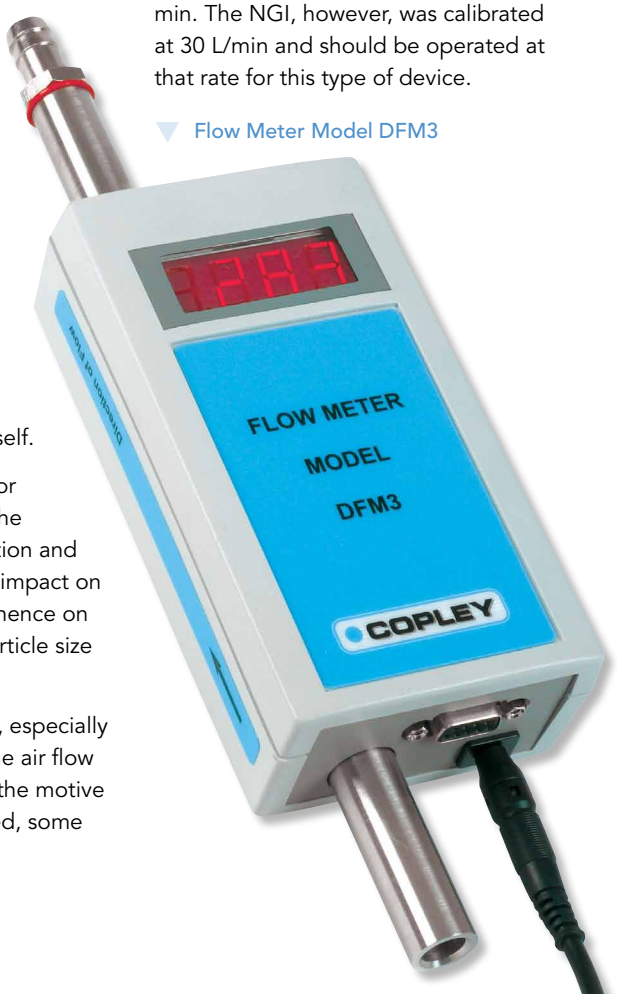
In addition, for some devices, especially dry powder inhalers (DPIs), the air flow through the device provides the motive force for dose delivery; indeed, some breath-operated devices trigger only when the flow rate through them exceeds a certain value.

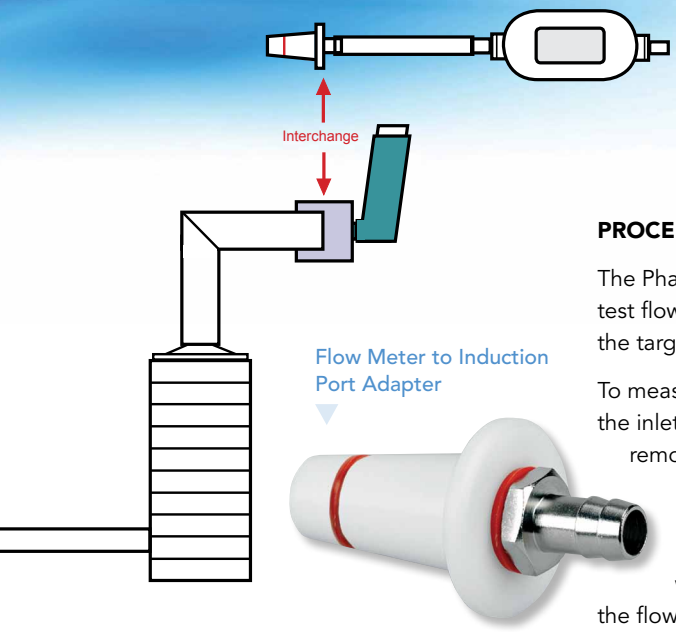
DETERMINING THE PROPER TEST FLOW RATE

Although patient inspiration subjects inhalers to varying flow rates, cascade impaction requires a constant volumetric air flow: within this constraint, the flow rate must, as far possible, reflect the conditions of use.

For propellant or pump-driven delivery, particle aerosolisation is generally insensitive to test flow rate. MDIs and the majority of nasal sprays are therefore normally tested at 28.3 L/min equivalent to 1 cubic foot/min. The NGI, however, was calibrated at 30 L/min and should be operated at that rate for this type of device.

Flow Meter Model DFM3





FLOW METERS

Inspiration-dependent devices, where aerosolisation is sensitive to air flow, are more complex.

For DPIs, specifications call for a flow rate that induces a 4 kPa pressure drop across the device, typical for adult patient inspiration, or 100 L/min, whichever is lower. Because flow resistance differs from device to device, the easiest way to determine the correct flow rate for a particular DPI is to use a modified delivered dose sampling apparatus in conjunction with a flow controller that has the capacity to measure and record the required parameters.

For nebulisers, which rely on tidal breathing instead of a single forced inspiration, a flow rate of 15 L/min, the typical adult mid-inhalation flow rate, is employed.

PROCEDURE

The Pharmacopoeias specify that the test flow rate should lie within +/-5% of the target flow.

To measure the required flow rate at the inlet of the impactor, the user must remove the mouthpiece adapter and the device under test from the induction port and replace it with an appropriate flow meter, which should be used to adjust the flow to the correct rate. The flow meter is connected to the Induction Port by means of a suitable adapter.

The flow meter must:

- Be capable of measuring volumetric flow (L/min)
- Be calibrated for exit flow as opposed to inlet flow
- Account for ambient conditions

Copley Scientific provides two flow meters that meet these criteria.

The **DFM3** operates on the Differential Pressure (Venturi) principle, has a range of 15-100 L/min, a resolution of 0.1 L/min and an accuracy of 0.75% FSD.

The **DFM 2000** operates the thermal mass principle, has a range of 0-200 L/min, a resolution of 0.01 L/min between 0 and 90 L/min (0.1 L/min between 90 and 200 L/min) and an accuracy of +/- 2% of flow rate. It is fitted with temperature and pressure sensors, in order to calculate the ambient volumetric flow rate.

Both units have RS 232 interfaces that allow the communication of flow rate data to external devices, such as the Critical Flow Controller Model TPK 2000.

There seems to be a popular misconception that flow meters operating on differing principles give different results. This is not the case providing that they are calibrated and operated correctly. However, it is recommended to adhere to one particular type throughout the inhaler product lifecycle in order to reduce errors in use, when switching between types.

Cat. No.	Description
8002	Flow Meter Model DFM3
8061	Re-calibration Certificate for DFM
8764	Flow Meter Model DFM 2000
8765	Re-calibration Certificate for DFM 2000
8060	Flow Meter to Induction Port Adapter
5238	Mouthpiece Adapter (UIP to DFM 2000)

Flow Meter DFM3	Flow Meter DFM 2000
Portable Hand-Held	Portable Hand-Held
Venturi (Pressure Drop) Principle	Hot-Wire Mass Flow Principle
Metal flow tube with 12 mm hose fitting at outlet	Plastic flow tube with 1/2" hose fitting at inlet and outlet
Range: 15-100 L/min	Range: 0-200 L/min
Accuracy +/- 0.75% FSD	Accuracy +/- 2% of flow rate
Resolution: 0.1 L/min	Resolution: 0.01 L/min (0.1 L/min from 90 to 200 L/min
Universal mains input voltage	Universal mains input voltage
Low flow Resistance (1.0 kPa @ 100 L/min)	High Flow Resistance (4.0 kPa @ 100 L/min)
Calibrated for outlet flow (preferred)	Calibrated for outlet flow (preferred)
Direct measurement of volumetric flow	Requires conversion from mass to vol. (using in-built sensors)
No inlet filter required	Inlet filter required in un-filtered laboratory environment
Cannot be used "in-line"	Can be used "in-line" (for non-pharmacopoeial methods)
RS232 Data Output (Flow Rate & Calibrate Date)	RS232 Data Output (Flow Rate & Calibrate Date)
Conforms with USP 38 and Ph.Eur. 8.0	Conforms with USP 38 and Ph.Eur. 8.0

Example of Mouthpiece Adapter Engraving

Example of Mouthpiece Adapter Tool

Mouthpiece Adapters for a range of different inhalers

MOUTHPIECE ADAPTERS

MOUTHPIECE ADAPTERS

The mouthpiece adapters supplied by Copley Scientific are specially moulded from high quality silicone rubber in order to guarantee an airtight seal between the inhaler under test and the test apparatus.

There is no standard mouthpiece adapter *per se* as each inhaler design is different. Adapters are available however for the more common devices on the market (see ordering information).

For other unlisted inhalers, we require a sample of the inhaler to be tested, so that we can make a "cast" of the mouthpiece concerned and produce an appropriate moulding tool.

This moulding tool is used to mould the mouthpiece adapter(s) to that particular inhaler design.

The tool is then supplied along with the mouthpiece adapter(s) to the end user so that it can be reused should any additional mouthpiece adapters be required of that design, in the future.

The Induction Port used with the ACI, NGI, MMI and MSLI together with the Sampling Apparatus for both MDIs and DPIs and the WSC2 all have the same external dimensions at the inlet and hence the same mouthpiece adapter is transferable between all of these instrument types.

The Glass Twin Impinger however, because of its glass construction, and the Fluticasone Propionate (FP) Induction Port, do have different external dimensions at the inlet and so require their own mouthpiece adapter.

Cat. No.	Description
5003	Custom Mouthpiece Adapter (for Induction Port and/or DUSA for MDIs/DPIs)
5237	Custom Mouthpiece Adapter (for Glass Twin Impinger and FP Induction Port)
5004	Tooling Charge for 5003 & 5237 (per inhaler design)
5003C	Easyhaler® Mouthpiece Adapter
5003D	Cyclohaler® Mouthpiece Adapter
5003E	Handihaler® Mouthpiece Adapter
5003F	Diskus® Mouthpiece Adapter
5003G	Novolizer® Mouthpiece Adapter
5003H	Rotahaler® Mouthpiece Adapter
5003I	Turbuhaler® Symbicort Mouthpiece Adapter
5003J	Diskhaler® Mouthpiece Adapter
5003K	Respimat® Mouthpiece Adapter
5003L	Evohaler® Mouthpiece Adapter
5003M	Pari LC Plus® Mouthpiece Adapter
5003N	Trudell AeroChamber® Plus Mouthpiece Adapter
5003O	Tobi Podhaler® Mouthpiece Adapter
5003X	Inhaler Support Accessory for Mouthpiece Adapter
5003Y	Mouthpiece Adapter Engraving (each)
5238	Mouthpiece Adapter (Induction Port to DFM 2000)

Induction Port with Diskus® Mouthpiece Adapter and Inhaler Support Accessory

High Capacity Pump Model HCP5 (left) and Low Capacity Pump Model LCP5 (right)

PUMPS

INTRODUCTION

The Copley Scientific Low and High Capacity Pumps Models LCP5 and HCP5 are vacuum sources that have been specifically designed for use in the testing of MDIs, DPIs, nebulisers and nasal sprays in accordance with the specifications laid down in the European and US Pharmacopoeias.

The units represent the very latest in high performance, low maintenance, oil-free rotary-vane vacuum pump technology.

Foremost in the design specification were those features that you, the user, identified as being essential to inhaler testing, namely that the pump should:

- **Be equipped with the correct fittings to link to the test system concerned**
- **Have sufficient capacity to provide the required test flow and in the case of DPIs to ensure critical (sonic) flow**
- **Have low noise levels, suitable for a laboratory environment**
- **Be low maintenance**

Both pumps, for example, come with the appropriate fittings to connect to any inhaler testing system and to allow the user to position the pump to either right or left of that system depending on the available space on the laboratory bench. Provision is also made to vent the exhaust to an extraction system.

It should be noted that the resistance to flow imposed by the test apparatus, in conjunction with the requirement to achieve sonic flow in the case of DPIs, can reduce the effective capacity of the pump to less than 20% of the flow rate measured in free flow (unrestricted) conditions.

In practice, this means that in order to achieve 60 L/min sonic flow through the system a vacuum pump having a free flow of 300 L/min must be used. Even Metered-Dose Inhaler (MDI) systems provide significant resistance to flow typically in the region of 50% of free flow conditions.

Stable flow control is critical to good impactor measurement practice. This is because the aerodynamic particle sizing ability of inertial impactors is dependent on the velocity of the entrained particles as they pass through each stage and that velocity is directly related to air flow.

For this reason, the Pharmacopoeias insist that, in the case of dry powder inhalers, critical (sonic) flow conditions are achieved within the system prior to testing, to ensure that the vacuum pump employed is of sufficient capacity for the task.

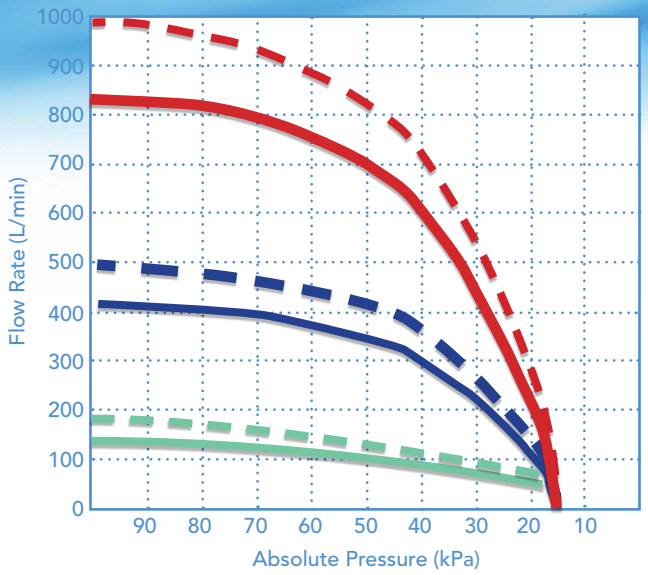
To meet these considerations the Copley LCP5 and HCP5 Pumps have been carefully designed to cover a range of free flow conditions between **133 and 833 L/min.**

Both pumps are fully encased with an internal acoustic lining and vibration damping to reduce noise levels to less than or equal to 60 dB (A).

Being oil-free, neither pump requires oil changes or regular replacement of oil filters.

Self-sealing compound carbon vanes continually adjust so that the pump effectively performs with "as new efficiency" throughout its service life.

Backs of High Capacity Pump Model HCP5 (right) and Low Capacity Pump Model LCP5



PUMPS

LOW CAPACITY PUMP MODEL LCP5

The Low Capacity Pump Model LCP5 is a small footprint vacuum pump designed for optimal operation at low flow rates.

This makes it ideal for **Metered-Dose Inhalers (MDIs)** and **Nasal Sprays** which are tested at 28.3 or 30 L/min and **Nebulisers** which are typically tested at 15 L/min. These devices do not generally require the use of a Critical Flow Controller.

In this instance, the test apparatus (the dose unit sampling apparatus (DUSA) in the case of delivered dose testing and the cascade impactor in the case of particle size determination) is connected directly to the pump.

The unit contains a 0.35 kW motor capable of generating a maximum of 133 L/min free flow (at 50 Hz mains frequency).

The flow rate can be adjusted between 0 and 133 L/min free flow using the flow control valve mounted on the front panel.

The unit is provided with two vacuum inlets such that the user can decide whether to place the pump on the right or left side of the test system dependent on available bench space.

The LCP5 has an in-built cooling fan located on the top side of the pump and a ventilation grill on the bottom of the front panel. Two handles are located on the top of the pump for lifting and positioning.

The pump measures 270 x 310 x 300 mm (w x d x h) and weighs 18 kg.

HIGH CAPACITY PUMP MODEL HCP5

The High Capacity Pump Model HCP5 is a well established high capacity pump for the higher, sonic flow rate testing requirements of **Dry Powder Inhalers (DPIs)**, although it can equally well be used for MDIs, Nasal Sprays and Nebulisers.

Like the LCP5, an on/off switch and flow control valve are located on the front panel of the unit. Two sets of vacuum inlets on either side of the pump allow the user to choose the location of the pump in relation to the test apparatus. Each set of vacuum inlets consists of a regulated and unregulated inlet.

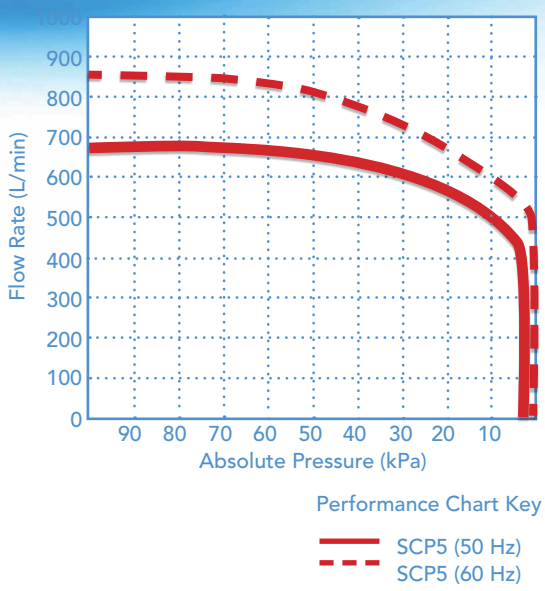
The regulated inlet is connected to the pump via the flow control valve and is used to regulate flow between 0 and 250 L/min for MDI, nasal spray and nebuliser applications.

The unregulated inlet bypasses the flow control valve and is used in conjunction with the Critical Flow Controller for dry powder applications. It provides a maximum flow of 416 L/min.

In instances where this flow rate is still not adequate, it is possible to connect a Secondary HCP5 in parallel to the primary pump to give a maximum unregulated flow rate of 833 L/min. This is typically required when testing DPIs under sonic flow conditions with the NGI, at high flow rates. Special hose fittings are supplied with the secondary pump to connect it to the primary unit.

The pump measures 320 x 560 x 390 mm (w x d x h) and weighs 45 kg.

Cat. No.	Description
7903	Low Capacity Pump Model LCP5
7904	Overhaul Kit for LCP5
7901	High Capacity Pump Model HCP5
7902	High Capacity Pump Model HCP5 (with additional hose fittings for use as a secondary pump)
7905	Overhaul Kit for HCP5



Super Capacity Pump Model SCP5

SUPER CAPACITY PUMP MODEL SCP5

The Super Capacity Pump Model SCP5 is a bench-top vacuum pump for the laboratory capable of generating sonic (P3/P2 ≤ 0.5) flow rates through the Next Generation Impactor (NGI) up to 100 L/min.

It is designed to provide a viable alternative to the use of two HCP5 Pumps to achieve these conditions.

The flow rate is controlled by means of a valve on the front panel of the unit. Two sets of vacuum inlets on either side of the pump allow the user to choose the location of the pump in relation to the test apparatus. Each set of vacuum inlets consists of a regulated and unregulated inlet.

The regulated inlet is connected to the pump via the flow control valve and is used to regulate flow between 0 and 280 L/min for MDI, nasal spray and nebuliser applications. A maximum unregulated flow of 683 L/min is available for DPI applications.

The vacuum is provided by an oil lubricated rotary vane pump having a 1.5 kW motor and exceptionally low noise levels for its size.

The SCP5 is fitted with two access panels to allow easy access for replenishing oil and changing the oil filter. A dual filtration process, ensures that there is no oil vapour in the exhaust air, making it suitable for use in a laboratory environment.

The pump measures 420 x 600 x 450 mm (w x d x h) and weighs 45 kg.

Important Note:
Special electrical supply requirements are necessary for UK and US applications. Please check details prior to placing your order.

Pump Model (50 Hz Version)	LCP5	HCP5	2 x HCP5	SCP5
Type	Rotary Vane	Rotary Vane	Rotary Vane	Rotary Vane
Lubrication Type	Dry	Dry	Dry	Oil
Max. Flow in L/min (unrestricted)	120	416	833	683
Max. Sonic Flow through NGI	N/A	80	100	100
Max. Vacuum Level	< 15 kPa	<15 kPa	<15 kPa	<0.1 kPa
Applications: Nasal	Yes	Yes	Yes	Yes
Nebulisers	Yes	Yes	Yes	Yes
MDIs	Yes	Yes	Yes	Yes
DPIs	No	Yes	Yes	Yes
Noise in dB (A)	55	60	70	65
Routine Maintenance	None	None	None	Oil/Filter Change
Dimensions (w x d x h)	27 x 31 x 30 cm	32 x 56 x 39 cm	74 x 56 x 39 cm	42 x 60 x 45 cm
Weight (kg)	18	45	90	70

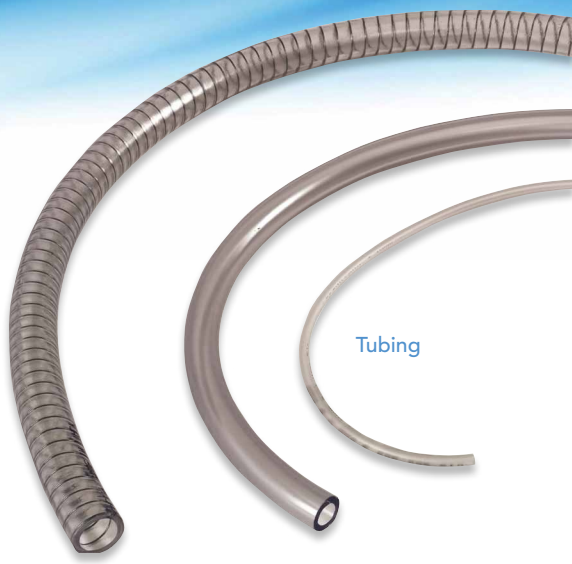
Cat. No.	Description
7908	Super Capacity Pump Model SCP5
7909	Maintenance Kit for SCP5

SUNDRIES

SPARE / ADDITIONAL TUBING

Used to provide the connections between the various components making up your inhaler testing system. The 3 mm tubing is used to provide the P1 connection between the DUSA for DPIs and the Critical Flow Controller.

Cat. No.	Description
5015	10 mm i.d. PVC Tubing (per metre)
5016	16 mm i.d. Wire Reinforced PVC Tubing (per metre)
5017	3 mm i.d. PVC Tubing (per metre)



Tubing

QUICK RELEASE CONNECTORS

A range of quick release connectors in polypropylene or stainless steel in two sizes, 12 mm and 17 mm designed for use with 10 mm i.d. and 16 mm i.d. tubing respectively for rapidly disconnecting test equipment from ancillaries.

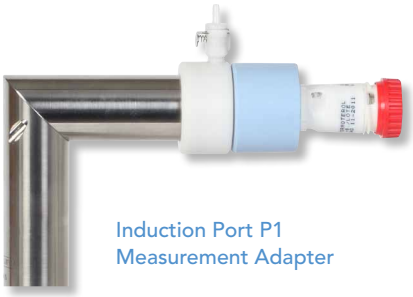
Cat. No.	Description
5018	12 mm Quick Release Connector in Polypropylene
5019	17 mm Quick Release Connector in Polypropylene
5020	12 mm Quick Release Connector in Stainless Steel
5021	17 mm Quick Release Connector in Stainless Steel

Quick Release Connectors

DEVICE RESISTANCE MEASUREMENT

A simple device that is placed between the inhaler and the induction port and is used in conjunction with a Critical Flow Controller to measure the flow resistance of the inhaler under test.

Cat. No.	Description
8502	Induction Port P1 Measurement Adapter



Induction Port P1 Measurement Adapter

RINSING CAPS

Silicone rubber and 316 stainless steel rinsing caps are available for capping off the open ends of the ACI and NGI induction ports and the NGI preseparator during manual drug recovery. Simple rubber stoppers are also available.

Cat. No.	Description
8504	Set of 2 Silicone Rubber Rinsing Caps for ACI Induction Port
5265	Set of 2 Silicone Rubber Rinsing Caps for NGI Induction Port
5266	Set of 2 Silicone Rubber Rinsing Caps for NGI Preseparator
5227	Set of 2 Stainless Steel Rinsing Caps for NGI Induction Port
5228	Set of 2 Stainless Steel Rinsing Caps for NGI Preseparator
5232	Set of 2 Silicone Rubber Stoppers for NGI I.P./Preseparator

Rinsing Caps

Special Applications

INTRODUCTION

The purpose of this section in the brochure is to cover those aspects of inhaler testing equipment that cannot otherwise be categorised in the sections under Delivered Dose Uniformity and Aerodynamic Particle Size.

DISSOLUTION TESTING

Dissolution Testing is widely employed in the development and manufacture of oral dosage forms such as tablets and capsules which rely on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation.

In the case of inhaled and nasal drug delivery products, the first prequisite is to deliver an appropriate amount of drug to the target site. For that reason, *in vitro* testing is concentrated on drug delivery (emitted dose) and lung or nasal deposition (APSD) as opposed to dissolution or drug release.

Once deposited, the absorption or lung uptake, and hence the therapeutic effectiveness of the drug, depends on the active dissolving in the small amounts of aqueous fluid and lung surfactant available at the target site.

Designing a standardised method relevant to the lung is not easy because of the small amount of aqueous fluid involved and the presence of endogenous lung surfactants.

The method described on Pages 98-99 provides one possible solution to this problem.

GENERIC DRUG DEVELOPMENT

In recent years, there has been increased interest in the development of generic OIP drugs as the patents on the original formulations expire.

This generic drug development has led to the reintroduction into the Pharmacopoeia of some of the test methods employed in the development of the original drugs.

Three such methods, and the test equipment required to perform them, now embedded in USP and relating to **fluticasone propionate** (aerosol and powder), **salmeterol** (powder) and **fluticasone propionate/salmeterol combinations** (aerosol and powder) are described on Pages 100-102.

The test equipment concerned comprises two Glass Sample Collection Apparatuses for the DDU testing of aerosols (MDIs) and powders (DPIs) and a modified Andersen Cascade Impactor (ACI) for APSD studies.

COLD FREON

Users of pressurised metered dose inhalers (MDIs) may well be familiar with the "cold freon" effect - the inadvertent reaction to the chilling sensation that hits the back of the throat following actuation of the device.

Caused by impaction of the delivered dose and the rapid evaporation of any remaining propellant, the "cold freon" effect strongly influences the efficiency of drug delivery.

It may, for example, cause the patient to abort or be unsuccessful in completing the inhalation manoeuvre.

The "cold freon" effect is a function of **aerosol spray force** and **plume temperature.**

Copley Scientific offers two instruments designed to quantify these two parameters: the **Spray Force Tester**, which measures the force caused by high velocity impaction at a range of user-defined distances from the origin of the plume, and the **Plume Temperature Tester**, for measuring temperature under controlled laboratory conditions.

Both units are described on Pages 103 and 104.

Dissolution Tester
Model DIS 8000

DISSOLUTION TESTING – DOSE COLLECTION

INTRODUCTION

Dissolution is a critical quality attribute in the development and manufacture of oral dosage forms such as tablets and capsules, which rely on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation.

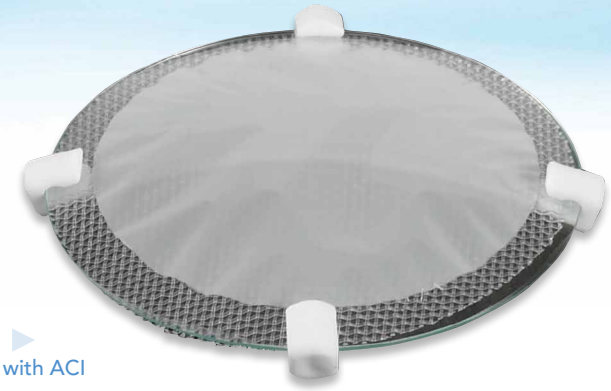
Indeed, dissolution testing is widely used for optimising efficacy during development (often by using modified or controlled release techniques), ensuring quality during batch to batch manufacture and in some cases to predict bioavailability *in vivo* and assess bioequivalence.

In the case of inhaled and nasal drug delivery products, the first prerequisite is to deliver an appropriate amount of drug to the target site. For that reason, *in vitro* testing is concentrated on drug delivery (emitted dose) and lung or nasal deposition (aerodynamic particle size distribution) as opposed to dissolution or drug release.

Once deposited, the absorption or lung uptake, and hence the therapeutic effectiveness of the drug, depends on the active dissolving in the small amounts of aqueous fluid and lung surfactant available at the target site.

At present, there are no official dissolution test methods described that are applicable to inhaled products. One of the main problems facing the developers of such methods is the identification and segregation of that part of the total emitted dose actually reaching the target site (as opposed to the whole dose) in a form readily adaptable to conventional dissolution testing techniques.

Membrane Holder in Dissolution Vessel



Watchglass/PTFE Assembly for use with ACI

DISSOLUTION TESTING – DOSE COLLECTION

DESCRIPTION

Based on a concept developed by Professor Jason McConville at the College of Pharmacy, University of Texas, USA the **NGI Dissolution Cup and Membrane Holder** incorporates a modification of the standard NGI collection cup. It allows size-fractionated particles from an aerosol cloud to be collected and then tested in a conventional tablet dissolution tester.

The Dissolution Cup only differs from the standard cup in that it has a 50 mm removable insert in the impaction area. Particle sizing is carried out in the conventional manner. Once collection is complete, the insert is carefully removed from the cup, covered with a pre-punched 55 mm diameter polycarbonate membrane and secured in position in a Membrane Holder, using a ring, to form a sealed "disc" or "sandwich".

The Membrane Holder can now be placed in a conventional Dissolution Tester such as the Copley DIS 8000 and tested in a manner similar to the "Paddle over Disc" Method described in USP Method 5 and Ph.Eur. 2.9.4 using ca. 300 ml of dissolution medium and the paddle at 75 rpm.

A similar technique can be employed using the Andersen Cascade Impactor, in this case, by applying a 76 mm polycarbonate filter to the collection plates prior to analysis, such that the drug is captured directly on the membrane, and then sandwiching the inverted membrane between the glass and PTFE surfaces of the **Watchglass/ PTFE Assembly** normally used for transdermal patches.

The small amount of aqueous fluid and surfactant found in the lung make it extremely difficult to mimic *in vitro*.

Marques, Loebenberg and Almukainzi list five of the most used simulated lung fluids in Table 11* of their article, "Simulated Biological Fluids with Possible Application in Dissolution Testing".

The first of these, SLF1, has been used to evaluate different interstitial conditions in the lung following exposure to various environmental emissions.

SLF2 was designed to model the interaction of particles with extracellular lung fluids, in this case, exposure to Hg due to the inhalation of airborne calcines from mine waste.

Another fluid that replicates interstitial fluid, SLF3, was used to evaluate the *in vitro* release of insulin following pulmonary delivery.

In the method described here, Son and McConville suggested the use of two standardised fluids, described in the article under the designation,SLF3 and its modified version, SLF4.

Finally, SLF5 was used to measure the dissolution of titanium tritide particles used as components of neutron generators.

** Margareth R.C.Marques, Raimar Loebenberg and May Almukainzi, Simulated Biological Fluids with Possible Application in Dissolution Testing. Dissolution Techologies (August 2011) p. 15-23.*

NGI Dissolution Cup and Membrane Holder

Cat. No.	Description
6001	NGI Dissolution Cup and Membrane Holder (each)
6002	55 mm Punch
6003	Watchglass/PTFE Assembly for use with ACI (each)
6004	Pack of 100 Polycarbonate Filters (0.1 micron x 76 mm diameter)

FLUTICASONE PROPIONATE / SALMETEROL (GENERIC DRUG DEVELOPMENT)

Sample Collection Apparatus for FP/ Salmeterol Aerosols

FDA GUIDANCE AND BIOEQUIVALENCE

The FDA has recently issued product-specific guidance for a number of active ingredients including albuterol (salbutamol), budesonide, ipratropium bromide and fluticasone propionate (FP)/salmeterol combinations that are used globally for the treatment of asthma and COPD and are consequently routine targets for generic development.

FDA product-specific guidance is designed to streamline the process of demonstrating bioequivalence (BE) for a certain active ingredient - a popular subject of Abbreviated New Drug Applications (ANDAs) - delivered via a specific route.

Levels of generic activity have increased exponentially over the last decade or so. The success of a generic submission relies on the robust demonstration of bioequivalence (BE) to a reference labelled drug (RLD). This normally involves presentation of *in vitro* data to help demonstrate that the generic will perform in a clinically identical way to the RLD.

Where equipment is specified in the regulatory guidance, it is generally identical to that described in the general chapters of the pharmacopoeias for OIP testing; specifically, the existing dose uniformity sampling apparatus for DDU testing and the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) for APSD measurement.

These test methods have been refined over a number of years such that, in the most part, they represent current agreed best practice for the development of new orally inhaled and nasal drug products (OINDPs).

However, it may be useful to demonstrate BE by showing equivalent results using directly comparable *in vitro* test methods and identical test equipment as originally used to develop the RLD.

However, for many of the popular targets of inhaled drug ANDAs, the original research work may predate generic development by a period of close to 20 years.

As a result, the test equipment and methods used in the development of the RLD may differ significantly from those employed today.

This difference in the original type of equipment and method used, in comparison with their current equivalents, can potentially have an effect on the expected results and/or acceptance criteria used for delivered dose and APSD.

Duplicating the original equipment and test methods as closely as possible eliminates the uncertainty about test results that might result from such sensitivities.

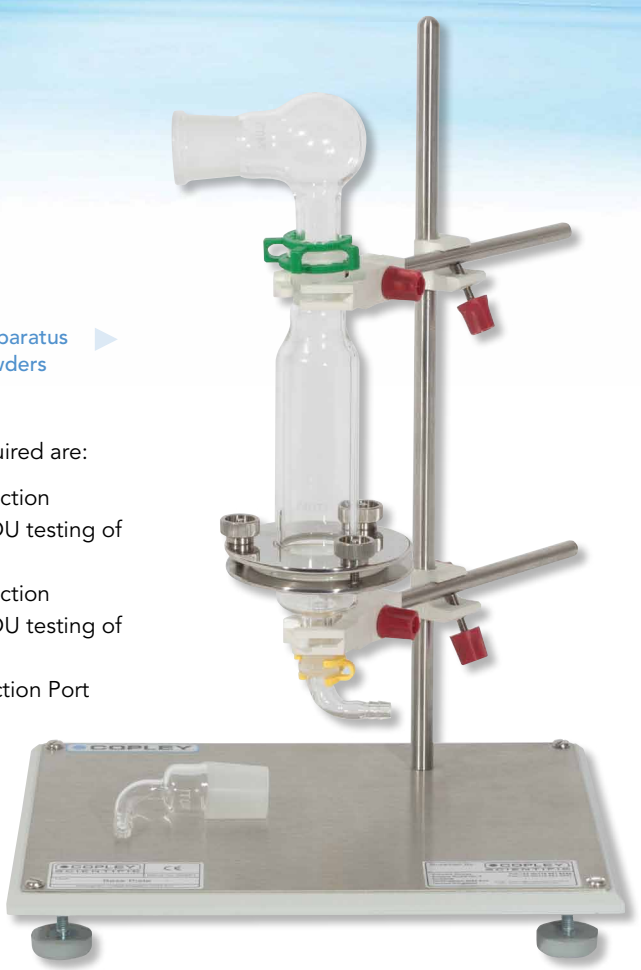
THE PHARMACOPEIA

In recent times, USP has also introduced product-specific monographs for **fluticasone propionate** and **salmeterol**. USP monographs are most commonly used for product release testing, but may also be considered during product development.

These product-specific monographs call for the use of test equipment not hitherto specified in the general USP/ Ph.Eur. chapters on orally inhaled products and are based on equipment and methods used in the original development of these products.

Two such monographs for fluticasone propionate (FP) are described in the Second Supplement monographs to USP 36 released in December 2013.

One relates to the use of FP as an aerosol via a metered dose inhaler (MDI). The other is for FP as an inhalation powder for delivery by a dry powder inhaler (DPI). The latter was joined by a third monograph released in the Second Supplement to USP 37 in December 2014 relating to salmeterol inhalation powder.



Sample Collection Apparatus for FP/Salmeterol Powders

Further monographs are currently under revision for **FP/salmeterol combination** products.

The monographs concerned cover both delivered dose uniformity (DDU) testing and aerodynamic particle side distribution (APSD).

Delivered dose and APSD are required performance metrics for all orally inhaled products (OIPs) because of their defining influence on the success and consistency of drug delivery.

EQUIPMENT

The monographs concerned specify two different **Glass Sample Collection Apparatuses** for the DDU testing of aerosols and powders respectively.

APSD measurement is conducted using a standard **Andersen Cascade Impactor** equipped with a specially **modified induction port** common to both aerosols and powders and a specially **modified inlet cone and preseparator** for aerosols and powders respectively.

Andersen Cascade Impactor for FP/Salmeterol Aerosols

Therefore, items required are:

- Glass Sample Collection Apparatus for the DDU testing of Aerosols
- Glass Sample Collection Apparatus for the DDU testing of Powders
- Modified ACI Induction Port for the APSD of both Aerosols & Powders together with a:
  - Modified ACI Inlet Cone for Aerosols
  - Modified ACI Preseparator for Powders

The inlet geometry of the modified induction port is similar to that of the Glass Twin Impinger except that it is manufactured from either aluminium or 316 stainless steel.

The similarity in geometry allows for the use of mouthpiece adapters designed for the Glass Twin Impingers. The modified induction port also features a tapered exit with no O-ring, which is why modified versions of the ACI inlet cone and preseparator are required in order for the ACI to accommodate the induction port.

It is important to note that these product-specific monographs do not currently appear in the European Pharmacopoeia.

Indeed, the Ph.Eur. and USP are not fully harmonised with respect to orally inhaled and nasal drug products in general.

PROCEDURAL COMMENT

According to the monographs, the 28.3 L/min version of the ACI (Stages 0 to 7 plus filter stage) should be used to measure APSD for both aerosol and powder methods despite the fact that the powder method specifies testing at 60 L/min.

This requirement probably derives from the fact that the original method predates the development of the 60 L/min and 90 L/min modified versions of the ACI called for in the general USP chapter.

The inhalation powder monographs also require that DDU measurements be conducted for a duration consistent with the withdrawal of 2 litres of air.

This volume is generally considered to be representative of a typical patient with asthma or COPD.

Induction Port - FP/Salmeterol Aerosols and Powders

Preseparator for FP/ Salmeterol Powders

Inlet Cone for FP/ Salmeterol Aerosols

Andersen Cascade Impactor for FP/Salmeterol Powders

FLUTICASONE PROPIONATE / SALMETEROL (GENERIC DRUG DEVELOPMENT)

For APSD measurements, the duration of the breathing cycle is adjusted to give the volumetric equivalent of 3 litres of air. This is likely due to the need to achieve adequate volume changes in the ACI.

This sort of accurately-timed flow control can be achieved using the set-ups specified in USP <601> for testing DPIs with a fast acting solenoid valve, such as those typified by the **Critical Flow Controllers** described on Pages 80 - 83 or the **Breath Actuation Controller** described on Page 84.

ANCILLARIES

The following ancillaries are recommended to complete a fully operating test system for the delivered dose testing and APSD measurement of fluticasone propionate and FP/ salmeterol aerosols and powders:

- **Mouthpiece Adapter (see Page 92)**
- **Andersen Cascade Impactor (see Page 43)**
- **Vacuum Pump (see Page 93)**
- **Breath Actuation Controller (see Page 84)**
- **Flow Meter (see Page 90)**

Cat. No.	Description
Fluticasone Propionate / Salmeterol Products	
8372	Inlet Cone for Aerosols (MDIs)*
8405	Preseparator for Powders (DPIs)*
8406	Set of 2 O-rings for ACI Preseparator (Spare)
8505	Induction Port - Aerosols & Powders (MDIs & DPIs)*
8505SW	Induction Port - as above but one-piece 316 stainless steel
8506	Flow Meter Adapter for FP/S Induction Port
8646	Sample Collection Apparatus for Aerosols (MDIs)
8640	Sample Collection Apparatus for Powders (DPIs)
Spare Parts for Sample Collection Apparatus for Aerosols (Cat. No. 8646)	
8649	Pack of 500 Cotton Wool Balls
8647	Separating Flask
8648	Flow Meter Adapter
5249	Vacuum Pump Adapter
Spare Parts for Sample Collection Apparatus for Powders (Cat. No. 8640)	
8641	Pack of 100 Glass Fibre Filters 70 mm
8903	Throat
8642	Upper Chamber
8643	Lower Chamber
8610	Stainless Steel Filter Support Disc
8645	Clamp Assembly
8909	Flow Meter Adapter
8910	Vacuum Pump Adapter
8644	Spare Set of Glassware (complete)
5237	Custom Mouthpiece Adapter (FP/S Induction Port)
5004	Tooling Charge for 5327 (per inhaler design)

* Please specify **Aluminium (A)** or **316 Stainless Steel (S)** when placing your order.

1. Set Distance from Impaction Plate

2. Actuate the Device

3. Display Impaction Force

SPRAY FORCE AND PLUME TEMPERATURE TESTING ("COLD FREON")

INTRODUCTION

Spray pattern and **plume geometry** are common techniques employed in the pharmaceutical industry to characterise and quantify the shape of the emitted spray from Metered-Dose Inhalers (MDIs) and Nasal Sprays.

However, possibly of as much concern as either of these two parameters is the reaction of the user to the impaction force of the MDI or spray on the throat or nasal passages.

The **"cold freon"** effect (the initial reaction to the cold blast of MDI propellant on the back of the throat) can often result in the patient aborting the inhalation process resulting in inconsistent delivery to the lungs.

Similar reactions can be generated by nasal sprays.

The "cold freon" effect is a function of aerosol spray force and plume temperature.

This effect is widely recognised amongst the inhaler community. Indeed, the "cold freon" effect is specifically mentioned as one of the criteria required to substantiate therapeutic equivalence in EMA's "Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents" published in January 2009.

The sensation is due to the high velocity blast and subsequent evaporation of liquid propellant remaining in droplets that impact on the back of the user's throat.

The ability to produce a **softer, warmer aerosol plume** by:

a) changing the formulation (drug, propellant, co-solvent) or
b) changing the device (metering volume, actuator orifice diameter) or
c) using add-on devices such as spacers or holding chambers

is an important tool in product development to ensure better patient compliance.

Studies into various CFC and HFA based suspensions and solutions, for example, together with different orifice geometries have shown that plume temperature can be widely affected by these parameters.

SPRAY FORCE TESTER SFT 1000

The amount of aerosol deposited on the throat is largely dependent on inertial impaction i.e. the velocity and APSD of the aerosol cloud concerned.

It follows that since velocity is directly related to impaction force the latter should be a good indicator of local delivery equivalence for an inhaled drug.

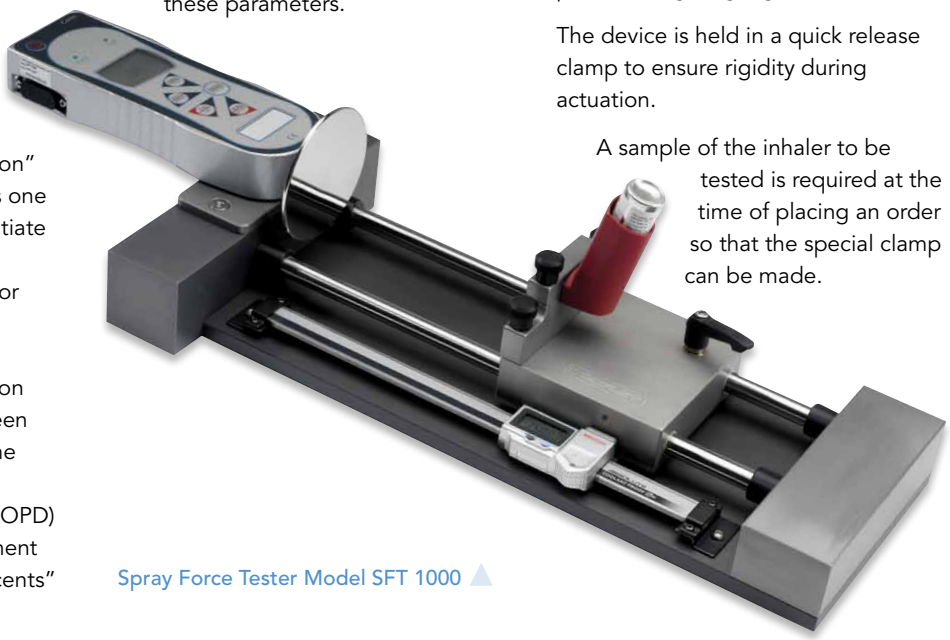
The Spray Force Tester Model SFT 1000 is a high precision instrument for measuring the maximum impaction force of MDIs and nasal sprays over the duration of the spray plume.

It has a range of 0 to 2500 mN and an accuracy of +/- 2.5 mN.

The distance of the inhaler relative to the impactor can be adjusted between 0 and 200 mm +/- 0.03 mm using the precision digital gauge.

The device is held in a quick release clamp to ensure rigidity during actuation.

A sample of the inhaler to be tested is required at the time of placing an order so that the special clamp can be made.



Spray Force Tester Model SFT 1000

Plume Temperature Tester PTT 1000

SPRAY FORCE AND PLUME TEMPERATURE TESTING ("COLD FREON")

The main features of the SFT 1000 include:

- High sensitivity digital load cell
- Range: 0 to 2500 mN +/- 2.5 mN
- Circular impaction plate – easily removed for cleaning
- High visibility load cell display
- Menu-driven controls
- RS 232 output to computer or printer
- Memory capability for up to 100 spray force measurements
- Pass/Fail alarms for user-programmable limits (for QC)
- Precision slides for positioning of inhaler relative to impaction plate
- Quick-release device clamp ensures rigid inhaler support
- Special rubber feet eliminate vibration transmission to load cell
- Battery or Mains powered
- Compact dimensions: 580 mm (L), 200 mm (W), 80 mm (H)
- Supplied complete with calibration certificates for load cell and gauge
- Digital load cell and gauge easily removed for re-calibration
- Load cell calibration verification easily performed by user

PLUME TEMPERATURE TESTER MODEL PTT 1000

The Plume Temperature Tester PTT 1000 consists of a polypropylene sampling tube, 130 mm long x 96 mm o.d. having the same internal dimensions as the horizontal section of the Ph.Eur./USP Induction Port.

The temperature profile of the plume is measured by 4 centrally aligned thermocouples mounted vertically at 25 mm, 50 mm, 75 mm and 100 mm from the inlet and linked to a data acquisition system under the control of a PC. The thermocouples are easily removed for cleaning and calibration.

The outside diameter of the inlet of the sampling tube is reduced such that it is the same as the induction port in order to accommodate a similar mouthpiece adapter (and therefore MDI or nasal spray).

The outlet of the Plume Temperature Tester is normally connected to a Waste Shot Collector (see photo on this page and Page 31) and vacuum pump to capture the measured doses at the relevant flow rate.

It can, however, easily be connected directly to a DUSA tube or Ph.Eur./USP Induction Port if preferred, since the outside diameter of all of these three accessories is identical.

Cat. No.	Description
9000	Spray Force Tester Model SFT 1000
9001	Additional Device Clamp
9002	Re-calibration of Spray Force Gauge
9003	Re-calibration of Distance Gauge
9004	Spare Impaction Plate
9005	Compact Printer (Force Gauge)
9006	IQ/OQ Documentation for SFT 1000
9010	Plume Temperature Tester Model PTT 1000 (incl. Software)
5001	Waste Shot Collector WSC2
8060	Flow Meter Adapter (PTT 1000 to Flow Meter)
9011	IQ/OQ Documentation for PTT 1000
9012	Re-calibration of 4 Thermocouples
9013	Shortened Mouthpiece Adapter
5004	Tooling Charge for above

Automation

INTRODUCTION

The requirements of the regulators responsible for the safety, quality and efficacy of orally inhaled and nasal drug products (OINDPs) place a heavy burden on the companies involved in the development and manufacture of those products in terms of testing.

As far as OINDPs are concerned, the main focus of testing is concentrated on **Delivered (or Emitted) Dose** and **Aerodynamic Particle Size**. The manual performance of both of these tests is labour intensive, time consuming and prone to human error.

Fully automated test systems have been developed to address these problems, however they do tend to be expensive (>US$ 1M), complex to operate and resource intensive to develop, validate and maintain.

In this instance, semi-automated systems available at a fraction of the cost of their fully-automated counterparts can provide a viable solution. Semi-automation is normally used to replace repetitive manual operations such as waste firing, cup coating, sample recovery and preparation, etc. Such systems provide robust off-the-shelf solutions at low cost, are normally available on a relatively short delivery time and require little or no validation.

Cascade impaction, for example, is a particularly labour intensive process when performed manually, with a maximum of just five to eight tests per day being typical in terms of output. Recent work suggests that semi-automation significantly improves this throughput with as much as a four-fold increase in productivity.

At the same time, reduced manual handling and operator input gives enhanced reproducibility, eliminating the risk of repetitive strain injury and reducing overall cost.

Copley Scientific supplies a broad range of **labour saving devices** and **semi-automated systems** supporting both the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI).

The Andersen and NGI Sample Recovery Systems (A-SRS and N-SRS respectively) are, for example, fully integrated systems which automate and accelerate the entire sample recovery process reducing work-up times to around 15 minutes (depending on method).

DUSA Shaker for MDIs

LABOUR SAVINGS TOOLS - DELIVERED DOSE UNIFORMITY

DUSA SHAKER

Both Ph.Eur. and USP state that *dose uniformity* tests should be carried out on a minimum of 10 doses (from 1 inhaler in the case of Ph.Eur. and 10 inhalers in the case of USP).

If then the inhaler fails to meet the Tier 1 dose uniformity criteria concerned, it may be necessary to repeat the test involving the collection of a further 20 doses.

In addition, in the case of USP, further tests have to be carried out throughout the life of the inhaler i.e. *Dose Uniformity through Container Life* which involves capturing a further 10 doses from a single inhaler.

All of these tests require the collection and drug recovery of individual doses into the collection tube of a Dosage Unit Sampling Apparatus (DUSA) appropriate to its type (MDI or DPI) prior to assay.

To maximise throughput, most users utilise a number of collection tubes, each sealed with rinsing caps, to collect the required samples.

Once the samples have been collected, solvent is then added to each of the tubes and each tube shaken manually to facilitate drug recovery.

This manual shaking process:

- is time consuming
- can be highly variable (both inter- and intra-analyst) due to inconsistent and incomplete wetting of internal surfaces and
- can lead to Repetitive Strain Injury (RSI)

DESCRIPTION

The DUSA Shaker has been designed to automate the internal rinsing of the DUSA collection tubes to ensure full, fast and repeatable drug delivery from all internal surfaces whilst freeing up analysts to perform other tasks and reducing analyst exposure to RSI.

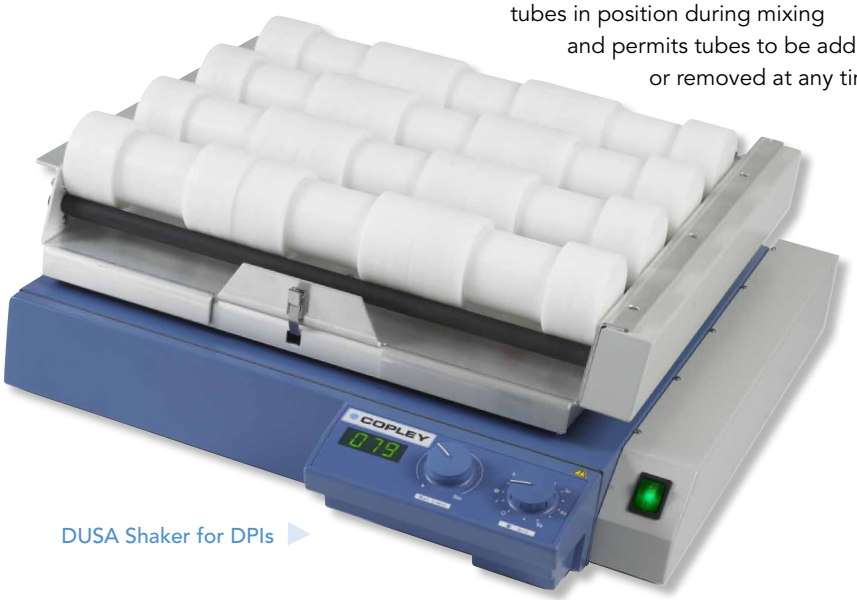
The Shaker accepts DUSAs for both MDIs and DPIs.

The **rinsing action** is achieved by a combination of lateral (side-to-side) shaking whilst simultaneously rolling the sealed collection tubes.

The resultant multi-directional mixing action ensures that all internal surfaces are wetted and that agitation is performed with a consistent, smooth but vigorous action.

The rubber coated rollers are specifically designed to grip the collection tubes during processing whilst reducing noise to a minimum.

This eliminates the necessity to use clamps or other fixtures to hold the tubes in position during mixing and permits tubes to be added or removed at any time.



DUSA Shaker for DPIs

Control Panel

LABOUR SAVING TOOLS - DELIVERED DOSE UNIFORMITY

MAIN FEATURES

The Shaker is designed to accept up to a maximum of **21 MDI Collection Tubes** or **12 DPI Collection Tubes** (or a combination of both).

Partial loads are quite acceptable. The rollers do not have to be fully filled as the rubber coating on the rollers provides sufficient friction to prevent lateral movement of the DUSA tubes during operation.

The lateral (side to side) shake is adjustable between **0 and 200 shakes per minute** via the left-hand knob on the control panel and displayed on the speed indicator.

The duration of the shaking action is controlled via the right hand knob on the control panel. This control allows for either simple on/off control or, if preferred, the setting of a timed period between 0 and 55 minutes.

The controls are such that once the optimum processing conditions have been established that they can be easily replicated.

The rollers rotate at a fixed **speed of 30 rpm** which corresponds to 9.4 rpm for the DUSA for MDIs and 6.5 rpm for the DUSA for DPIs. Control is by an independent on/off switch.

Designed with a small footprint of 570 mm (W) x 610 mm (D) , the shaker fits comfortably onto a laboratory bench.

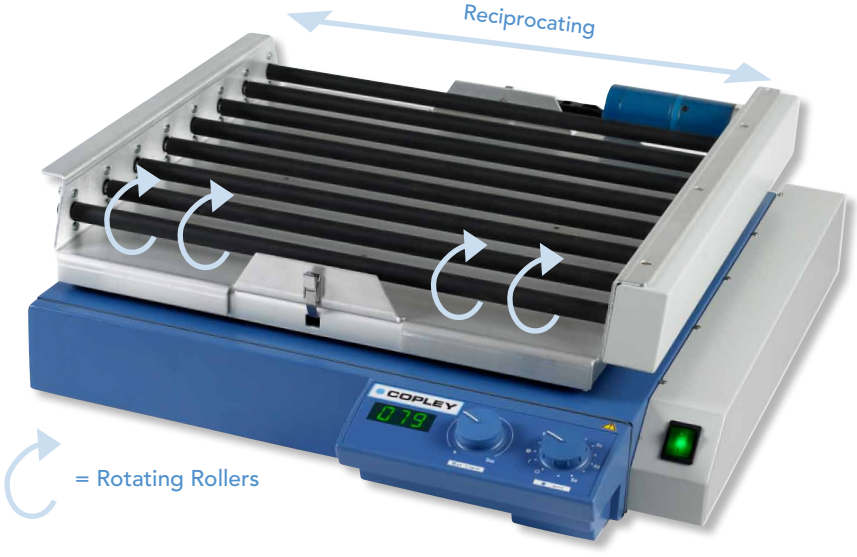
Full supporting IQ/OQ documentation is available.

Note: In order to allow rotation, the DUSA Shaker is only compatible with DPI Collection Tubes that have the P1 port blanking plug fitted.

Alternatively DPI Collection tubes without the P1 port are available as Cat. No. 8608A Collection Tube without P1 Port.

Spare Rinsing Caps are available with either Silicone Rubber (Cat. No. 8607) or LDPE Seals (Cat. No. 8607A).

See Page 30 for further details.



Cat. No.	Description
8620	DUSA Shaker (without collection tubes)
8621	IQ/OQ Documentation for DUSA Shaker
8623	DUSA Shaker Qualification Tools
8624	Re-calibration of DUSA Shaker Qualification Tools
8622	Pack of 10 Plugs (to plug P1 Port on DUSA for DPIs)

SPU 2000 with 2 x NGI Preseparator Fixtures

SPU 2000 with NGI Preseparator and ACI/NGI Induction Port Fixtures

LABOUR SAVING TOOLS – SAMPLE PREPARATION (ACI & NGI)

SAMPLE PREPARATION UNIT MODEL SPU 2000

A significant number of the procedures performed during inhaler testing are highly repetitive but not technically complex and do not necessarily justify full automation.

Relatively simple and inexpensive sample preparation tools can help reduce the unwanted effects of repetitive strain injury (RSI), alleviate bottlenecks and ensure that testing is carried out in a consistent, reproducible and controlled manner.

DESCRIPTION

The Copley Sample Preparation Unit Model SPU 2000 is designed to provide an inexpensive means of recovering active drug from the induction ports employed on the ACI and NGI and the preseparator of the NGI.

The fixtures feature custom made brackets and use simple silicone rubber end caps to secure and seal the equipment during operation.

The SPU 2000 is designed to accept two fixtures at any one time.

On initialisation, the Sample Preparation Unit automatically adjusts the orientation of the two fixtures to the loading position prior to starting the rinsing process.

The SPU 2000 has variable speed control between 20 and 60 rpm (+/- 1 rpm). This allows the user to adjust the mixing intensity and consequently the dissolution conditions applicable to that particular formulation.

Similarly, the duration of the rinsing cycle can be selected in either revolutions of the fixture (0-9999) or time in hours, minutes and seconds (up to 8 hours).

Control of the unit is provided by a membrane keypad linked to a 4-line 20 character back-lit LCD screen.

During processing, both the nominal duration and remaining duration to the end of the cycle are displayed on screen in terms of either rpm, or time together with the selected speed. The bi-directional process cycle (50% clockwise, 50% anti-clockwise) ensures thorough "wetting" of all the internal surfaces.

Cat. No.	Description
9202	Sample Preparation Unit Model SPU 2000 (without Fixtures)
9216	Fixture for ACI/NGI Induction Port (each)
8504	Set of 2 Silicone Rubber Rinsing Caps for ACI Induction Port
5265	Set of 2 Silicone Rubber Rinsing Caps for NGI Induction Port
9217	Fixture for NGI Preseparator (each)
5266	Set of 2 Silicone Rubber Rinsing Caps for NGI Preseparator
9212	IQ/OQ Documentation for SPU 2000
9213	SPU 2000 Qualification Tools
9214	Re-calibration of SPU 2000 Qualification Tools

Gentle Rocker with Dust Cover (included)

LABOUR SAVING TOOLS – SAMPLE PREPARATION (NGI)

GENTLE ROCKER

One of the main objectives of the NGI Consortium when designing the NGI was that the unit should be easy to use and automate.

Crucial to this objective and one of the unique features of the NGI is the design of the collection cup tray.

During the test, the size-fractionated particles are deposited in a series of eight cups located in a removable cup tray in the base of the impactor. This allows all eight cups to be removed in a single movement. It is then a simple matter to insert a new tray containing eight clean cups into the NGI to perform a further test.

Once a test has been performed, the analyst is required to dissolve the active drug present in each sample by adding a small amount of solvent to each cup and then agitating the cup to dissolve the active drug in the cup prior to analysis. A similar technique must be employed with the mouthpiece adapter, induction port and preseparator (if used).

Whilst the NGI itself has been designed to increase productivity in a standalone form using conventional wash and assay methods, the design has also led to further improvements in productivity through the use of a number of specially designed labour saving devices.

These sample recovery tools can be divided into manual or semi-automated systems dependent on the degree of automation provided.

A significant number of procedures performed during inhaler testing are highly repetitive and their performance can lead to bottlenecks which compromise overall laboratory operations and efficiency.

Relatively simple and inexpensive sample recovery tools have been designed to alleviate such problems and to ensure testing is carried out in a consistent, reproducible and controlled fashion.

DESCRIPTION

The **Gentle Rocker,** for example, is a simple, economical device for gently agitating the contents of the NGI collection cups in order to dissolve the active drug in the solvent prior to analysis.

The unit comprises a pivoting platform specifically designed to accept the NGI cup collection tray linked to a synchronous motor drive unit (20 or 40 rpm models) and controller.

In operation, the Gentle Rocker rocks back and forth about a central longitudinal axis. The resulting constant motion helps to dissolve the drug in a controlled manner freeing up analyst time for other tasks.

Approximately 10-15 mL of solvent in the small cups and 20-25 mL in the large cups is normally sufficient to provide good coverage of the cup surface whilst avoiding spills during operation.

The run time can be set by the user, dependent on the nature of the dissolution. An evaporation-eliminating cover is available as an optional extra in order to minimise any solvent loss during operation.

Cat. No.	Description
5220	Gentle Rocker (complete with dust cover and 20 rpm motor)
5221	Gentle Rocker (complete with dust cover and 40 rpm motor)
5223	Evaporation Cover (with seals and clips to prevent solvent loss)
5255	Dust Cover (Spare)
5224	Storage Cabinet for 6 NGI cup trays
5225	IQ/OQ Documentation
5235	Verification of Gentle Rocker
5256	Gentle Rocker Qualification Tools
5257	Re-calibration of Gentle Rocker Qualification Tools

NGI Cup Coater

LABOUR SAVING TOOLS - CUP COATING (NGI)

NGI CUP COATER

Particle bounce and re-entrainment can be a particular problem when using cascade impactors to measure the aerodynamic particle size distribution of OINDPs.

Particle bounce is a phenomenon whereby the particle impacts against the collection surface appropriate to its size but rather than adhering to that surface "bounces" back into the air stream, whereupon it is re-entrained and passes to a lower stage than that intended.

This effect is particularly noticeable when the collection surface is solid, as in the case of the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI), and where the particles are hard and dry as in the case of dry powder inhalers (DPIs).

It may also be prevalent in some formulations dispensed by Metered-Dose Inhalers (MDIs) particularly where only a few actuations are delivered to the impactor.

The result is to over-estimate the amount of active available in the form of the fine particle dose and hence bias the measured size distribution data to finer sizes.

For this reason, it is important to assess the likely effect of particle bounce and subsequent **re-entrainment** of the particles down-stream to lower stages, at an early point in development with a view to taking corrective action.

The normal method of addressing this problem is to coat the collection surfaces with a tacky viscous material such as, for example, glycerol or silicone oil.

Another solution is to use an impinger, such as the Glass Twin Impinger or Multi-Stage Liquid Impinger (MSLI) in which the collection surfaces are liquid, as opposed to an impactor in which the collection surfaces are solid.

If a surface coating is employed, then the amount, its uniformity, the method in which it is applied and its potential to affect the drug recovery process (if applicable) should all be carefully assessed during method development, as these all could impact on the final results.

There is no one solution for all inhaler devices – each drug/device combination must be assessed as a separate entity.

The amount, uniformity and method of application are critical parameters within the coating process.

The **NGI Cup Coater** has been designed as a standardised approach to this problem and eliminates many of the variables inherent in this process.

DESCRIPTION

According to the Pharmacopoeias, "To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent" unless, in the case of USP, "it has been demonstrated to be unnecessary".

A wide variety of methods are currently in use for coating impactor collection surfaces to meet this requirement.

The NGI Cup Coater is unique in providing a reproducible method of applying coatings directly to NGI Collection Cups whilst *in situ* in the Collection Cup Tray, thus eliminating the problem of inter-analyst variability.

NGI Cup Coater (Open)

NGI Cup Coater (from above)

The micro-processor controlled unit comprises two modules:

- a Coating Station which provides the filling, levelling and drying functions which make up the coating cycle, combined with
- a High Precision Multichannel Dispenser having 8 channels, one for each collection cup

The **Coating Station** consists of a frame specifically designed to accept the NGI Cup Collection Tray containing the cups to be coated.

The frame is fitted with a hinged lid which incorporates the eight precision bore dispense tubes and also the individual fans used to drive off the solvent vapour following dispensation.

The stainless steel dispense tubes are spring-loaded to ensure that they always remain in contact with the cup surface. The tubes are PTFE tipped to avoid scratching and are connected to the Dispenser by solvent-resistant tubing.

Operating on the peristaltic pump principle, the **Multichannel Dispenser** has 8 channels, 2 large and 6 small bore relating to the small and large collection cups respectively.

Two graduated solvent reservoirs are available, 500 mL or 1000 mL. Both units are fitted with an airtight 9-way PTFE cap to avoid evaporation.

During normal operation both Coater and Dispenser are controlled by a single micro-processor located on the Coating Station frame. The controls comprise a simple illuminated push button switch together with a 3-digit thumbwheel switch to set the drying time.

The Coating Station measures 600 mm x 170 mm x 230 mm and the Dispenser 150 mm x 220 mm x 130 mm (w x d x h).

PROCEDURE

The unit is designed to ensure that the number of operations required to carry out a coating cycle is kept to a minimum.

Once the cup tray is loaded, the only action required on the part of the operator is to press the start button on the Coating Station which initiates the following procedure:

1. Dispenser dispenses preset volume of coating media into cups to ensure the base of each cup is covered.
2. Coater tilts to allow excess media to drain to rear of cups.
3. Dispenser reverses to remove excess media from cup and return it to the solvent reservoir leaving thin film of media on cups*.
4. Coater returns to horizontal, fans activate and drying cycle commences.
5. Drying cycle ends and light on coater illuminates to indicate end of coating cycle.
6. The cup tray containing the coated cups can now be removed and replaced with a fresh tray.

* Saves on solvent and reduces overall drying time.

The dispense and reverse cycle times are preprogrammed in the factory and equate to a combined time of 2 minutes. The drying time can be adjusted between 1 and 999 minutes using the 3-digit thumbwheel switch located on the Coater front panel.

Cat. No.	Description
5900	NGI Cup Coater (excl. NGI Cup Tray & Cups)
5901	500 mL Solvent Reservoir complete with 9-way Cap
5902	1000 mL Solvent Reservoir complete with 9-way Cap

ACI Carrying Rack in Ultrasonic Cleaning Bath

ACI Carrying Rack in Rinse Bath

ACI Carrying Rack in Drying Oven

LABOUR SAVING TOOLS – IMPACTOR CLEANING (ACI & NGI)

IMPACTOR CLEANING SYSTEM

Cascade impactors are precision instruments and should be treated with care. Regular cleaning and drying is an essential element of good impactor practice in ensuring that the instrument is free of debris prior to testing and that the unit remains in optimum condition throughout its life.

The importance of proper, consistent, reproducible and controlled cleaning and drying procedures should not be overlooked. The **Impactor Cleaning System** has been specifically designed to clean both ACI and NGI component parts.

One of the most common methods of cleaning impactors is through the use of an ultrasonic bath.

This consists of immersing the various impactor parts in an ultrasonic bath containing clean water to which has been added a small amount of cleaning agent and then pre-heated to approximately 50 degrees C.

Decon Neutracon (www.decon.co.uk) is a near neutral (pH 7) concentrate specifically designed for use on materials which have been "corroded, etched, discoloured or weakened by acidic or alkaline agents" and is eminently suitable for this purpose.

The impactor parts are normally placed in a rack prior to immersion (a) to segregate them during the cleaning process and (b) to maximise the surface area exposed to the cleaning process.

Processing times vary dependent on the materials of construction employed in the impactor, e.g. aluminium, stainless steel, titanium and the degree of soiling but are typically between 2 and 15 minutes.

Ultrasonic baths use ultrasound (usually from 15-400 kHz) to penetrate holes and other difficult-to-access places, and to remove sticky, adhering or embedded particles from solid surfaces.

Following cleaning, the parts are normally rinsed in clean cold water and then placed in a heated cabinet at approximately 35 to 40 degrees C for about 30 minutes to dry.

The key to the Impactor Cleaning System are the purpose designed racks which accept the various parts of the Impactor concerned.

ACI Carrying Rack in Drain Mode on Rinse Bath

DESCRIPTION

The **Impactor Carrying/Wash Racks** are constructed from heavy duty polypropylene and fitted with neoprene cushions where appropriate to prevent scratching to the outer surfaces of the parts concerned.

The **ACI Rack** has 21 apertures corresponding to the eight stages, the eight collection plates, the inlet cone, induction port and the two parts of the preseparator of the ACI.

It not only acts as a carrying rack but also a handy storage facility for individual ACIs whilst not in use, thus assuring the correct stage order and preventing mix-ups with the corresponding parts on other impactors.

The **NGI Rack** is similar in construction and has 12 apertures corresponding to the eight cups, induction port and the three parts of the NGI preseparator.

Both racks measure 420 mm long x 230 mm wide and are designed to fit comfortably within the confines of the basket used in the Ultrasonic Cleaning Bath. The basket is necessary to prevent the carrying rack from touching the bottom or sides of the bath.

Impactor Cleaning System

ACI Carrying/Wash Rack

NGI Carrying/Wash Rack

The **Impactor Ultrasonic Cleaning Bath** has a temperature range of ambient + 5 to 69 degrees C in 1 degree C increments.

It measures 540 mm long x 340 mm wide x 290 mm high and has a capacity of 22 litres.

Main features of the bath include:

- Illuminated mains power, heater, timer and alarm indications
- Digital temperature control
- Electronic variable run back 0 - 30 minute timer
- Audible buzzer ends timed period
- Clearly visible LED display
- Time/temperature display
- Menu-driven data entry
- Low liquid level audible alarm
- Constant tuning ultrasonics (eliminates need for frequency sweeping)
- Crevice-free, corrosion-resistant stainless steel bath
- Heating element, safety cut-out, liquid level and temperature sensors as standard

The **Impactor Rinse Bath** comprises two parts, the bath and the drain rack - it is used to rinse (in cold water) and drain the impactor parts following sonication. Specifically designed to accept the Carrying Racks, the Bath measures 520 mm wide x 610 mm deep.

The **Impactor Suction Aspirator** is used to remove the small amounts of excess water that inevitably collect in the bottom of the impactor stages and preseparator parts following rinsing and prior to drying. It comprises a hand-held probe linked via a water collection jar to a vacuum pump, which provides the necessary suction.

The **Impactor Drying Oven** is a forced air circulation unit having a capacity of 133 litres and a temperature range of 25 – 70 +/- 1 degrees C. It is designed to accept three individual Carrying Racks.

The unit is fitted with an inner glass inspection door together with a wipe-clean all stainless steel interior as standard. Internal and external dimensions are 515 x 430 x 600 mm (w x d x h) and 705 x 625 x 820 mm (w x d x h) respectively.

All controls are located on a single panel. The in-built microprocessor controls all the various functions including adjustable alarm limits, acoustic alarm, data logging, timer, fan, speed and PID control of temperature via a LED display. The respective parameters are entered by means of a touch-sensitive button linked to a LED display which is also used to display the temperature, time and fan speed.

The unit is provided with timed operation as standard (0-999 minutes or 0-999 hours). The timer is programmed such that the timed period commences only when operating temperature has been reached.

The 4-speed forced air circulation means that the oven reacts rapidly to change. In the case of impactor drying, where maximum accuracy and warm-up are required and the door is to be opened on a frequent basis, a high fan speed is normally recommended.

The complete Cleaning System requires a bench space of 1.8 metres.

Cat. No.	Description
5400	Impactor Cleaning System (excluding Carrying/Wash Rack)
5401	ACI Carrying/Wash Rack
5205	NGI Carrying/Wash Rack
Modules Only	
5402	Impactor Ultrasonic Cleaning Bath (including basket and lid)
5403	Impactor Rinse Bath
5404	Impactor Suction Aspirator
5405	Impactor Drying Oven
5406	Stainless Steel Drip Tray

SEMI-AUTOMATION – ANDERSEN CASCADE IMPACTOR (ACI)

ANDERSEN SAMPLE RECOVERY SYSTEM (A-SRS)

Of the preferred methods of inertial impaction used to measure the particle size distribution of inhalers, the Andersen Cascade Impactor (ACI) and the Next Generation Impactor (NGI) are the most common.

The manual recovery of samples from such impactors can be tedious, time consuming and prone to human error.

Systems that automate the sample recovery process can be a valuable asset to the pharmaceutical laboratory.

The **Andersen Sample Recovery System (A-SRS)** has been specifically designed to provide an accurate, reproducible and efficient means of recovering samples from the ACI following testing thereby increasing throughput and reducing analyst-related variability.

Once the test is complete, the operator simply disassembles the ACI and places the various components (the mouthpiece adapter, the induction port and the various stages and collection plates) into their respective holders on the sample recovery bed.

Each of the 10 components has its own dedicated recovery sample channel in the form of a closed liquid rinsing loop. (**Note**: The Inlet Cone and Stage 0 are treated as one component).

Typically between 30 and 50 mL of solvent is required to create an effective wash cycle. Up to 4 different solvents can be employed during any one test.

Andersen Sample Recovery System

During operation, all of the impactor parts are held rigidly in position by a rinsing head to create a sealed system. This allows a fixed volume of solvent to be introduced into each of the various components in order to flush out the contents and circulate them through a rinsing loop.

Once the rinsing process is complete, an aliquot from each of the 10 lines is extracted from the loop and injected into a septum vial located in a storage rack which can then be subsequently removed for analysis. The storage rack has provision for a back-up run, i.e. 20 vials in total. The HPLC vial can be sealed or open according to preference.

The Sample Collection and Waste Modules are located on the right of the main processing area and are fitted with their own shatterproof transparent safety window. The system also incorporates an analytical balance for calibrating the volumetric dispensing process.

The whole operation takes approx. 15 minutes. Once the run is complete, the mixing head retracts into the ceiling of the sample processing area to allow the operator full access to the sample preparation area and the system is flushed out ready for the next run.

The whole system is controlled by means of a separate PC. Remarkably simple to use, the Windows based software stores individual test methods and provides an on-screen display of progress throughout the run. It is 21 CFR Part 11 compliant.

"Emergency stop" safety features and ventilation extraction systems are provided as standard. The system comes complete with all the necessary documentation and includes Factory Acceptance Testing (FAT), IQ/OQ documentation and on-site installation and completion of the IQ/OQ.

Cat. No.	Description
5420	Andersen Sample Recovery System (A-SRS)
5428	Quadruple Sample Capability
5426	A-SRS Spare Parts Kit
5427	A-SRS On-site Preventative Maintenance Service

NGI Induction Port Rinser

NGI Preseparator Rinser

NGI Assistant

SEMI-AUTOMATION – NEXT GENERATION IMPACTOR (NGI)

INDUCTION PORT AND PRESEPARATOR RINSERS

The **Induction Port** and **Preseparator Rinsers** are two similar devices designed to automate the process of rinsing the NGI Induction Port and Preseparator.

Both units are bench standing and can accommodate three induction ports or preseparators respectively.

Operation is extremely simple. A known volume of solvent is added to each induction port (ca. 20 mL) or preseparator (ca. 30 mL) and the ends secured using the end caps provided.

The induction ports or preseparators are then mounted on special fixtures and clamped in position using sets of solenoid valve operated plungers. A programmable logic controller is used to control the rinse time (normally 10 minutes).

The actual rinsing action takes the form of a tumbling end-over-end motion, combined in the case of the preseparator rinser with an axial turning motion such that the preseparator rotates simultaneously about two axes (35 rpm in the case of the Induction Port; 25 rpm in the case of the Preseparator).

This action together with the special rinsing caps employed maximises the potential for solvent to reach the cup in the centre of the insert and hence reduce rinsing times.

Under normal operating conditions, the control of both rinsers is achieved by a 3-position switch – off / clamp / run. Safety interlocks and an emergency stop button are provided as standard.

NGI ASSISTANT

The **NGI Assistant** is a labour saving device that places a known quantity of solvent in each cup of three NGI cup trays, gently agitates the contents in order to dissolve the active drug in the solvent and then places a representative sample of solution from each of the cups into HPLC vials for subsequent analysis.

It takes approx. 45 – 60 minutes to process 3 trays.

By removing two of the three cup trays, the NGI Assistant can also be used to dispense known quantities of solvent into either three Induction Ports or Preseparators simultaneously prior to rinsing.

The operator then places up to three collection trays on the location lugs provided and adds a dust cover (or an optional sealed evaporation cover) to prevent solvent loss. An x-y-z robotic pipette is then used to add a precise volume of solvent to each collection cup whereupon the rocking motion starts to dissolve the active in the solvent.

After dissolution, the robot then aspirates an aliquot of each of the dissolved samples into HPLC vials for further analysis. Software controlled, the system allows pre-defined methods to be saved and recalled as necessary.

All of the above systems come complete with all the necessary documentation and include Factory Acceptance Testing (FAT), IQ/OQ documentation and on-site installation and completion of IQ/OQ.

Cat. No.	Description
5407	NGI Induction Port Rinser
5227	Set of 2 Stainless Steel Rinsing Caps for Induction Port (spare)
5411	NGI Preseparator Rinser
5228	Set of 2 Stainless Steel Rinsing Caps for Preseparator (spare)
5415	NGI Assistant (3-Tray)
5223	Evaporation Cover to prevent solvent loss*

* Note: 3 required for NGI Assistant

NGI Sample Recovery System

SEMI-AUTOMATION – NEXT GENERATION IMPACTOR (NGI)

NGI SAMPLE RECOVERY SYSTEM (N-SRS)

The **NGI Sample Recovery System (N-SRS)** has been specifically designed to provide an accurate, reproducible and efficient means of recovering samples from the NGI following testing thereby increasing throughput and freeing up analysts to pursue other duties.

Once the test is complete, the operator simply disassembles the impactor and places the various components, the mouthpiece adapter, the induction port and the cup tray containing the collection cups into their respective holders on the sample recovery bed.

Each component has its own dedicated sample recovery channel in the form of a closed liquid rinsing loop. In the case of Cups 1 to 7 and the micro-orifice collector, this comprises a syringe pump, a bi-directional metering pump, a solvent retention bottle, 3-way solenoid valve, a fixture for mounting the component, a check valve and a dispensing needle. The ninth line is shared between the mouthpiece adapter and the induction port and has two of every component with the exception of only one solvent bottle and one dispensing needle.

Typically between 15 and 50 mL of solvent is required to create an effective wash cycle although smaller volumes can be used if required. Up to 4 different solvents can be employed during any one test.

During operation, the cup tray is held rigidly in position by a mixing head (in a similar manner to the NGI Seal Body) to create a sealed system. This allows a fixed volume of solvent to be introduced into each of the cups in order to flush out the contents and circulate them through a mixing loop.

Two pneumatic actuators perform the same function on the induction port.

Once the mixing process is complete, an aliquot from each of the 9 lines is extracted from the loop and injected into a sealed septum vial located in a storage rack which can then be subsequently removed for analysis.

The Sample Collection and Waste Modules are located on the right of the main processing area and are fitted with their own shatterproof transparent safety window.

The sampling area will accommodate four Agilent or Waters HPLC vial racks each capable of accepting 48 vials in an 8 x 6 configuration. Other racks can be accommodated on request.

The whole operation takes approx. 12-15 minutes. Once the run is complete, the mixing head and pneumatic actuators for the induction port retract to allow full access to the sample preparation area and the system is flushed out ready for the next run.

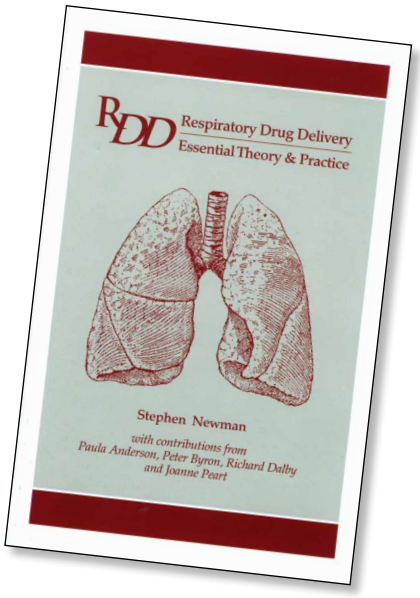
The whole system is controlled by means of an in-built computer via a touch sensitive screen. Remarkably simple to use, the Windows based software stores individual test methods and provides an on-screen display of progress throughout the run. It is 21 CFR Part 11 compliant.

"Emergency stop" safety features and ventilation extraction systems are provided as standard. The system comes complete with all the necessary documentation and includes Factory Acceptance Testing (FAT), IQ/OQ documentation and on-site installation and completion of IQ/OQ.

Cat. No.	Description
5417	NGI Sample Recovery System (N-SRS)
5434	Quadruple Sample Capability
5423	N-SRS Spare Parts Kit
5429	N-SRS On-site Preventative Maintenance Service

Qualification

INTRODUCTION



Good Manufacturing Practices (GMP) regulations require that:

a) the test methods used to monitor pharmaceuticals must meet proper standards of accuracy and reliability and

b) companies should establish procedures to ensure the fitness for use of instruments that generate data supporting product testing

However, these GMP regulations do not provide definitive guidance as to how these aims are to be achieved.

The United States Pharmacopeia (USP) has sought to address this problem by the introduction of a series of chapters as follows:

<1058> Analytical Instrument Qualification
<1225> Validation of Compendial Procedures
<1226> Verification of Compendial Procedures

It is interesting to note that, hitherto, the scientific community has used the terms "validation" and "qualification" on an interchangeable basis thus creating a degree of ambiguity as to their use.

For this reason, USP have suggested that:

a) the term "qualification" be applied to instrumentation and

b) the term "validation" to processes and software

Hence the term **"Analytical Instrument Qualification" (AIQ)** is used for ensuring that an instrument is suitable for its intended application, and the term **"Analytical Method Validation"** is used for ensuring that the analytical and software procedures employed are suitable for their intended application.

The USP Chapter <1058> Analytical Instrument Qualification describes in detail the four phase approach to qualification based on design (DQ), installation (IQ), operational (OQ) and performance (PQ) qualification.

It is important to note that the purpose of Analytical Instrument Qualification and its counterpart, Analytical Method Validation, is to ensure the quality of analysis before conducting the test, whereas system suitability tests and quality control checks ensure the quality of analytical results immediately before or during sample analysis.

Copley Scientific recognises the regulatory importance of these new initiatives. The following pages describe a selection of products, services and documentation designed to guide and assist you through the regulatory process as applicable to inhaled products.

Qualification Documentation

IMPACTOR TESTING - POSSIBLE SOURCES OF ERROR

The performance of cascade impactors and the methods associated with them can be influenced by factors other than the impactor itself.

Nevertheless, in broad terms, most of the errors identified in APSD testing emanate from two sources:

- Analytical (human error)
- Instrument (errors in instrument and/or ancillary equipment)

If these sources of error can be eliminated then it is fair to assume that any anomalies in results are a product of the device/formulation combination itself.

These analytical and instrument factors have been systematically reviewed by the PQRI (see Page 18) Particle Size Distribution Mass Balance Working Group in an article entitled "Considerations for the Development and Practice of Cascade Impaction Testing including a Mass Balance Failure Investigation Tree", J.Aerosol. Med., 2003; 16(3):235-247.

ANALYTICAL ERRORS

Analytical (human) errors can be largely eliminated by the implementation of robust documented policies and validated procedures specific to the product, apparatus and test method concerned.

INHALER RELATED ERRORS

Inhaler related errors can also be controlled in a similar manner by using (a) properly qualified instrumentation and (b) validated analytical procedures to use them.

PQRI list the following impactor related issues as potential causes of error in the day-to-day measurement of particle size distributions:

1. Instrument Qualification
- Instrument not qualified prior to or during use
- Inter-stage losses (in excess of 5%)
- Inadequate cleaning between tests
- Worn/corroded/clogged nozzles
- Improper sample recovery

2. Impactor Assembly
- All collection plates or cups present
- All collection plates or cups in the correct order
- All collection plates or cups seated correctly
- Final filter present and located correctly
- Inappropriate liquid levels (MSLI/ Preseparators)

3. Air Leaks into System:
- Air leaking into impactor through the inter-stage seals
- Poor seal between induction port/ preseparator/impactor interfaces
- Improper seal between inhaler mouthpiece and induction port

4. Collection Surface Preparation
- Problems in coating collection surfaces (ACI, NGI, etc.)
- Ensuring collection surfaces are moist (MSLI)

5. Flow Related Factors
- Incorrect flow rate setting
- Incorrect timer operation of solenoid valve (DPIs)

6. Inhaler Actuations
- Insufficient or excessive number of inhalations

7. Environmental Factors
- Barometric pressure (failure to account for)
- Temperature and humidity (failure to account for)
- Electrostatic effects

IMPACTOR QUALIFICATION

PHARMACOPOEIAL CRITERIA

Both European and US Pharmacopoeias lay down certain criteria which the cascade impaction system and technique selected for the inhaler must fulfil prior to and during use.

1. Stage Mensuration

The performance and reproducibility of a cascade impactor are dependent on a number of factors, the most critical being the nozzle dimensions (and their spatial arrangement) on each stage together with the air flow rate passing through it.

Providing these critical dimensions are within the quoted specification, then the impactors concerned can be expected to give comparable results.

The process of measuring the nozzle diameters and other critical dimensions of cascade impactors is called stage mensuration.

Both Ph.Eur. and USP recommend stage mensuration of impactors prior to use and periodically thereafter.

2. Re-entrainment

Re-entrainment can be a particular problem with DPIs and certain MDIs where measurements are based on a limited number of actuations from the inhaler.

Particle re-entrainment may be minimised by coating each collection surface with glycerol, silicone oil or similar high viscosity liquid typically deposited from a volatile solvent (see Pages 110-111).

Plate coating must be part of method validation and may be omitted where justified and authorised.

3. Mass Balance

Mass Balance (MB) may be defined as "the sum of the amounts of Active Pharmaceutical Ingredient (API) collected from all stages of a cascade impactor including the induction port and preseparator (if used) as a % of target delivery per actuation".

The European Pharmacopoeia state that the total mass of active should not be less than 75% and not more than 125% of the average delivered dose during testing for uniformity of delivered dose. The FDA recommends that the mean amount of active be between 85 and 115% of label claim on a per actuation basis.

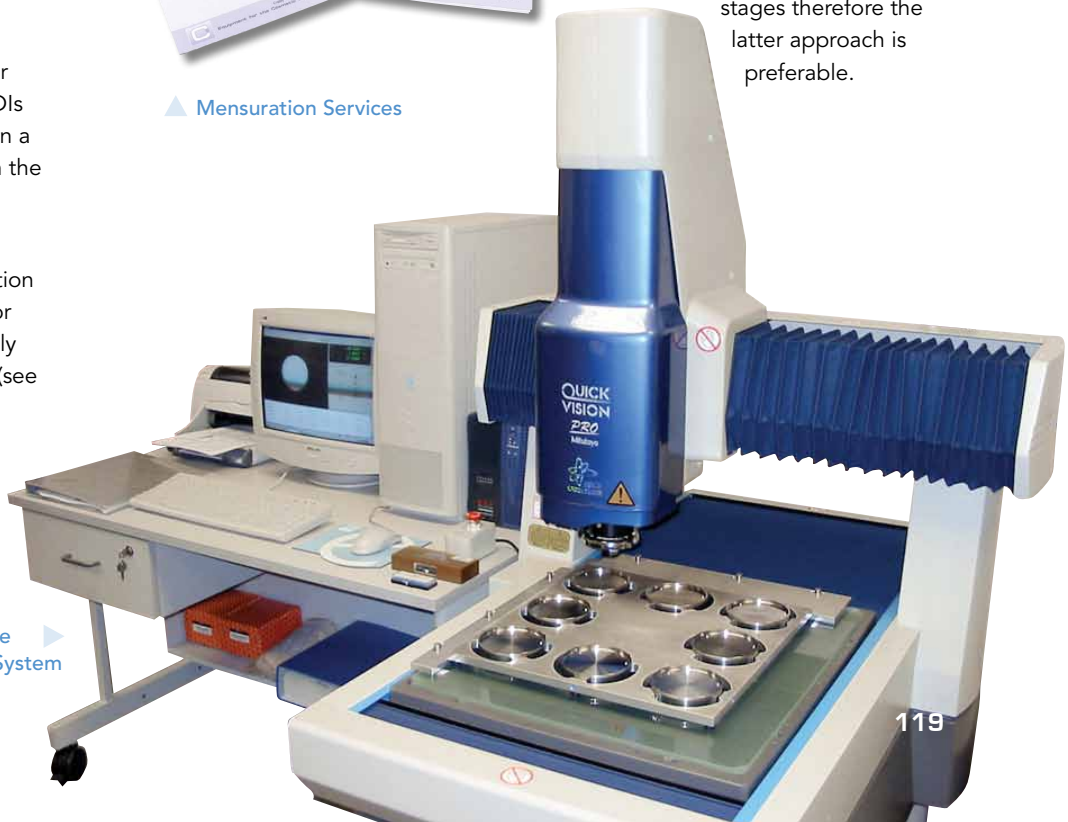
Mensuration Services

Mass Balance by itself should not be used as a system suitability test since it is still possible to obtain erroneous APSD results owing to other factors even though the MB meets the compendia criteria concerned. Rather, a MB with expected limits merely indicates that the inhaler collected the expected mass of drug and should be used as just one more diagnostic tool to assess the validity of aerodynamic particle size distribution (APSD) data.

4. Inter-Stage Drug Loss (Wall Losses)

In addition to the criteria common to both Pharmacopoeias, above, USP also states that not more than 5% of the inhaler's total delivered drug mass into the impactor is subject to inter-stage losses.

If the losses are known to be greater than 5% then those losses should be included with the associated collection plate, or an alternative type of impactor used. In practice, it is often impossible to apportion such losses to individual stages therefore the latter approach is preferable.



Mensuration of ACI Stages using the Mitutoyo QV404 Vision Inspection System

STAGE MENSURATION

INTRODUCTION

The performance and reproducibility of a cascade impactor is dependent on a number of factors, the most critical being the nozzle dimensions and their spatial arrangement.

In practice, cascade impactors often corrode and wear with use owing to their repeated exposure to formulations and recovery solvents. This is particularly applicable to aluminium impactors.

This can lead to full or partial nozzle occlusions causing changes in the impactor aerodynamics and hence particle collection characteristics.

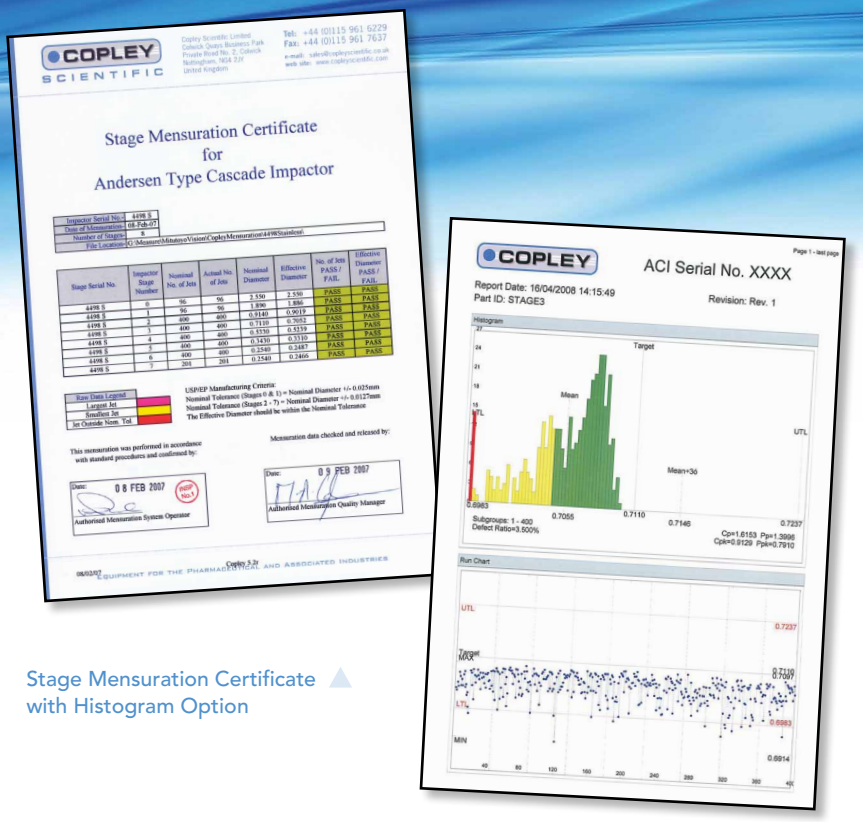
The process of measuring stage nozzle diameters and other critical dimensions, known as stage mensuration, is used to ensure that cascade impactors conform to the critical dimensions stated in USP Chapter <601> and Ph.Eur. Chapter 2.9.18 and are therefore fit for use.

Stage mensuration replaces the need for repetitive calibration using standardised aerosols.

Copley Scientific provides a one-stop, quick turn-around mensuration service for all types of Ph.Eur. and USP specified impactors, including induction ports and preseparators.

Mensuration certificates are supplied as standard with all new impactors, preseparators and induction ports, detailing how each component conforms to the pharmacopoeial requirements.

As impactors and ancillaries are put into use, regular re-mensurations (at least annually) should be performed to monitor and confirm their "in-use" compliance.



Stage Mensuration Certificate with Histogram Option

MENSURATION

To ensure high levels of reproducibility between measurements, Copley Scientific utilises a **Mitutoyo QV404 Automated Vision Inspection System** for optical inspection of impactor nozzles.

The same system is also used by our US partner, MSP Corporation. This ensures that any impactor, whether ACI or NGI, is mensurated using the same system and mensuration parameters in Europe and the USA.

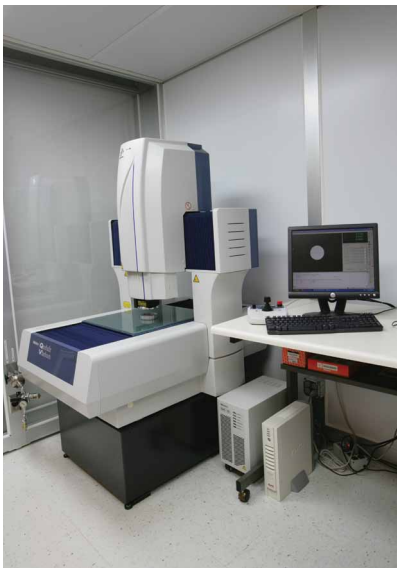
Mitutoyo is widely acknowledged to be a world leader in vision measuring systems. Fully automatic, this non-invasive optical system sets a new standard for measurement precision.

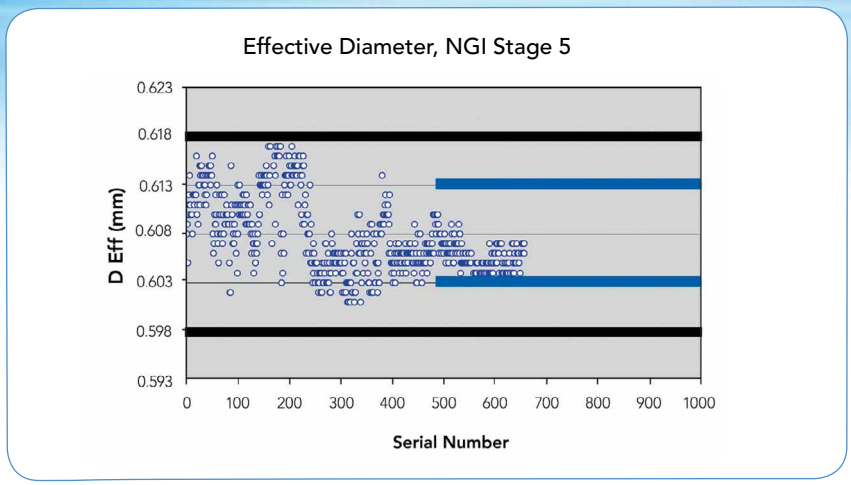
The QV404 features auto-focus, automatic stage illumination and dual measurement principles (edge detection and illuminated pixel count). This combination results in an unprecedented optical precision of <1 micron in comparison with the approx. 5 microns quoted by other providers.

Copley's QV404 is verified daily using a NPL glass reticle containing nominal hole sizes covering every hole size of the ACI and NGI (down to 0.206 mm), and is calibrated annually to UKAS traceable standards (UKAS Laboratory 0332). This is preferable to ring gauges, used by other providers, since these typically only go down to 1 mm diameter, which means that approximately 75% of the nozzles measured by the system fall outside its calibrated range.

A Mitutoyo Co-ordinate Measuring Machine (CMM) and Surface Roughness Measurement System are also used and are calibrated to national standards for the measurement of other critical components.

QV404 Vision Inspection System used by MSP Corporation





STAGE MENSURATION

CLEANING

Excessive accumulation of deposits in stage nozzles can affect particle size distribution measurements.

For this reason, all cascade impactors should be cleaned (see Page 112) and, if necessary, pinned (see Page 122) on a regular basis to avoid build-up of unwanted debris.

The fully automated **Ultrasonic Cleaning System** used by Copley Scientific for cleaning, rinsing and drying both newly manufactured and used impactors prior to mensuration, was specifically designed and commissioned for this purpose.

This is a unique service included in the mensuration process and ensures that any transient surface debris is removed prior to mensuration.

It incorporates a 5-stage process:

1. Coarse clean ultrasonic bath (new impactors only)
2. Fine clean ultrasonic bath
3. Pre-rinse bath with air agitation
4. Rinse with de-ionised water
5. Dryer

An x-y-z robot, in conjunction with special carrying racks incorporating purpose built fixtures, is used to transport the impactor parts from station to station (see picture below).

INTERPRETATION OF DATA

The interpretation of mensuration data is the key to understanding the importance of impactor performance.

Copley Scientific adopts **"Effective Diameter"** and **"In-use Margin"** as recognised by the European Pharmaceutical Aerosol Group (EPAG) as a means of determining the suitability of cascade impactors for use. Additional graphical and statistical information from individual stages is also now available as an option in the form of a histogram (see Page 120).

Derived from the area-mean and area-median diameters of multi-nozzle impactor stages, Effective Diameter (ED) is a useful parameter that can be used to monitor "drift" in impactor stage D50s.

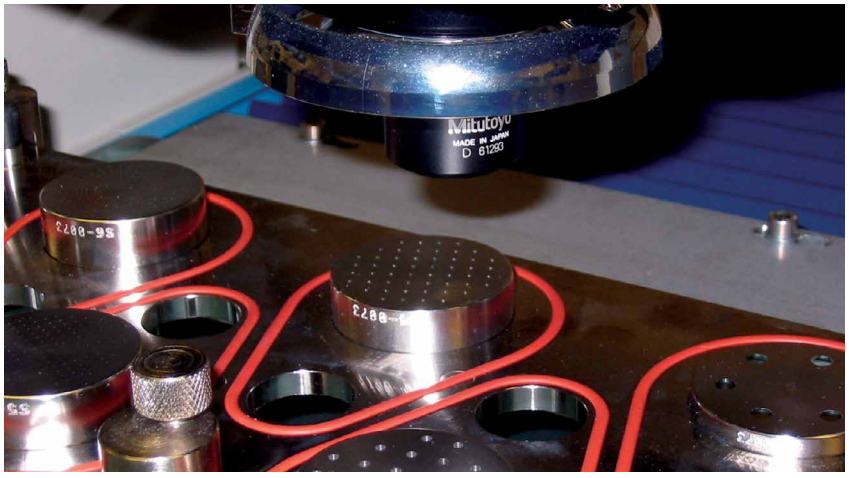
The In-Use Margin is calculated as the % of USP/Ph.Eur. tolerance that remains relative to the Effective Diameter. If the ED is equal to the stage nominal diameter then the In-Use Margin would be 100%. If, however, the ED is equal to the upper or lower USP/Ph.Eur. tolerance then the In-Use Margin would be 0%.

It follows that if the ED falls outside the compendia tolerance then the In-Use Margin would be a negative value.

Successive mensuration reports allow the tracking and monitoring of any deterioration of In-Use Margin, a useful way of investigating how an impactor is wearing with time. This approach allows the likelihood of an **out-of-specification (OOS) stage** occurring within the next calibration cycle to be predicted, indicating when remedial work will be required.

Such data can provide useful information. The graph above, for example, shows the effects of improvements in the NGI manufacturing processes relating to Stage 5 of the NGI with serial number.

Every nozzle on the NGI has always met pharmacopoeial specifications (heavy black lines). Now, with the improvements, every NGI has an ED within just half the range of the pharmacopoeiall specification (heavy blue lines). This is an indication of our commitment to constant quality improvement.



Stage Mensuration of NGI Nozzles using the Mitutoyo QV404 Vision Inspection System

X-Y-Z Robot Ultrasonic Cleaning System

Pinning various stages of the ACI

Pinning Kit with close-up of Pin

STAGE MENSURATION

RESTORING IMPACTOR PERFORMANCE

If stage mensuration results in an Effective Diameter in excess of an upper limit, then the stage must be replaced. This is a sign that the nozzles have worn, either as a result of corrosion from the solvents used to dissolve the active drug or erosion from the constant rapid passage of particles through the nozzles concerned. In this case there is no further option available as it is not practical to reapply metal to impactor nozzles.

This situation is, however, rare, as the vast majority of impactors tend to drift out of specification because Effective Diameter decreases below the lower limit for the stage.

This can be caused by a build-up of hardened particulates or, more likely, because the corrosion process produces metal salts that occlude the nozzle. The formation of oxidised impurities at the nozzle exit is a commonly encountered cause of occlusion, particularly for aluminium impactors, which is why materials such as stainless steel and titanium are now also used.

If the Effective Diameter is too small, performance can sometimes be improved or restored. Ultrasonics (see Page 112) can be used to clean all impactors prior to mensuration. A combination of this and other rigorous cleaning is often sufficient to remove deposits and restore performance.

Otherwise, stage pinning is a secondary option. Pushing stainless steel "go" pins with a diameter between the nominal diameter and the lower tolerance limit for the stage through each nozzle can serve to clear accumulated debris.

Extreme care should be exercised in performing this function to avoid nozzle damage, particularly for aluminium impactors.

The pins are precision manufactured in a range of sizes corresponding to the nozzle dimensions of the impactor stages concerned. For each stage, there are two pin diameters provided, one pin having a slightly smaller diameter than the other. The smaller diameter pin in each case can be used as an initial probe in cases, for example, where the holes in the stage are heavily occluded and the larger pin cannot be inserted into the nozzle. In this instance, the pinning becomes a two-stage process.

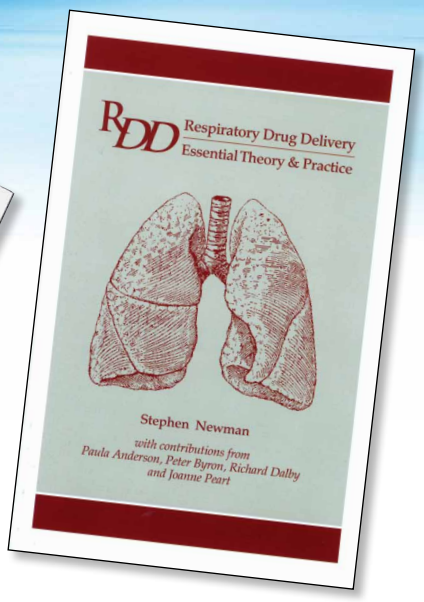
The pins are supplied in wooden boxes. Small pins are supplied in protective tubes with sealing corks. The ACI Pinning Kit is supplied with 14 pins, 2 pins to each of the 7 stages concerned.

The NGI Pinning Kit is supplied with 12 pins commensurate with Stages 1 to 6. In the case of Stage 7, it is not practical to use a pin due to the small size of the nozzles. A special brush with fine bristles is supplied instead.

ADVANTAGES OF REGULAR MENSURATION

A paper by Cooper and Blatchford (3M Drug Delivery Systems) entitled "Statistical analysis of Andersen Cascade Impaction mensuration data" presented at Drug Delivery to the Lungs 19, December 10-12, 2008, demonstrates the advantages of regular mensuration. Download the paper at: www.copleyscientific.com.

Cat. No.	Description
8590	Induction Port Mensuration
8390	ACI Stage Mensuration
8391	ACI 'Returns' Box
8990	60 L/min Conversion Kit Mensuration
5236	90 L/min Conversion Kit Mensuration
8490	ACI Preseparator Mensuration
5430	ACI Pinning Service (per stage)
5431	ACI Pinning Kit
8311	ACI Stage Mensuration Histogram (per stage)
8890	MSLI Stage Mensuration and Leak Test
5290	NGI Stage Mensuration
5291	NGI Preseparator Mensuration
5292	NGI Seal Body 'Returns' Box
5432	NGI Pinning Service (per stage)
5433	NGI Pinning Kit
8312	NGI Stage Mensuration Histogram (per stage)
8591	Alberta Idealised Throat Mensuration
8340	FSA Stage Mensuration
5270	FSI Insert Mensuration
8917	Glass Twin Impinger Mensuration



QUALIFICATION DOCUMENTATION

IQ/OQ DOCUMENTATION

According to USP Chapter <1058>, **Analytical Instrument Qualification** is "the collection of documented evidence that an instrument performs suitably for its intended purpose'"

It is important to note that the stage mensuration process described on previous pages is intended to replace the need for repetitive impactor calibration based on standard aerosols. It ensures that only impactors that conform to specification are used in testing.

Whilst mensuration or calibration is an important part of the qualification process, it does not in itself qualify the whole inhaler testing system for use. This is a separate process.

The Installation Qualification/ Operation Qualification Documentation (IQ/OQ) Documentation provided by Copley Scientific guides the user through this important process and confirms that the system is fully qualified for use.

DESCRIPTION

The IQ/OQ Documentation is written to GxP standards and is designed for qualifying the complete test system including the test apparatus (e.g. Dosage Unit Sampling Apparatus or Cascade Impactor), vacuum pump, critical flow controller (where applicable), flow meter and/or any other accessories that form part of an inhaler testing system.

The IQ/OQ Documentation is divided into three chapters:

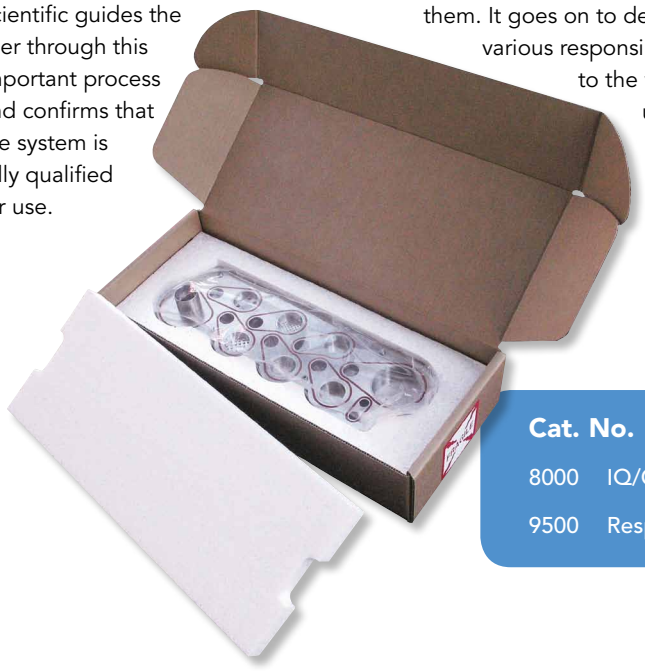
1. The Master Plan
The purpose of this 33-page Master Plan is to define the aim and scope of the qualification.

The first section of the Master Plan describes in detail the various constituents that normally make up an inhaler testing system and provides an analysis of the likely risks associated with the parameters required to test them. It goes on to describe the various responsibilities assigned to the various parties undertaking the qualification, the qualification concept and the documentation structure to be used during the qualification work.

The second section comprises the Qualification Report Summary which gives details and a summary of the test results together with a list of users trained in the system use.

2. Installation Qualification
This 16-page Section outlines the test plan, the standard operating procedures and test protocols necessary to perform the IQ for the system concerned. It includes a general description of the system, delivery check, utilities/facility/ environmental factors, system installation and verification.

3. Operation Qualification
This 44-page Section outlines the test plan and the standard operation procedures and test protocols to perform the OQ of the system concerned. It includes the information necessary to carry out both fixed parameter and functionality testing of the system.



◀ NGI Seal Body 'Returns' Box

Cat. No.	Description
8000	IQ/OQ Documentation for Inhaler Testing Systems
9500	Respiratory Drug Delivery Essential Theory & Practice Book

Impactor Leak Test Kit Model LTK2 (left) and NGI Leak Tester (right)

QUALIFICATION TOOLS

LEAK TESTING

The seals on cascade impactors can deteriorate with repeated use and exposure to solvent. Leaks then occur which, because the system operates under vacuum, allows air into the system causing erroneous results due to incorrect flow rates and poor aerodynamic performance.

For this reason, all cascade impactors should be tested on a regular basis to check the integrity of the sealing system. The most common method used for leak testing is to block the entry to the impactor inlet, generate a vacuum within the impactor using a vacuum source and then monitor any rise in pressure using a pressure meter located within the enclosed system.

This method is sensitive, accurate, straightforward and fast. It is ideal for verification checks during the life of the impactor or, indeed, as a fast system suitability test before an impactor is used.

The **Leak Test Kit Model LTK2** employs a separate vacuum source and can be used for vacuum levels up to 15 kPa below atmosphere for the ACI and MSLI.

The **NGI Leak Tester** is an alternative to the standard LTK2. It incorporates its own syringe as the vacuum source and is designed for use with vacuum levels up to 5 kPa below atmosphere.

QUALIFICATION KIT

The **ITS Qualification Kit** includes all the tools required to perform your IQ/OQ Qualification procedures (see Page 123).

It comprises all of the tools included in the LTK2 Leak Test Kit (Cat.No.5438), plus the additional tools required to carry out the in-house qualification of the inhaler testing system as a whole (Cat.No. 5439), supplied in a handy carrying case with all required calibration certificates.

IMPACTOR PERFORMANCE

The Pharmacopoeias recommend stage mensuration at regular intervals to ensure that only impactors within specification are used for testing inhaler output.

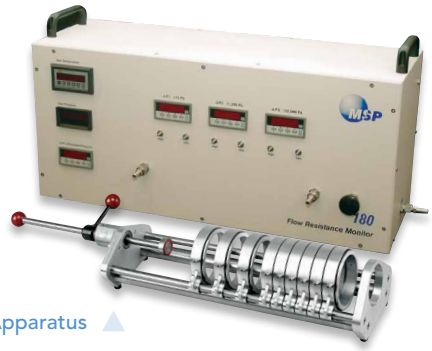
Unfortunately, because of the instrumentation, skill and time required to conduct a test, it is not practical to use stage mensuration on, for example, a daily basis. Currently therefore, there is no practical means of checking the system suitability of an impactor on a daily or individual test basis.

Nozzle dimensional performance can, however, be indirectly monitored by measuring the pressure drop (Delta-P) across each stage of the impactor at a particular flow rate. Theoretically, for example, a 2% shift in D_{50} corresponds to an approximate 5% shift in Delta-P.

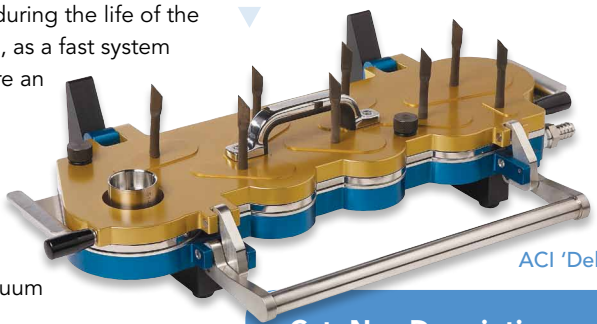
Delta-P (pressure drop) can be measured by the addition of a pressure port at each stage. This may be achieved by adding a series of rings, having suitable pressure tappings in the case of the ACI and a specially designed lid in the case of the NGI. It is then a simple matter to determine the pressure drop across each stage using sensitive pressure meters.

The **Flow Resistance Monitor Model 180** is equipped with three pressure gauges to cover the range of values to be found in a typical cascade impactor, together with the necessary instrumentation to measure inlet temperature, pressure and flow, to ensure accuracy.

Flow Resistance Monitor Model 180



NGI 'Delta-P'Apparatus



ACI 'Delta-P' Apparatus

Cat. No.	Description
5438	Impactor Leak Test Kit Model LTK2
5439	Additional Tools for Inhaler Testing System Qualification and TPK 2000 Pressure Sensor Calibration
5207	NGI Leak Tester
5214	Flow Resistance Monitor Model 180 (includes 5215 or 5216)
5215	'Delta-P' Apparatus for Andersen Cascade Impactor
5216	'Delta-P' Apparatus for Next Generation Impactor

ITS Qualification Kit comprising Cat. Nos. 5438 and 5439

Digital Static Meter

Electrostatic Eliminator

QUALIFICATION TOOLS

ELECTROSTATIC EFFECTS

The build-up of static electricity on plastic, non-conductive surfaces such as those found in inhaler actuators and/or spacers can present specific problems when working with inhalers, particularly dry powder devices.

Generally speaking, metal objects such as impactors do not present such a problem. Indeed, most problems of this nature emanate from the movement of the analyst around the laboratory prior to handling static sensitive equipment.

These problems can be exacerbated by the low humidity levels often found in air conditioned laboratories (<40% RH) and also if the analyst is seated on a stool/chair and thereby isolated from the ground.

Irrespective of the source, it is preferable to take action to reduce static to a minimum on the grounds that it is one less variable capable of affecting the results.

The **Antistatic Grounding** Kit comprises a user wrist-band and bench mat, both grounded through the earth of an electrical socket. This dissipates any static when handling the impactor/inhaler and all parts coming into contact with the laboratory bench during preparation.

The **Electrostatic Eliminator** is an efficient ioniser with variable speed fan and wide angle diffuser capable of eliminating static over a lab bench area of 2 m x 0.6 m.

A **Digital Static Meter** is also available which shows both intensity and polarity of static charge in the range 0 to +/- 20 kV. This is a useful tool for ensuring that the static levels around equipment are not excessive and are controlled.

QUALIFICATION SERVICES

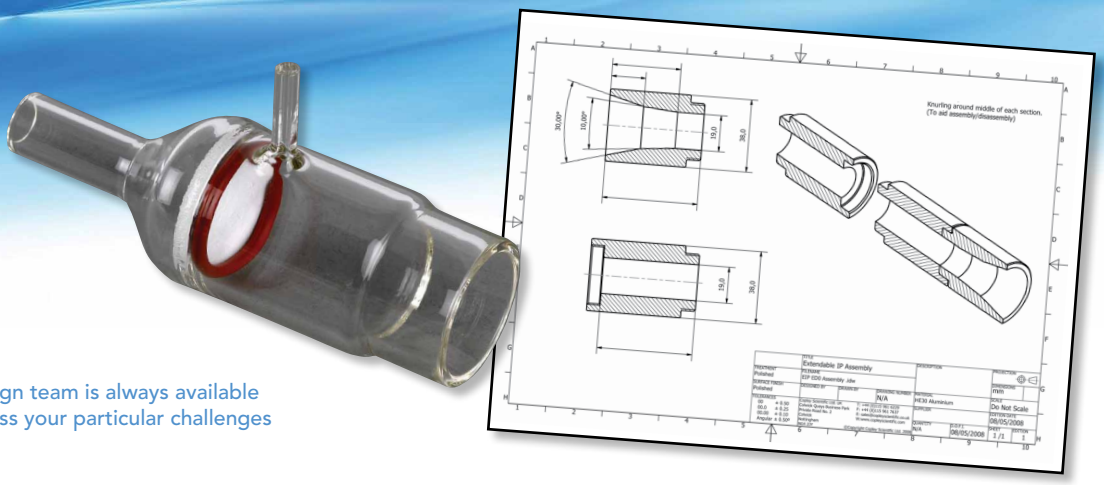
Leak test and Delta-P data can also be provided as an addition to our normal mensuration service. Many users take advantage of this service and incorporate the resulting data together with the mensuration data into their performance qualification files, to determine the impactor's continuing suitability for its intended use.

Such data is particularly relevant if a stage or micro-orifice collector has been replaced as a result of the mensuration process.

We are also able to offer a Cut-Point Particle Calibration Service for individual impactors based on the use of standard aerosols. This is achieved by passing standardised particles, of known dimensions, through the impactor at a precisely controlled flow rate. The deposition of such particles within the impactor is then measured to determine the effective cut-off diameters applicable to each stage.

Whilst mensuration replaces the need for repetitive calibration using standard aerosols, cut-point calibration may be of interest where specific cut-points are required at flow rates that are less commonly used or specified by the manufacturer.

Cat. No.	Description
5233	ACI or NGI Leak Test Certificate
5234	ACI or NGI Delta-P Certificate
5251	LTK or NGI Leak Tester Re-calibration Certificate
5443	Re-calibration of Additional Tools (Cat. No. 5439)
5442	ACI Cut-Point Particle Calibration Certificate
9300	Antistatic Grounding Kit
9301	Electrostatic Eliminator
9302	Digital Static Meter



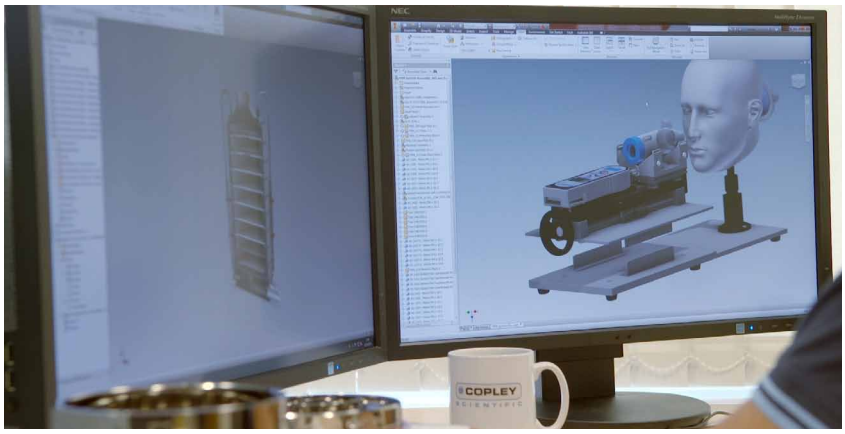
Our design team is always available to address your particular challenges

DESIGN, SERVICING AND TRAINING

DESIGN

Our design team has many years' experience working closely with the inhaler testing community in helping to develop their ideas for solving particular problems.

Whether you have a longstanding problem, or one that has been created by the introduction of a new process, or an idea for a new product, or even a bespoke design that you need manufacturing, we would be delighted to hear from you.



SERVICING

Copley Scientific offers a comprehensive range of both in-house and on-site service contract options tailored to individual customers' needs and designed to provide quality maintenance and calibration procedures at really competitive prices.

Contracts can be prepared for individual instruments or complete calibration management systems.

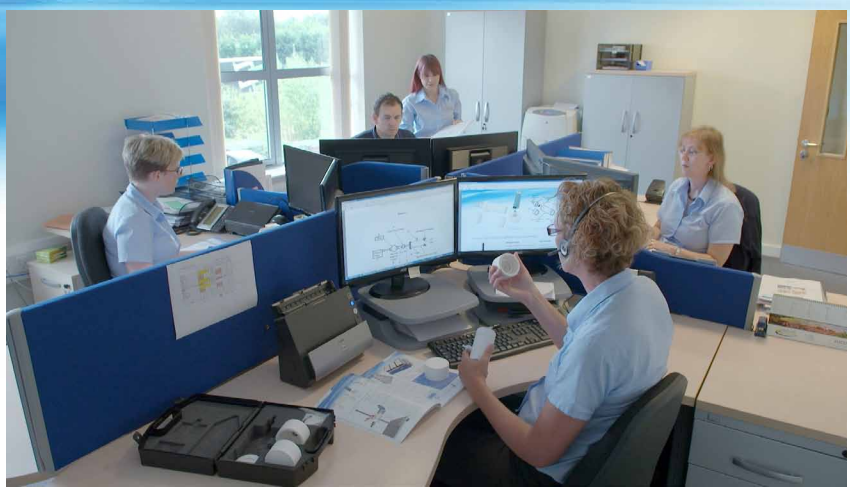
The creation of a typical service contract follows a structured format, which starts with determining the scope. This usually involves the customer supplying a detailed asset list of equipment requiring calibration, from which a proposal is made. This is reviewed by the customer and then if acceptable implemented, typically on an annual basis.

Our skilled engineers and technicians are trained to a high standard on the complete range of Copley Scientific and other related products and fully understand all aspects of calibration and qualification (IQ/OQ/PQ) procedures from performance to document control and storage.

All documentation supplied conforms to GxP standards as required by the international regulatory authorities.

We will be pleased to discuss your individual requirements and quote accordingly.

Copley Scientific offers a range of in-house and on-site service options



TRAINING

As a world leader in the provision of equipment for testing OINDPs, Copley Scientific offers a range of tailored training packages for both analysts and lab managers of pharmaceutical companies developing such products.

Training courses vary depending on existing levels of knowledge and can be conducted at Copley Scientific's training facility in Nottingham, UK, or at the customer's facility (in most cases).

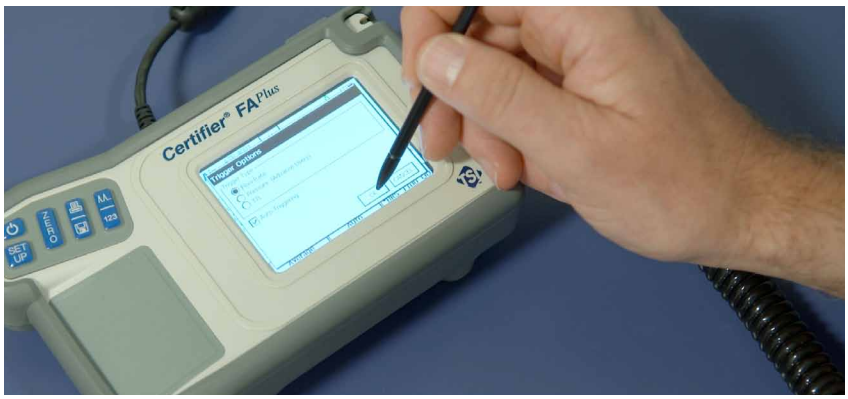
Typical training programs include:

- Presentation on inhaler technology, test equipment, regulatory requirements, monographs and methodology, new industry developments, etc.
- Provision for the supply of technical papers and documents where appropriate
- Audit of current system set-up and procedures used (on-site training courses only)

Training courses can be tailored to your specific requirements

- Training of users in operation of the equipment supplied
- Troubleshooting, Questions and Answers

Please feel free to contact us to discuss your requirements. We will be pleased to provide you with a quotation for a training program designed to meet your particular needs.



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