# Inhalation Exposure

Precise, reproducible experiments with cutting-edge technologies from respiratory research experts











Inhalation Toxicology • Bioaerosol • Environmental • Disease Models • Pharmaceutical



# **Table of Contents**

#### Introduction

- System Introduction
- Application Area

# System Composition

- Inhalation Exposure Equipment
  - Nose-Only Exposure and Inhalation Tower
  - Single Animal Exposure
    - Oral and Nasal Exposure
    - Whole Body Exposure
  - Group Exposure and Mass Dosing
- Controllers
  - Inhalation Tower Main System Controller
  - Inhalation Tower Auxiliary Controller
  - Single Animal Exposure Controller
  - Mass Dosing Controller
- Exposure Source Generators
  - Smoke Generation
  - Dust Generation
  - Aerosol Generation
- Environmental Monitoring
  - Temperature and Humidity
  - 0,/CO, Concentration Ratio
- Particle Weighing and Analysis
  - Concentration Detection
  - Particle Size Detection
  - Weight Inspection

# Software Platform

- Software Introduction
- Inhalation Tower Controller Software
- Buxco FinePointe Software
  - Respiration Parameter
  - Accumulated Inhaled Aerosol (AIA)

# Appendix

- Inhalation Use Cases
- References

# System Introduction

DSI Buxco® Inhalation exposure solutions are primarily used for exposure studies including environmental toxins, drug compounds, tobacco or vape smoke, and more. DSI inhalation exposure system uses patented technologies to ensure precise exposure. This flexible system offers many add-on options including particle weighing and environmental monitoring allowing the system to expand as your research does!

The system has been carefully developed by a team of experts in the field of respiratory research who have worked with scientists around the world for more than 50 years. Scientists currently use this system in inhalation toxicology, drug research and development, environmental toxicology research, and disease research. DSI continuously optimizes product design, animal welfare, and user experience.



#### Data Sciences International (DSI)

DSI is a brand of Harvard Bioscience Inc., a U.S. listed company. Since its establishment in 1984, DSI has been pioneer in the field of experimental animal physiology telemetry and provides the preferred platform for pre-clinical laboratory research. Buxco was established more than 50 years and is an industry leader in solutions for pre-clinical respiratory research. Buxco was acquired by DSI in early 2014 and became a DSI brand.

DSI is committed to assisting researchers in advancing science and medicine to improve lives. Researchers all over the world use DSI technology Including multinational pharmaceutical companies, CROs, research institutions, and major universities. There are now more than 11,000 peer-reviewed journal articles citing use of DSI solutions. DSI is headquartered in St. Paul, Minnesota, USA, and has an office in Shanghai, China to provide high-quality service to clients in China and Asia Pacific.

#### Nose-Only Exposure and Inhalation Tower

DSI's Buxco inhalation tower is primarily used for oral and nasal exposure in animal models using a variety of substances including dry and wet aerosols, dust, or smoke. or steam. The tower can be used for nose-only exposure in mice, rats, guinea pigs, and ferrets. The system uses a patented Allay™ collar for improved animal comfort and data integrity, as the animal can breathe naturally. The tower uses a stackable, flow-past design to ensure consistent exposure for up to 42 animals.

Its unique features are as follows:

- The optional addition of plethysmography allows researchers to monitor respiratory function in real time during and after exposure, allowing for precise exposures, improved animal welfare, and an understanding of immediate effects on the lungs.
- The flow-past design uses inner and outer cores to eliminate rebreathing and reducing CO<sub>2</sub> levels.
- Closed system, the internal pressure of the tower can be controlled by the controller Force velocity, negative pressure environment in the tower avoids exposure to media Leakage; verified, concentration between each layer of exposure tower The difference is within 5%.
- The tower's stainless-steel construction is corrosion resistant, making it ideal for harsh chemicals, and its ultrasmooth finish minimizes test article loss.
- The modular design of the tower is flexible, easy to operate, and easy to disassemble making cleaning easy and therefore, improving experimental efficiency.
- The picture on the right shows a single-layer exposure tower with the Allay restraint and plethysmography chamber for rats.





#### Single Subject Nose-Only Exposure

DSI's Buxco Single Site Exposure Station is a cost-effective version of the exposure tower. It is a single port nose-only exposure device, which allows uniform exposure, one subject at a time and supports a variety of substances including dry and wet aerosols, dust, smoke, or steam via Aerogen Aeroneb® nebulizer. The nose-only exposure restraint can be used with both the Single Site Exposure Station and the Inhalation Tower to support flexibility in experiments. As with the inhalation tower, Plethysmography chambers can be used with the

Single Site Exposure Station to monitor respiratory function. The station is commonly used for animal models such as mice, rats, guinea pigs, and ferrets.







#### **Allay Patented Technology**

The Allay restraint is one of the key components of the exposure cavity. It is available in multiple sizes to accommodate a variety of animals. The Allay eases the animal acclimation and loading time due to its simple operation. It also improves animal welfare and data quality as the subject is positioned for normal breathing in a non-stressed environment. The thorax is not compressed as it is with traditional methods and subjects are placed in a consistent manner, maintaining normal breathing patterns. The Allay collar sits between the base of the animal's skull and its shoulders.



# **Traditional Restraints**



Pushing the rod against the animal's chest and abdomen restricting breathing

The rubber ring tightens around the animal, compressing the respiratory tract, restricting breathing

# **Allay Restraint**

The Allay restraint clamps around both sides of the neck, behind the ear, allowing the animal to breathe normally without constriction providing high quality, reproducible data.



#### Single Subject Whole Body Exposure

Whole Body Plethysmography (WBP) allows for unrestrained, non-anesthetized single animal exposure while measuring respiratory endpoints such as tidal or minute volume. DSI's patented Halcyon® noise reduction technology ensures both sensing ports on the differential pressure transducer measure the same pressure from an atmospheric event. As a result, artifacts due to slamming doors, air ventilation ducts, or other air disturbances are minimized to ensure accurate data is recorded.



The primary features of the WBP system include:

- Ability to monitor laboratory animals in awake and unrestrained state, which is one of the core group tests of safe pharmacology GLP
- Halcyon<sup>®</sup> patented noise reduction technology, reduces environmental noise by up to 70% compared to other chambers.
- The flexible system enables combination studies with the addition of a tower lid to integrate simultaneous blood collection, drug administration, biopotential measurement, or optogenetic stimulation.
- Pre-calibrated digital temperature and humidity signals
- Automated calibration for up to 4 chambers with a single click, reducing the risk of error and increasing reproducibility of studies. Continuous monitoring of bronchial stenosis (PenH and Pause), airway inflammation (TB and TP), and more.

**Applicable species:** mouse pup (P3 and older), mouse, rat, guinea pig, rabbit, ferret, dog, cat, non-human primate, and swine. Animals larger than a guinea pig must be equipped with a QT signal modulator, flow sensor, pressure sensor, plethysmograph chamber, and other equipment to detect the flow.

**Available parameters:** respiratory frequency, tidal volume, minute volume, bronchostenosis, apnea, breathing waveform exhalation shape ratio, respiration compensation, peak inspiratory flow rate, peak expiratory flow rate, inspiratory time, exhalation time, expiratory flow rate at 50% ventilation, relaxation time, end time of inspiration, end time of expiration lnhibition degree, etc.

## DSI Buxco Halcyon Patented Noise Reduction Technology

The Halcyon® pneumotach is used in most of DSI's Buxco plethysmographs. It cancels out noise by ensuring that both sensing ports on the differential pressure transducer measure the same pressure from an atmospheric event. As a result, artifacts due to slamming doors, air ventilation ducts, or other air disturbances are minimized. This pneumotach is especially important for sensitive flow measurements required by whole body plethysmography or functional residual capacity experiments.

See the difference our patented Halcyon noise reduction technology makes compared to conventional plethysmographs under the same conditions in the graph below.





#### Multiple Subject Whole Body Exposure

Chambers for exposing multiple animals simultaneously (Mass Dosing) are primarily used when general dosing can be tolerated. The Buxco Mass Dosing Chamber accommodates up to four Aerogen Aeroneb® nebulizer heads. The cover of the animal exposure chamber is a movable, non-sealed design for use inside a containment hood. Integration of a smoke generator enables

the study first- and second-hand smoke effects. Mass dosing is also commonly used to create animal models of asthma and COPD. The chamber's perforated floor improves animal welfare by collecting urine discharge. It also allows for the integration of barriers to separate animals if required. The chamber has four air supply interfaces, which can be connected to equipment such as a bias flow if needed.



The number of animals the chamber can accommodate varies depending on the size of the animal as shown in the table below.

Chamber Size	Animal Accommodation	Size	Part Number
Standard Chamber	Up to 15 mice, 6 rats, or 2 guinea pigs	24.77 x 27.36 cm	601-2039-001
Large Chamber	Up to 25 mice, 10 rats, or 4 guinea pigs	34.29 x 36.88 cm	601-2036-001

# System Controllers

Controllers are used with all inhalation systems to manage air flow and pressure within the inhalation environment. The table below shows all controllers used with inhalation systems and their corresponding specifications.

Controller	Part Number	Size	Voltage	Power
Inhalation Exposure	601-2202-003	63.5 x 34.3 x 20.3 cm	100-240VAC, 50 / 60HZ, 4.0A	External PS, 12V, 15A, 180W MAX
Auxiliary	601-2410-001	24.1 x 23.1 x 16.5 cm	100-240VAC, 50 / 60HZ, 4.0A	External PS, 12V, 15A, 180W MAX
Auxiliary Tower Flow	601-2204-001	24.1 x 11.7 x 11.4 cm	Shared power with auxiliary system controller	Shared power with auxiliary system controller
Whole Body (2-site)	601-1401-001	46.9 x 16.5 cm	100-240VAC, 50 / 60HZ, 4.0A	External PS, 12V, 15A, 180W MAX
Whole Body (4-site)	601-1400-001	74.9 x 18.7 cm	100-240VAC, 50 / 60HZ, 4.0A	External PS, 12V, 15A, 180W MAX
Mass Dosing	601-2075-001	20.3 x 19.6 x 12.5 cm	100-240VAC, 50 / 60HZ, 4.0A	External PS, 12V, 15A, 180W MAX

#### Inhalation Exposure System Controller

Key benefits of this Smart Controller include:

- Microprocessor manages tower environment air flow, pressure, etc.
- Push/Pull air flow design can create positive or negative pressure configuration
- Integrated support for collection of respiratory endpoints
- Software displays and records multiple tower parameters:
  - Pressure, Flow, Temperature, Humidity, 0, /C0, Test Article Concentration



# Controller for Exposure Tower Auxiliary System

Can be used independently with the inhalation tower or single subject exposure systems or as an expansion of the main controller.

Key benefits include:

- Support for up to 8 signal amplifier interfaces
- Control and calibrate up to 4 nebulizer heads
- Ability to monitor 02/C02 levels in the inhalation tower
- Run gas analysis and system calibration
- Control of mixing of substances



# Whole Body Plethysmography Controller

This controller supports multiple control modes on the hardware side and software side and enables connection of an external air source to support a variety of exposure substances. There is a 2-site and a 4-site version of the controller. The 2-site can simultaneously expose and monitory respiratory function of two animals and the 4-site exposes and monitors four.





# Mass Dosing Controller

The controller can be connected to external air sources with corresponding accessories to support a variety of exposure substances. A bias flow is included to control nebulization.





#### **Smoke Generation**

#### Electronic Cigarette, Vape, and Tobacco (EVT) Smoke Generator

DSI's latest Smoke Generator, EVT, combines all the necessary research requirement to provide a state-of-art instrument that meet today's research needs. Featuring multiple simultaneously working smoking stations, and support for both traditional and all types of e-cigarettes, the EVT is flexible and satisfies all study requirements.

The design features a main controller unit, which accept up to 3 smoke stations on top of it. The controller connects to a PC via USB where unique software program uses puffing and study criteria from the user to create countless reproducible protocols. Each smoke station works independently of each other, allowing the user to run multiple, comparative studies at the same time, reducing variability and increasing productivity.



Part Number: 601-2060-001 Size: 24.4 x 13 x 9.3 cm Voltage: 100-240VAC, 50 / 60HZ, 4.0A Power: External PS, 12V, 15A, 180W MAX

The EVT was designed with longevity and accuracy in mind. The smoke station creates puff profiles utilizing a volumetric cylinder and CAN-bus driven stepper motor, yielding long-lasting, precise, user defined puffs. Sophisticated software control of the motor creates ISO conforming puff profile shapes. Each station's exposed particle matter is reported in real-time, and all system data is captured through the reporting features.

In order to protect the smoke station's mechanical components, DSI has designed a patentpending Smoke Bellows, which acts as a buffer between the cigarette and puffing mechanism. The Smoke Bellows is designed as a disposable part, significantly reducing the users cleaning and equipment maintenance.

The EVT can be seamlessly combined with DSI's inhalation and exposure system, producing unparalleled real-time, subject delivered dose and respiratory end-points correlation. For more basic exposures, mass dosing systems, and free-roaming inhalation towers are readily available.

### Multiple Cigarette Smoke Generator

The cigarette smoke generator adopts the industry standard "artificial lung" to simulate a human smoking pattern. The robotic instrument delivers, detects, lights, puffs, ejects, and extinguishes up to 300 tobacco cigarettes without user interaction. Simply press the "start" button to start the generator. It can run continuously for 8-24 hours. The standard version can carry up to 80 cigarettes and the extended version up to 300.



Part Number: 601-2050-002 Weight: 29.4 kg Size: 70.4 x 36.1 x 23.9 cm Voltage: 100-240VAC, 50 / 60HZ, 4.0A Power: External PS, 12V, 15A, 180W MAX

- Enables delivery of both first-hand and second-hand smoke, to mass dosing, whole body, or nose-only inhalation solutions
- Ability to customize the amount and length of inhalation, number of inhalations per minute for each cigarette, time between cigarettes, and the total number of cigarettes to be smoked according to study requirements
- Prevent leaking of smoke with a pressure sealed combustion chamber door
- Can be used in small laboratories and equipment such as standard fume hoods or biological safety cabinets due to its compact and integrated design

# Single Cigarette Smoke Generator

Single Cigarette Puff Generator enables delivery of smoke from one conventional or electronic cigarette at a time. A variety of smoking schemes can be implemented. Suitable for smoking and human respiratory diseases (such as COPD, pulmonary fibrosis, Lung cancer, etc.), and animal disease modeling.

- Uses industry standard "artificial lung" to simulate human aspiration. Smoke mode with independent "first-hand smoke" channel. Smoke can be delivered to mass dosing, whole body, or nose-only inhalation solutions
- Allows the user to customize the amount and length of inhalation, number of puffs per minute, number of minutes per cigarette, total ignition time, and other parameters



Part Number: 601-2055-001 Weight: 7.5 kg Size: 50.2 x 27.5 x 16.3 cm Voltage: 100-240VAC, 50 / 60HZ, 4.0A Power: External PS, 12V, 15A, 180W MAX

# **Dust Generation**

# Palas RBG 1000ID dust generator

The dust generator is primarily used to deliver solid substances, such as granules or dust, to the exposure system. The powder sample is inserted into a cylindrical storage container and

passed through the piston. Conveyed to the rotating brush, the rotating brush will accurately deliver a certain amount of sample to the diffusion head through the nozzle acceleration. The airflow will be accelerated to a high speed of 180 m / s. High-speed airflow provides the necessary turbulence for the full dispersion of the powder. Through flow and shear force, the agglomerated particles are dispersed and output, and the output substance is polydisperse.

Technical Parameters:

- Granular material: non-sticky powder or dust
- Particle size: <0.1μm-100 μm
- Mass: 40 mg / h-560 mg / h
- Volume flow: 0.3-5 m<sup>3</sup> / h
- Power requirements: 220V / 50 Hz, 110V / 60 Hz
- Dimensions: 465 × 320 × 200 mm
- Weight: 19 kg

# **Aerosol Generation**

#### Aerogen Nebulizing Drug Delivery Head

The nebulizer head is used to aerosolize liquid substances. Two sizes are available, 2.5-4µm and 4-6µm. Benefits of the Aerogen nebulizer include:

- Strong versatility: can deliver all treatment candidates for infants to adult patients; The pharmacy has a volume of up to 10ml, which can reach 17% of the lung deposits, compared with 3% of traditional small-volume spray
- Simple operation: The atomization head control system is integrated in the main controller, auxiliary controller and group animals of the exposure tower The whole body is exposed to the controller, which can correct its own atomization efficiency and set the atomization amount and atomization time through software and hardware.
- Affordable and Reusable: can be autoclaved at 132-135°C











## **Collision Jet Nebulizer**

Collision Jet nebulizer for efficient atomization of solutions or suspensions in the range of atomization

The main features are as follows:

- Vertical or horizontal fog support
- Equipped with a safe and durable polymer container, which can handle small volumes of rare or expensive value liquid
- Stable performance, standardized operation, support long-term continuous operation
- Can adapt to harsh chemical environments

# Germany Barry atomizer PARI Boy Sx (085G3005)

PARI nebulizer (model 3005) is suitable for long-term nebulization inhalation. The main characteristics are as follows:

- Fewer components, installed vertically to prevent incorrect operation.
- Equipped with an intermittent control button allowing continuously or intermittent output.
- The sprayer is equipped with a valve which controls treatment time resulting in less waste of exposed substances.
- Two different inner cores, suitable for various applications:
  - Blue core: inhalation treatment is completed in a short time, and the drug deposition rate in the lower respiratory tract such as the bronchus is high.



- Red core: the drug is deposited in the alveoli and is suitable for patients with severe airway obstruction.
- Equipped with peak inspiratory flow rate (PIF) control system, which restricts the inspiratory airflow to 25 L / min or less. In the controllable mode, it helps subjects learn deep and slow inhalation methods for effective drug deposition in the lungs
- The total output of mist particles is up to 590 mg / min
- The average median diameter of mist particles is 2.9 microns
- The percentage of mist particles <5 microns is 75%
- Weight: 1.7 kg
- Size: 19.2 cm × 14.5 cm × 15 cm



#### Multiple Aerogen Nebulizer Plenum

The plenum is primarily used to provide a mixing environment for exposed substances. It can be equipped with up to 4 nebulizer heads for large gas solubility and humidify in a relatively dry and exposed environment. Experimental animals are exposed to nasal inhalation and pulmonary sedimentation.



#### **Bypass Exposure Control Valve**

The exposure medium is directly connected to the exposure tower, so the concentration in the exposure tower quickly reaches a uniform, stable state. This bypass valve reduces premature exposure of animals and allows the user to temporarily turn off the aerosol while removing a subject from the tower for any reason.



#### **Drying Equipment**

Dry the exposed environment to reduce excessive humidity caused by the exposed environment. Excessive humidity can cause alterations in the exposure substance and reduce the effect on the subjects inhaling it, in part due to increased particle size. Condensation can also occur which will cause the subjects to swallow the exposure substance rather than inhale it.



# **Environmental Monitoring**

#### **Temperature and Humidity Monitoring**

The temperature and humidity probe boasts an integrated design and fully digital automatic operation. It is primarily used for real-time monitoring of temperature and humidity conditions.





Multifunction sampling adapter

# O<sub>2</sub> / CO<sub>2</sub> Concentration Ratio Monitoring

The gas analyzer is mainly used to measure the breathing gas concentration from small insects to humans. It is equipped with an infrared carbon dioxide sensor and an optical oxygen detector.

- Power supply: 85–250 VAC 50/60 Hz
- Peak power requirement: 60 VA
- Temperature range: 5–35 ° C
- Humidity: 0–90% (non-condensing)
- Analog output: BNC connector

Technical specifications:

- Sampling system: Built-in miniature damping vacuum pump, autonomously pumping for sampling by built-in CO<sub>2</sub> and O<sub>2</sub> sensors
- Gas: Must be non-corrosive and non-flammable gas. Dehumidification must be used at the front of the sampling inlet
- System sampling flow: about 35-200 ml / min (user variable)
- Internal damping volume: 75 mL
- Gas connector: plastic Luer connector
- Moisture filter: It is recommended to install a 0.45 µm hydrophobic membrane filter in front of the sampling inlet.
- Materials in contact with gas: 316 stainless steel, sapphire, nylon 66, silicone rubber, epoxy varnish
- Warm-up time: 10 minutes at 20°C

Requires corresponding adapter, as shown on the right P/N 601-2135-001

O<sub>2</sub> CO<sub>2</sub> Tower Adapter





# **Particle Weighing and Analysis**

#### **Concentration detection**

Microdust Pro is a handheld data logger that detects air dust, smoke, and suspended particles in real time. It also displays the amount of dust in real time and can be used to quickly and easily obtain other qualitative data, which cannot be collected by gravity analysis air sampling methods alone. The instrument has a variety of accessories and versatile functions.



Port Photometer Adapter (with Photometer) Stainless Steel: 601-3105-001

Inflow - Photometer Adaptor with Photometer, Stainless Steel: 601-3141-001

- Wide range: 0.001mg / m<sup>3</sup> to 250 g / m<sup>3</sup> (automatic range setting)
- TSP sampling, respirable dust sampling, PM2.5 sampling or PM10 sampling (optional adapter)
- Real-time graphic display of dust amount for instant evaluation
- The user interface uses simple and clear icons for quick and easy dust measurement
- Unique removable sampling probe
- Robust design, suitable for various harsh environments
- Multilingual operation
- Unique on-site calibrator to ensure accurate measurement results
- Online environmental device that can be used in boundary monitoring applications

#### Particle size detection

#### **Optical Particle Size Spectrometer**

Optical Particle Size Spectrometer (OPS) is a lightweight and portable spectrometer that uses single particle counting technology to provide fast and accurate particle concentration and particle size distribution measurements. OPS enables measurement of 0.3-10 µm particles in 16 user-adjustable particle size channels. Users can also place the instrument in TSI's waterproof environmental monitoring box for measurement and collect particles for further analysis through the built-in filter. The instrument has a battery life of up to 20 hours and is equipped with a large color touch screen, suitable for a variety of applications from filter testing to industrial measurement, and indoor and outdoor environmental monitoring.

Quality optical instruments are widely used in a variety of applications due to their ease of use, fast test time, robustness, and reliability. Common applications are as follows:

- Filter test (e.g. ASHRAE 52.2)
- Indoor air quality
- Workplace monitoring
- Outdoor environmental monitoring
- Industrial measurement

# Features and advantages:

- Particle size resolution <0.5% at 0.5 μm
- User adjustable size channel
- Particle size range: 0.3-10 µm in up to 16 channels
- 0-3,000 particles / cm<sup>3</sup> wide concentration range
- Color touch screen with intuitive user interface
- Fully meets ISO 21501-04 standard
- Display particle number concentration and particle mass, with the ability to enter refractive index and particle density
- Filter-based sample collection, suitable for gravimetric or chemical analysis

# Marple Series 290 Personal Cascade Impactor

Marple Series 290 Personal Cascade Impactor is used to detect exposed particle size and supports dust samplers. It is commonly used in the fields of inhalation toxicology, indoor air pollution, aerosol research, and more. Substances used include, but are not limited to, sawdust, coal dust, silicon dust, and sand dust.

# Specifications

- Optimum Flow Rate: 2 liters per minute (lpm)
- Flow range: 1-5 lpm
- (Recommended traffic range: 1-3 lpm)
- Material: Finished aluminum

# Weight Inspection

Filters with different pore sizes can be selected to recover the exposed material according to the exposure source, to be weighed and analyzed after drying. The cascade impactor can simulate the total exposure of a single animal in a single experiment and further analyze the sedimentation coefficient of the animal at the target concentration of exposure.









#### Inhalation Tower Controller Software

This software is used to customize the flow and pressure of the inhalation tower. It supports nebulization and automatic calibration. Users can set customized alarms with the system according to defined parameters and can monitor precise substance inhalation in real time. Available parameters include:

- Flow and pressure
- Concentration of exposed substance
- Temperature and humidity
- 0, / CO, concentration ratio



#### Buxco FinePointe Software

FinePointe software is used for data collection and analysis in respiratory research. It supports the latest Windows operating system and stores data through Microsoft SQL Server®. It can run stand-alone, share data through the network, or remotely monitor from respiratory systems.

To set up a study, users first select a report template, set the data indicators that are of most interest in the report, and establish animal IDs and groups. The software wizard will guide the user to calibrate the system, set up the study, set parameters of interest, manage animal groups, and set up data reports for different detection indicators. The initial settings of the experiment can be modified at any time after the experiment. You can also simply follow the wizard to

create a study, and then start collecting data directly. After the experiment, set the required report format, group animals, and display data reports for each indicator. All raw data and data reports can be imported into a variety of external files such as Microsoft Excel®, GraphPad Prism®, or SPSS®.

Reporting parameters, animal group management, reporting algorithms, and monitoring cycles can be adjusted at any time.



#### **Respiratory Parameter Monitoring**

Monitoring of respiratory function can be performed during exposure experiments, real-time acquisition and analysis enables the user to accurately monitor the exposed dose for each animal.



#### Accumulated Inhaled Aerosol (AIA)

This feature is exclusively available in Buxco FinePointe software and enables the user to ensure precise, consistent exposure to all subjects in the experiment. Individual animals have unique breathing patterns, which, if not accounted for, can lead to inconsistencies in the data. AIA alerts the user when a subject has reached the defined deposition amount, allowing them to remove that subject from the inhalation tower. The other subjects can continue exposure until they also reach the desired deposition. This feature improves reproducibility as it removes variability in the amount inhaled by each subject. It also improves animal welfare as the animals are not inhaling unnecessary substances. Users also save time and money as they will use less compound and will not need to repeat studies due to data inconsistencies.

Time	f	TV	MV	AV	Cnc	IA	AIA	PIF	PEF
00:05:28.13	128.4	0.2456	31.54	11.72	349.8	8.593e-05	0.003624	2.336	1.704
00:05:28.64	117.4	0.2553	29.97	11.98	347.7	8.877e-05	0.003713	2.021	1.911
00:05:29.15	119.1	0.2436	29.03	12.22	347.7	471e-05	0.003798	2.141	1.561
00:05:29.70	109	0.31.51	34.46	12.54	34	0.0.01097	0.003907	2.567	2.246
00:05:30.21	116.4	0.2989	34.81	12.84	346.7	0.0001036	0.004011	2.432	2.218
00:05:30.73	116.3	0.2897	33.69	13.13	347	0.0001005	0.004111	2.563	2.075
00:05:31.22	121.6	0.198	24.07	13.32	347.1	6.871e-05	0.00418	1.702	1.363



#### **Inhalation Use Case 1**

# 

#### VALIDATION OF A MULTIPLE METERED DOSE INHALER ACTUATOR AND DSI BUXCO INHALATION TOWER TO ENABLE TRANSLATION FROM PRE-CLINICAL SPECIES TO FIH

Aileen House<sup>1</sup>, Maureen Marsales<sup>2</sup>, Carlos Santos<sup>2</sup>, Balaji Bharatwaj<sup>2</sup>, Kristina Najjar<sup>2</sup>, Jessica Durston<sup>3</sup>, Ayahna Sanders<sup>3</sup>, Erin Kinnucane<sup>3</sup>, Timothy Gil<sup>3</sup>, Jennifer Wylie<sup>2</sup>, Steve Sorota<sup>1</sup>, UV Shemesh<sup>4</sup> 1CMRO, Boston, MA, 2Biopharmaceuticals and Specialty Dosage Forms Merck & CO., Inc., Rahway NJ; 3LAR Boston, MA; 4DSI St. Paul, MN

#### Introduction

The differences in formulation and device between pre-clinical studies, toxicology studies, and first-inhuman (FIH) studies can provide a challengein ensuring consistent, translatable aerosol delivery throughout the course of an inhalation program. Pre-clinical inhalation studies that enable evaluation of a formulation and delivery method with a clear line of site to the clinic can help bridge the gap going from pre-clinical development to FIH. Toward this end, DSI has developed a Multi-can Metered Dose Inhaler Actuator (MC-MDI Actuator) that adapts to the DSI Inhalation Tower to help bridge the gap in device. To validate this new multi-can MDI actuator as an inhalation delivery device, Merck formulated a proprietary inhaled lead compound (IC) formulated is metered dose inhaler (MDI) canisters. Pharmacokinetic studies and in-vitro characterization of particle size, aerosol concentration, and tower efficiency with the MC-MDI Actuator and the 14-port tower was executed.

#### Materials and Methods

#### Animals

 Male Wistar Han rats (175-225 g) were acclimated to flow nose-only exposure chambers (CH Technologies, Westwood,NJ,USA) andenvironmental conditions prior to the start of the study using Positive Reinforcement Behavioral Conditioning.

#### Test System and Aerosol Concentration:

- Buxco/DSI 14 port inhalation tower with MC-MDI actuator (Buxco/DSI St. Paul, MN, USA), the test atmosphere is forced through an opening in the inner chamber towards the periphery of the chamber, directly towards the opening of the animal exposure tubes.
- The aerodynamic particle size distribution (APSD) and Mass Median Aerodynamic Diameter (MMAD) was measured by a Cascade impactor (Marphe 296, Anderson Instruments Inc. Atlanta, GA, USA) attached to the port supported by DSI's regulated flow system.
- Delivered Dose (DD) (mg/kg) is based on the equation from the Association of Inhalation Toxicologists.
- Formulation: MDI Canisters with increasing API and a 5% ethanol content were loaded into the MC-MDI actuator. Formulations chosen for this evaluation were 100, 300 and 500 µg per actuation.
- All doses were evaluated prior to testing for dose content uniformity (DCU), MMAD, and fine particle fraction (FPF).
- 40 shots of each dose actuated in one minute.





Results showed a linear relationship in Delivered Dose (DD), deposited dose, and aerosol concentration. The in-vitro tested iLC formulations exhibited FPFs between 75% and 78% with a MMAD of 1.3 microns. The Marple Cascade Impactor at the port of the tower confirmed the MC- MDI Actuator exhibited a range of MMAD of 1.1-1.7 microns during the in-vivo study, which is comparable to the in-vitro assessment of the iLC.



MDI In Vitro Data (Anderson Cascade Impactor, No Tower)





Plasma Concentration of iLC with the MC-Actuator and DSI's Buxco 14-port Inhalation Tower



#### Conclusions

- The Multiple Metered Dose Inhaler Actuator was successfully used to dose a solution based formulation to rats
  The actuator, in conjunction with the DSI tower,
- The actuator, in conjunction with the DSI tower, achieved linear results in both in vivo and in vitro
- parameters examined (Delivered Dose, Deposited Dose and Tissue PK) • The particle size distribution results are comparable
- to those generated with the clinical device

#### Inhalation Use Case 2

#### A Miniaturized Inhalation Tower to Deliver Small Amounts of API to Conscious Rats.

Aileen House, Walter Horodnik, Jennifer Wilson Wylie, UV Shemesh, Joe Lomask, Ester Carballo-Jane and Peter J. Mauser

Merck Research Laboratories, Kenilworth, NJ, Merck Respiratory Product Development, Summit NJ and Buxco Research Systems, Wilmington, NC, USA.



Proprietary

#### Inhalation Use Case 3



# THE WORLD'S LEADING PROVIDER OF LIFE SCIENCE WEBINARS

# Inhalation Exposure Systems for Aerosol Delivery Advancements: Perspective from a Bench Scientist

#### WEBINAR DETAILS

Date: April 30, 2015 (60 mins)



#### Featured Speakers:

Michael Girand, Principal Applications Engineer, Data Sciences International (DSI) Aileen House, Sr. Scientist, In Vivo Pharmacology – Cardiovascular Department, Merck & Co Pharmaceuticals

Inhalation exposure systems for preclinical research have evolved since their introduction in the early 1900s to meet the needs of many different research applications. These systems vary significantly depending on the type of research being conducted, which can include: Inhalation Toxicology, Biodefense Aerobiology, Pharmaceutical, Discovery and Drug Development, Basic Respiratory Physiology, and Environmental Toxicology and Exposure studies. With each of these research disciplines, the scientific approach will differ, as will the complexity of the study design and the desired endpoints. As a result, the type of equipment required will also differ. With each inhalation delivery method and application, a host of benefits and potential disadvantages follow.

Delivering aerosol compounds for preclinical inhalation research has been historically challenging. Even today, many inhalation exposure systems require large amounts of API (active pharmaceutical ingredient) and invasive techniques that necessitate anesthesia and intratracheal administration. Such techniques have potential disadvantages because they are not representative of methods used in clinical settings. The use of mass dosing chambers for delivery of an inhaled substance eliminates the issue of anesthesia and allows the animal to be unrestrained and roam freely. However, this approach may result in excess use of API and be an inefficient method to deliver compound to the animal's lungs.

Scientists from Merck & Co. pharmaceuticals determined that there was a need to develop a superior system for the delivery of liquid and dry powder aerosols. With input from Merck, Buxco Research Systems (which was acquired by Data Sciences International [DSI] in 2014) developed and validated a 14-port inhalation tower. The tower, with its all-inone controller, patented AllayTM restraint collar for rodents, and nose-only plethysmograph to deliver small amounts of API continuously to conscious rats, gives the researcher peace of mind that an inhaled substance will be delivered to all animals in a uniform and reproducible manner.

This webinar will include a discussion about inhalation exposure systems, specifically:

The variety of inhalation exposure applications currently being used in research, along with their advantages and disadvantages Identifying the need for better inhalation exposure tools Introduction of DSI's 14-Port Inhalation Tower and All-in-One Tower Controller Scientific perspective of 14-Port Inhalation Tower

The 14-Port Inhalation Tower now allows Merck to:

Minimize systemic exposure from fur or skin contamination utilizing nose-only delivery Deliver compound to conscious animals and eliminate complications associated with anesthesia

Decrease API amounts required, therefore minimizing the significant investment associated with compound scale-up, through controlled delivery Utilize the flexible design of the inhalation tower that allows the use of existing/conventional methods for restraint (push bar or barrier placed at the rear of the animal) or the use of the Allay restraint method

Obtain real-time measurement of changes in respiratory physiology during compound delivery in the same experiment when the 14-Port Inhalation Tower and the Allay restraint collar are used with a nose-only plethysmograph. This is a significant advancement for inhalation delivery because it uses the real-time minute ventilation measurement for delivered dose (DD) calculations, circumventing DD calculations based on estimated minute ventilation (RMV) and body weight

The 14-Port Inhalation Tower used with the Allay restraint collar and nose-only plethysmograph system yields reproducible, high-quality ventilation data for the duration of compound delivery and over a large range of flows. Merck has evaluated the 14-Port Inhalation Tower in conjunction with HD-S21 dual channel transmitters to evaluate pulmonary and systemic hemodynamics post-delivery.



1. Dong Y, Li Y, Sun Y, Mao J, Yao F, Tian Y, Wang L, Li L, Li S, Li J. (2015). Bufei Jianpi granules improve skeletal muscle and mitochondrial dysfunction in rats with chronic obstructive pulmonary disease. BMC Complementary and Alternative Medicine. (15)51.

2. House, A., Horodnik, W., Wilson Wylie, J., Shemesh, U., Lomask, J., Carballo-Jane, E., Mauser, P. (2014, October). A miniaturized inhalation tower to deliver small amounts of API to conscious rats. Poster presented at the American Institute of Toxicology, Princeton, NJ.

3. House, A., Marsales, M., Santos, C., Bharatwaj, B., Najjar, K., Durston, J., Sanders, A., Kinnucane, E., Gil, T., Wylie, J., Sorota, S., Shemesh, U. (2018, October). Validation of a multiple metered dose inhaler actuator and DSI Buxco inhalation tower to enable translation from pre-clinical species to FIH. Poster presented at the American Institute of Toxicology, Durham NC.

4. House, A., Shafer, R., Shemesh, Y., Lomask, J., Chapman, R. W., & Mauser, P. J. (2013). Use Of The Allay Restraint Collar To Facilitate The Measurement Of Ventilation In Conscious Rats. In C32. ANIMAL MODELS OF ASTHMA AND AIRWAY RESPONSIVENESS (pp. A4049-A4049). American Thoracic Society.

5. Li Y, Tian Y, Li J, Dong Y, Wang M, Su-Xiang Feng S, Li L, Mao J, Wang L Luo S. (2016). Bufei Yishen granules combined with acupoint sticking therapy suppress oxidative stress in chronic obstructive pulmonary disease rats: Via regulating peroxisome proliferator-activated receptor-gamma signaling. Journal of Ethnopharmacololgy. 193, 354-361.

6. Lu, X., Li, Y., Li, J., Wang, H., Wu, Z., Li, H., & Wang, Y. (2016). Sequential treatments with tongsai and bufei yishen granules reduce inflammation and improve pulmonary function in acute exacerbationrisk window of chronic obstructive pulmonary disease in rats. Evidence-Based Complementary and Alternative Medicine, 2016.

7. Pastor, M., Moreno-Sastre, M., Esquisabel, A., Sans, E., Viñas, M., Bachiller, D., ... & Pedraz, J. L. (2014). Sodium colistimethate loaded lipid nanocarriers for the treatment of Pseudomonas aeruginosa infections associated with cystic fibrosis. International journal of pharmaceutics, 477(1-2), 485-494.

8. Sellers, S., Horodnik, W., House, A., Wylie, J., Mauser, P., & Donovan, B. (2015). The in vitro and in vivo investigation of a novel small chamber dry powder inhalation delivery system for preclinical dosing to rats. Inhalation toxicology, 27(13), 706-716.

9. Tian, Y., Li, Y., Li, J., Xie, Y., Wang, M., Dong, Y., ... & Luo, S. (2015). Bufei Yishen granule combined with acupoint sticking improves pulmonary function and morphormetry in chronic obstructive pulmonary disease rats. BMC complementary and alternative medicine, 15(1), 266.

10. Wylie, J. L., House, A., Mauser, P. J., Sellers, S., Terebetski, J., Wang, Z., & Ehrick, J. D. (2018). Inhaled formulation and device selection: Bridging the gap between preclinical species and first-in-human studies. Therapeutic delivery, 9(5), 387-404.

1980s	1990s	2000s	2010s	
1984: DSI founded	<b>1987:</b> First DSI telemetry implant	2006: DSI acquires Ponemah	2012: PhysioTel	
	for large animals	2007: Jacketed External	Digital released	

1985: First DSI telemetry implant

# **Buxco Solutions**





Telemetry (JET) released

2014: DSI acquires Buxco







datasci.com Copyright© 2019 Data Sciences International

#### Headquarters and North American Sales: 1-800-262-9687 (U.S.)

1-651-481-7400 (International) sales@datasci.com

European Sales: Tel: 31-13-5479356 europe-sales@datasci.com



Asia Pacific Sales: Tel: 86-21-50793177 apac-sales@datasci.com