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 offer a choice of three Breathing 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 DPIs, 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 MDIs according to USP chapter <601>, Breath-Actuated (or Breath Operated) MDIs and the Spacers and VHCs used with MDIs and Nebulisers to USP chapter <1602>.

Flow rate is a critical parameter in the *in vitro* testing of OINDPs. Copley 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 similar readings provided they are calibrated and operated correctly.

Driving most inhaler testing systems is the **Vacuum 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 DPIs to generate sonic (critical) flow.

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

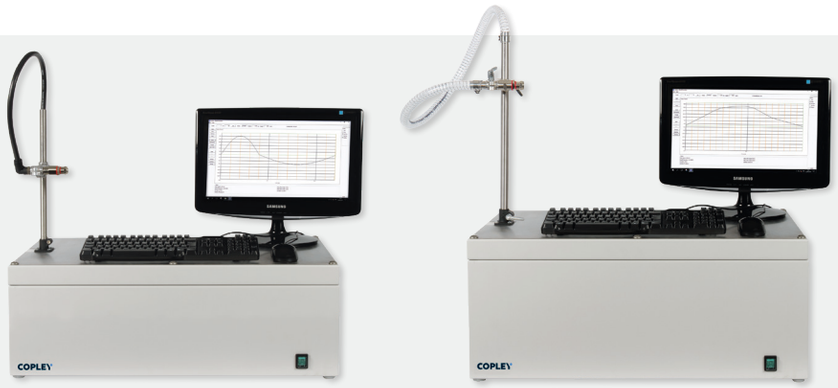
No inhaler testing system would be complete without the **Mouthpiece Adapters**, **Tubing** and **Quick Release Connectors** designed to link the various components of the system together.

Finally, the data analysis function, required for processing cascade impactor data, is provided by **CITDAS (Copley Inhaler 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.

Developed based on over 18 years of experience, today CITDAS has over 700 users and can be installed and up and running in minutes - it requires no specialist IT knowledge to install and 21 CRF 11 does not apply because the data output is in hard copy format. It will accept data from the ACI, NGI, MSLI and/or Marple-Miller Impactor (MMI). There is provision to customise the data options to individual needs.

Breathing Simulators

Breathing Simulators
Models BRS 2100 (left)
and BRS 3100 (far left)



INTRODUCTION

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

1. Pharmacopoeial

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

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

b) Metered Dose Inhalers (MDIs) when used in conjunction with spacers and valved holding chambers as per USP chapter <1602>

2. Improved *in vitro - in vivo* correlations (IVIVCs)

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*.

An MDI, 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 APSD of the delivered aerosol and/or the effectiveness of delivery.

This is not the case for dry powder inhalers (DPIs), nebulisers or MDIs used with spacers/VHCs. 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 Quality by Design (QbD) 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 produces a range of versatile breathing simulators, varying in functionality from the generation of simple sinusoidal patterns stated in USP and Ph.Eur. for nebuliser and MDI with spacer/VHC testing to complex user-generated profiles for advancing understanding as part of improving IVIVCs. The table below and following pages introduce each breath simulator and their intended applications.

BRS 1100	BRS 2100	BRS 3100
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)
Inhalation and exhalation profiles	Inhalation and/or exhalation profiles	Inhalation and/or exhalation profiles
Select start on inhalation or exhalation stroke	Start on inhalation or exhalation stroke User defined profiles (flow vs time)	Start on inhalation or exhalation stroke Userdefined profiles (flow vs time)
User Interface: Keypad & 4-line display	User Interface: Embedded computer (Windows 10)	User Interface: Embedded computer (Windows 10)
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>) Improving IVIVCs for MDIs with Spacers/VHCs and nebulisers: - With Filter Holder and Adapter (Dose Uniformity) - With Impactor and Mixing Inlet (APSD)	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)

Breathing Simulator Model BRS 1100 (0-800 mL Volume)

Breathing Simulator Model BRS 1100 with Next Generation Impactor (NGI) fitted with Mixing Inlet, Compressed Air Flow Controller and Inlet Manifold for tidal breathing tests, such as for Nebulisers and MDIs with Spacers/VHCs

DESCRIPTION

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 27427:2013 “Anaesthetic & Respiratory Equipment - Nebulising Systems and Components”, Ph.Eur. chapter 2.9.44 “Preparations for Nebulisation: Characterisation” and USP chapter <1601> “Products for Nebulization: Characterization”.

It can also be used to generate the profiles required in USP Chapter <1602> for testing “Spacers and Valve Holding Chambers used with Inhalation Aerosols” (see Table on facing page).

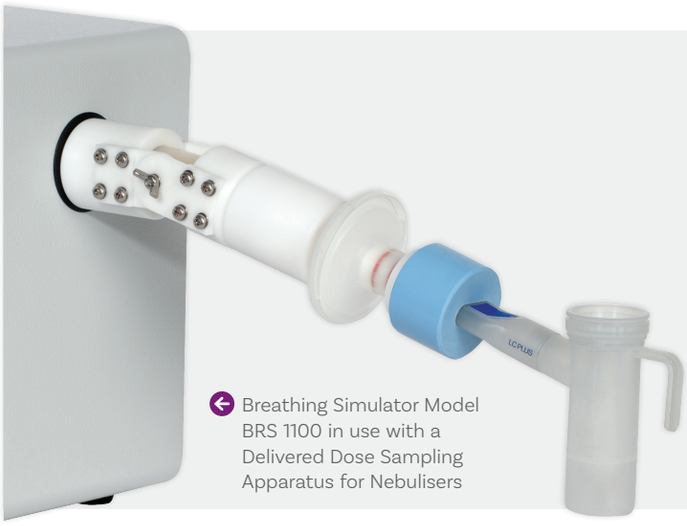
The unit can also be used in place of a standard vacuum pump with a cascade impactor such as the NGI or ACI and a Mixing Inlet (see photo above) to form a simple and inexpensive system for APSD studies.

The BRS 1100 has the following features:

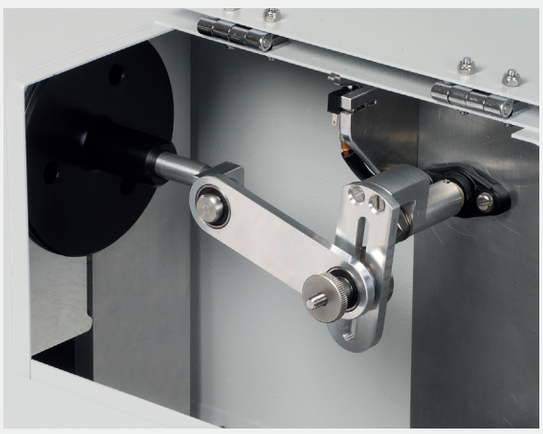
- Piston/cylinder arrangement, driven by motor with accurate speed and position control
- Inlet/outlet port for direct connection to the dose filter holder and nebuliser, spacer or VHC
- Tidal volume of 0 - 800 mL (155 to 770 mL certified)
- Frequency adjustable between 12 and 40 breaths per minute
- Sinusoidal waveform
- Inhalation/Exhalation Ratio (I:E Ratio) of 1:1, 1:2 or 1:3
- Selectable start position (inhalation or exhalation) for 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
- RS232 remote start capability

User interface with the BRS 1100 is menu driven by means of a membrane keypad fitted with a 4-line LCD.

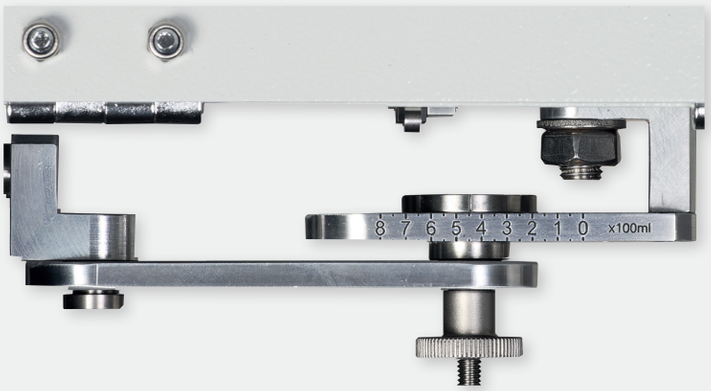
The volume required is set by means of an adjustable linkage accessed by opening the hatch on the right hand side of the casing (see photo below). The scale is graduated directly in mL.



Breathing Simulator Model BRS 1100 in use with a Delivered Dose Sampling Apparatus for Nebulisers



Volume is adjusted by means of a calibrated scale



Qualification Kit

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

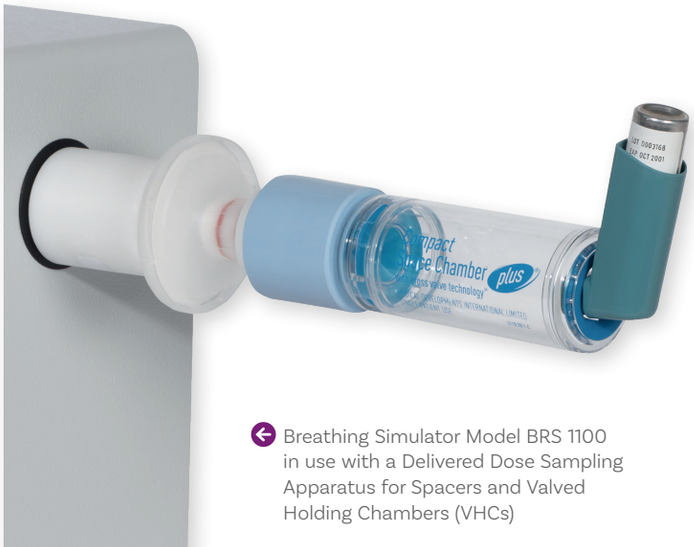
b) The operating speed in terms of breaths per minute (bpm)

c) The I/E Ratio

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

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

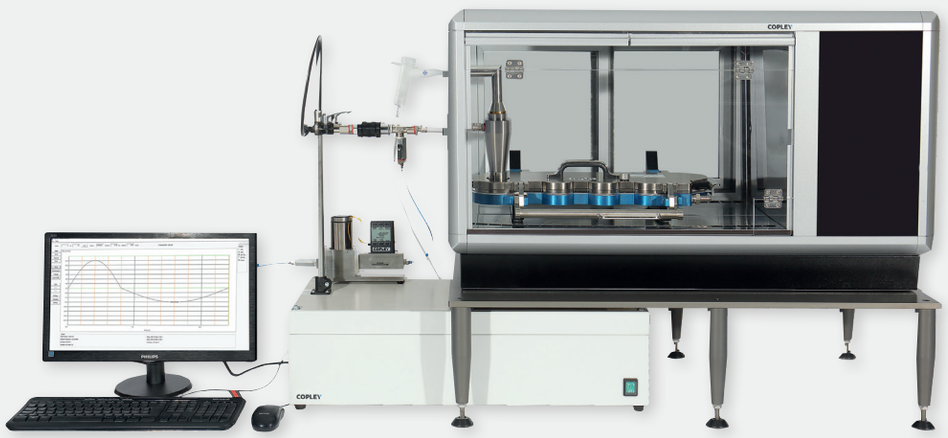
Tidal Breathing Pattern						
Parameter	**Adult 1**	**Adult 2**	**Adult**	**Child**	**Infant**	**Neonate**
Volume (mL)	770	500	500	155	50	25
Freq. (bpm)	12	13	15	25	30	40
I:E Ratio	1:2	1:2	1:1	1:2	1:3	1:3
USP <1601>	-	-	✓	✓	✓	✓
Ph.Eur. 2.9.44	-	-	✓	✓	✓	✓
USP <1602>	✓	✓	-	✓	✓	✓



Breathing Simulator Model BRS 1100 in use with a Delivered Dose Sampling Apparatus for Spacers and Valved Holding Chambers (VHCs)

Cat. No.	Description
9131	Breathing Simulator Model BRS 1100
9106B	IQ/OQ Documentation for BRS 1100/2100/3100
9105	BRS 1100/2100/3100 Qualification Kit
9107	Re-calibration of BRS 1100/2100/3100 Qualification Kit
9108	BRS 1100 Re-calibration Certificate

Breathing Simulator Model BRS 2100 (0-900 mL Volume)



IVIVC System for Nebulisers with Mixing Inlet, NGI, NGI Cooler and Stand, Air Flow Controller and Breathing Simulator Model BRS 2100

DESCRIPTION

The **Breathing Simulator Model BRS 2100** is a second generation, advanced, embedded computer controlled breathing simulator, with up to **900 mL** volume, suitable for the testing of Nebulisers and MDIs with Spacers and Valved Holding Chambers (VHCs).

The BRS 2100 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 32), namely neonate, infant, child and adult.

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

The BRS 2100 is also suitable for generating other wave forms used in improved IVIVC studies of nebulisers and other inhaled products requiring an inhalation volume of < 900 mL.

Flow rates can be displayed in mL/s or L/min and there is a function to simulate uncoordinated product use, in the case of VHCs, by **starting the breathing profile on the exhalation portion of the profile**.

The control function is provided in the form of an embedded computer running **Windows 10** used in conjunction with a colour monitor, keyboard and mouse. USB and ethernet connections are provided for 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).

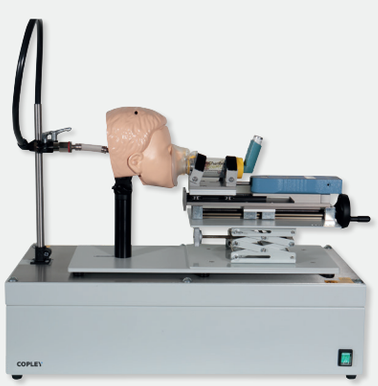
Breathing patterns, which can consist of single or multiple breaths, with or without exhalation phases, can be saved and loaded into the software, as required. Selecting Start activates the breathing cycle programme.

During operation, the current position within the cycle is indicated in the form of a rolling display on screen.

The BRS 2100 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 2100 will automatically abort the test.

The BRS 2100 measures 750 mm (w) x 350 mm (d) x 700 mm (h).

Breathing Simulator Model BRS 2100 Set-up for the testing of Spacers and VHCs with Facemasks



Breathing Simulator Model BRS 3100 (500 mL - 5 L Volume)

IVIVC System for DPIs with Adult Alberta Idealised Throat, Mixing Inlet, NGI, Breathing Simulator Model BRS 3100, Air Flow Controller and Manifold

DESCRIPTION

The **Breathing Simulator Model BRS 3100** is similar in design and operation to the BRS 2100 except that it has a volume of **500 mL - 5 L** (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 improved IVIVCs at an early stage in the product design.

In the case of DDU measurements, clinical realism can be improved by connecting the Dose Unit Sampling Apparatus (DUSA) directly to BRS 3100 using an adapter (see below). This allows realistic patient profiles to be applied to DDU tests, rather than the constant flow rate testing associated with the use of a vacuum pump specified in USP/Ph.Eur. methods.

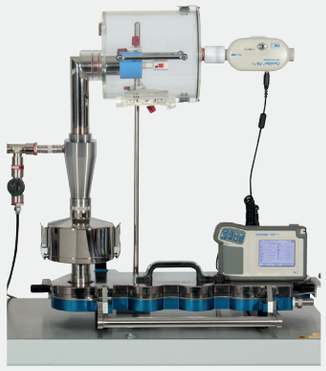
In the case of APSD measurements, a Mixing Inlet is required to decouple the variable flow through the inhaler (i.e. realistic patient profiles generated by the Breathing Simulator) from the steady-state flow rate required through the cascade impactor (see Page 72).

A Real-Time Breath Profile Verification Chamber is available (for use with USP induction port only) to allow measurement and recording of the breathing profile generated through the inhaler during the actual test itself, using the flow certifier incorported into the Qualification Kit.

An **NGI Cooler Stand** is also available when using the BRS 2100 to perform improved IVIVC APSD tests for nebulisers.

The BRS 3100 measures 800 mm (w) x 400 mm (d) x 850 mm (h).

Cat. No.	Description
9116	Breathing Simulator Model BRS 2100
9126	Breathing Simulator Model BRS 3100
9105	BRS 1100/2100/3100 Qualification Kit
9106B	IQ/OQ Documentation for BRS 1100/2100/3100
9107	Re-calibration of BRS 1100/2100/3100 Qualification Kit
9109	Real-Time Breath Profile Verification Chamber
9110	Accessory Support Stand for BRS 2100/3100
5025	NGI Cooler Stand for BRS 2100
9122	Adapter for BRS 2100/3100 use with DUSAs for MDIs and DPIs



Real Time Breath Profile Verification Chamber (with inhaler *in situ* during test) supported by the Accessory Support Stand on the Breathing Simulator BRS 3100

BRS 1100/2100/3100 Qualification Kit