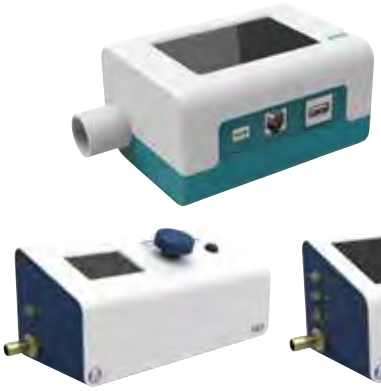
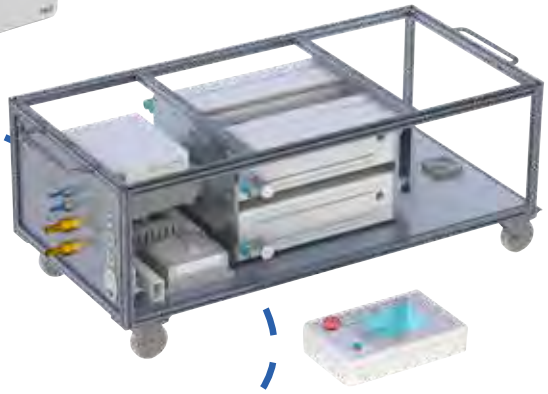
AB FIA
An Engineering Company
with a Chemistry Profile

AB FIA – Expanding the World of Inhaler Testing



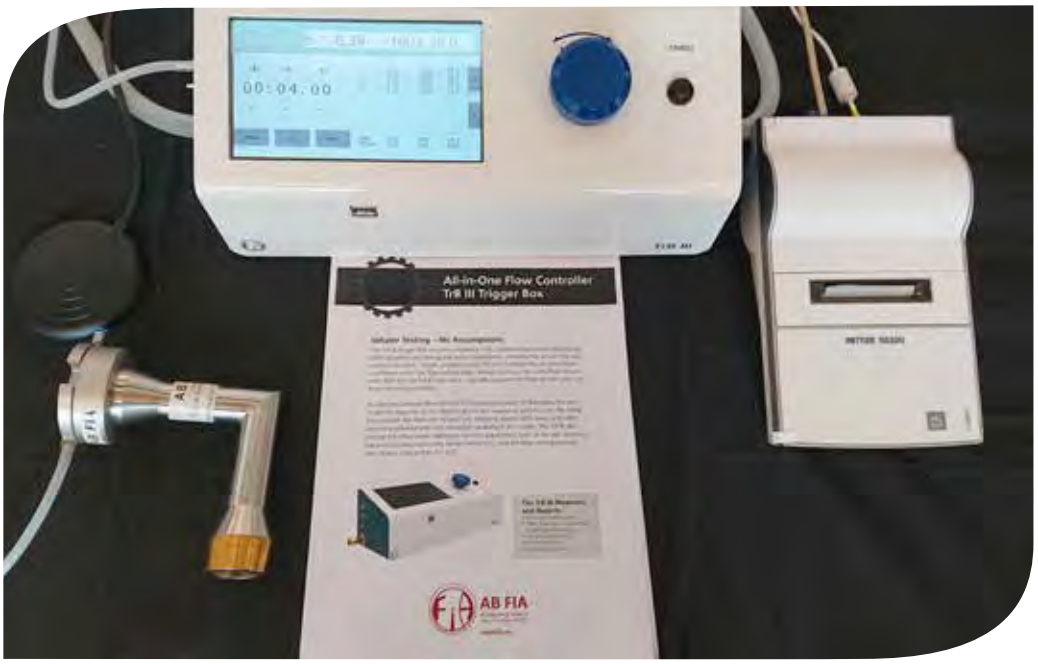
Air Flow
– Measurement
– Control
– Generation





Fully Automated
GMP-Compliant
Total Dose Testing

OUR World at YOUR Fingertips ▶ shop.fia.se & fia.se



We can fully equip your laboratory for a range of tests of OINDPs. Through our partnership with several lab equipment suppliers and with unique FIA-made products we can make your methods more precise, accurate and efficient.

Examples Based on Typical Inhalation Device Testing :

- Mouthpiece adapters moulded according to your device fitted onto induction ports and inlets of the NGI, ACI, MLI and EP <0671>/USP <601> collectors.
- P1 dP connection to
- Critical flow controller, depending on model presenting P1, P2, P3 and Q, incl. printouts.
  Versatile with small footprint.
- Foreign particle analysis, ergonomic lab tools designed for pollution reduction when working in LAF cabinets.
- Breathing Profile Generator F-SIG 6300, ranging from rodent (0.1 l), smoker and adult profiles up to 6 liters. Single inhalation or tidal cycles.
- Software Metivent designed specifically for inhalation testing connected to volumetric air flow or TSI mass flow meters. Applications are recording of flow profiles (import into F-SIG 6300!), trigger points and rise time determination.
- Fully automated DDU, waste and AIM analyses, combined with semi-automated impactor FPD dosing.
- High-throughput equipment for dispensing, agitation and sampling to make your lab work more efficient.

Contact

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Phone: +46 46 13 90 00 | i@fia.se | **www.fia.se** | **www.shop.fia.se**

Prototypverkstaden is *FIA Labs*. A capable and innovative place where we take customer ideas from sketch to prototype.
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Air Flow Control for Inhaler Testing – the FIA Way

Control and monitoring of the air flow is essential for performance testing of inhalation devices in accord with regulatory standards. FIA engineers have designed a user-friendly family of products that enable full compliance with the test requirements of the European Pharmacopoeia and the US Pharmacopeia. FIA offers three models of flow controllers – basic to advanced – that put you, the USER, in control – repeatably, reliably.

– Need to coordinate MDI dosing and flow sequences? No problem.
– Need to ensure proper flow in real time for DPI testing? Yes.
Flow control, however you want it.

AND with the absolute minimum footprint…as small as 23x13 cm PLUS easy-to-read displays that work even when you wear gloves – "hands-on" equipment made with the analyst in mind.



Trigger Box Model I



Optional output and inputs configurable according to customer needs.

Trigger Box Model I – Basic

This model gives the analyst the basic functionality in a very compact and easily managed format.

Trade Item Number: TriggerBox Model I



Trigger Box Model II

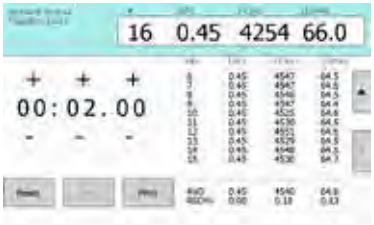
Trigger Box Model II – Critical Flow Controller

This model builds on the functions of Model I with the addition of differential pressure transducers for measuring and displaying pressure at P1, P2, and P3.

Trade Item Number: TriggerBox Model II
Trade Item Number: TriggerBox - Training and IQ Model II



Trigger Box Model III



Trigger Box Model III Screen dump

Trigger Box Model III – Critical Flow Controller with Flow Measurement

Trigger Box Model III has the same functions as Model II but is also equipped with an internal flow meter. With this equipment the user has full control of the testing, including volumetric flow measurement. The latter is enabled by an integrated laminar flow element downstream of the test set-up (e.g. dose collector or impactor). The air flow into the device is presented. The principle has proven to be robust and has been used by FIA's customers for over 25 years but has now been integrated into a compact format for routine use. Further, two additional pressure sensors ("dP") make it possible to do impactor stage mensuration by pressure drop.

Trade Item Number: TriggerBox Model III
Trade Item Number: TriggerBox - Training and IQ Model III

	TRB I	TRB II	TRB III
Flow actuation	0-99 min, 0.1s resolution	0-60 min, 0.1s resolution	0-60 min, 0.1s resolution
Actuation counter	Resettable, 8 digits	Resettable 0-999	Resettable 0-999
Foot switch	Optional	Yes	Yes
Display	4 and 8 digits	4.3" touch	7" touch
P1 Measurement	No	Yes, 0-16 kPa	Yes, 0-16 kPa
P3/P2 Measurement	No	Yes	Yes
Flow Measurement	No	No	Yes, 0-120 l/min
dP (e.g. stage dP)	No	No	Yes, high precision 0-6 kPa
Printable data	No	Prints new actuations continuously – Flow "on" time – Dose number – P1 – P3/P2 (if < 0.5)	Prints new actuations continuously or prints all actuations from reset. – Date/time of first dose – Instrument ID – Instrument ver – Flow "on" time – External relay timing – Atmospheric pressure – Dose number – P1 – P3/P2 (if < 0.5) – Flow – dP
Relay output for actuation of external equipment	No	No	Yes, configurable timing of output relative to vacuum opening.
Displayed history of recent actuation data	No	Last 3 actuations	All actuations from reset.
USB memory stick export	No	No	CSV format named with current date/time.
Automatic leak test	No	No	Yes
Dimensions (cm)	23x13x13	23x13x13	34x13x13

All-in-One Flow Controller TrB III Trigger Box



Inhaler Testing – No Assumptions

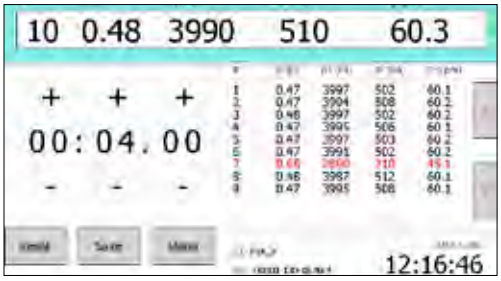
The TrB III Trigger Box ensures compliance with standard pharmacopeial methods, both recording and storing key system parameters, including the actual flow rate and run duration. Many inhaler test methods rely on critical flow conditions across the flow control valve, aiming to ensure the same flow rate on each test. But the TrB III does that and more – actually measures the flow of each test – so, there are no assumptions.

A calibrated laminar flow element (LFE) internal to each TrB III enables the user to set the flow rate at the beginning of a test sequence; with this LFE, the TrB III then records the flow rate of each test, ensuring against drift, leaks, and other non-ideal behavior that may introduce variability in test results. The TrB III also records the other more traditional run-time parameters, such as the test duration, the pressure drop across the inhaler device (P1), and the flow control pressure ratio (P3/P2, critical flow if ≤ 0.5). To measure pressure drop over, e.g., individual impactor stages to detect blockage, additional internal sensors are used.[1]

Additional user-friendly functions are leak checking and synchronized device actuation by using the integrated output port. Device actuation enables the flow to start simultaneously with dose actuation of a metered-dose inhaler, allowing a user-defined, fixed flow volume for MDI total dose testing. Query i@fia.se for details of actuator options.

Trade Item Number: TriggerBox Model III
Trade Item Number: TriggerBox - Training and IQ Model III

	TRB III
Flow actuation	0-60 min, 0.1s resolution
Actuation counter	Resettable 0-999
Foot switch	Yes
Display	7" touch
P1 measurement	Yes, 0-16 kPa
P3/P2 measurement	Yes
Flow measurement	Calibrated 0 - 120 l/min (operating range possibly higher)
dP (e.g. stage dP)	Yes, high precision 0-6 kPa
Automatic leak test	Yes
Printable data	Prints new actuations continuously or prints all actuations from reset. – Date/time of first dose – Instrument ID – Instrument ver – Flow "on" time – External relay timing – Atmospheric pressure – Dose number – P1 and flow – P3/P2 (if < 0.5) – dP (stage pressure drop)
Relay output for actuation of external equipment	Yes, configurable timing of output relative to vacuum opening.
Displayed history of recent actuation data	All actuations from reset.
Interfaces	– Relay output for actuation of external equipment – Foot switch actuator – USB for CSV export
Dimensions (cm)	34x13x13



Trigger Model III Screen dump

In-house calibration – **Possible** – no need to send to FIA for periodic calibration (ask our representative for suggested methods). FIA also provides calibration service if requested.



User-Friendly

With a large-handle flow control valve and easy-to-read display, the TrB III can quickly be set to go. Just press the start button (or foot pedal) and each run clicks off like clock-work – a reset-table run counter helps ensure that the correct number of actuations are made.

The TrB III has a 7" touch-screen that allows the system to be set up and measured values to be presented; this screen can be operated with or without gloves.

GMP-Friendly and Quality-Friendly

Need a data record from your testing – no problem; the equipment stores the data from each actuation, and at the end of each test the Print sign can be pressed. The TrB III readily connects to many standard laboratory printers; **print, sign, done**. Enquire for more information.

Printing eliminates the uncertainties of how many doses have been taken and under what conditions! It fits equally well within your R&D as in your GMP QC department. For the latter and if desired, simplified versions with less data ports of the TrBIII are available.

Specifications

Dimensions are surprisingly compact: 34x13x13 cm.
High-quality pressure sensors – for device pressure drop, critical flow control, flow measurement, and stage pressure drop.

Function	Full-Scale	Certified Accuracy
Device pressure drop, P1	16 kPa	± 160 Pa
Atmospheric pressure, Patm	160 kPa	± 800 Pa
Pressure upstream of flow control valve, P2	160 kPa	± 800 Pa
Pressure downstream of flow control valve, P3	160 kPa	± 800 Pa
Pressure drop of laminar flow element	250 Pa	N/A. See Volumetric Flow.
Volumetric flow	N/A	± 0.5 l/min for flows smaller than 20 l/min. ± 2 % for flows between 20 and 60 l/min. ± 1.5 % for flows between 60 and 125 l/min. ± 3 % for flows larger than 125 l/min.
Stage pressure drop sensor, dP*	0-600 Pa 600-6000 Pa	± 6 Pa ± 60 Pa

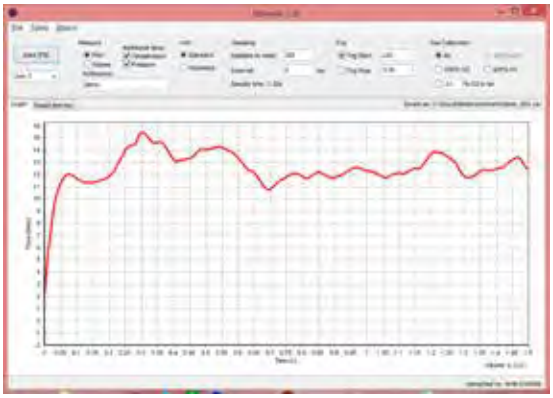
*The system automatically switches between the two ranges using the same port

Reference
1. Roberts, D.L., et. al., Experimental and Theoretical Investigation of a New Approach to In-Use Impactor Quality Specifications, Drug Delivery to the Lungs, DDL2018

Metivent Software
A Companion to TSI Flowmeters

Metivent is a Windows application for recording air flow measurements from TSI flowmeters (e.g. TSI4040). A standard Windows computer with the installed Metivent software connects to the flowmeter via a USB-serial converter or FIA's specialty USB cable (see picture) which also provides power. The acquisition of data from the flowmeter is then controlled by the software. Once started, the graph is updated continuously during measurement.







	A	B	C	D	E
1	Sample Reference	20170105-sample1			
2					
3	Program Version	1.2			
4					
5	Instrument:				
6	Model	4040			
7	Serial No	4040113900A			
8	Calibration Date	2014-10-15			
9	Firmware	3.5			
10					
11	Settings:				
12	Measurement	Flow			
13	Read Temp	Yes			
14	Read Pressure	Yes			
15	Flowunit	Standard			
16	Samples	300			
17	Sample Interval (ms)	3			
18	Trig Start	NA			
19	Trig Stop	NA			
20	Gas Calibration	Air			
21					
22	Time(ms)	Flow (l/min)	Temp (C)	Pressure (kPa)	
23	0	0,01	27,01	102,22	
24	3	0	27,01	102,19	
25	6	0	27,01	102,29	
26	9	0	27,01	102,14	
27	12	0	27,01	102,05	
28	15	0	26,99	102,15	
29	18	0	26,98	102,25	
30	21	0	26,98	102,07	
31	24	0	26,98	102,22	
32	27	0	26,98	102,32	
33	30	0,02	26,98	102,14	
34	33	0,03	26,98	102,1	
35	36	0,03	26,98	102,29	

20170105-sample1.csv

The software can be used in several modes and configurations

- Start trig (wait to start until the flow has reached the start trigger level)
- End trig (sample data until stop trigger condition)
- Gas calibration
- Number of samples to collect if not using trig
- Standard or volumetric flow
- Sampling rate 1-1000/s

Trade Item Number: Metivent Software
Trade Item Number: Training and IQ Metivent Software
Trade Item Number: USB/RS-232 power cable TSI

Measurements can be conveniently saved to CSV files and opened in Excel for further data analyses and presentations. The instrument is pivotal when recording inhalation profiles for lung simulation studies (such as FIA's F-SIG 6300).

The file presents flow, pressure and temperature along with instrument data, such as serial number, calibration date and currently used settings.

NEW from FIA's Automation Experts Nasal Spray Actuator



Take the worries out of Nasal Spray testing with FIA's configurable NASAL SPRAY ACTUATOR. This actuation system enables the user to define multiple actuation methods. The nasal actuator measures the stroke travel distance and the force constantly, most notably end force at actuation. The velocity can be calculated from the distance and the time, recorded by the software.

The nasal actuator control box can be used to set number of actuations for dosing, rest time between each actuation, number of waste dose etc. The equipment can be easily adapted to most device geometries. The compact and open design makes it perfect to integrate with dose collection on filter, and with optical techniques for determination of, e.g., spray pattern, plume geometry (laser pulsed camera) and droplet size (laser diffraction). We can guide you to the best possible solution based on our historic implementations.

Main benefits:

- Control pivotal parameters affecting the dose and the spray
- Release technical staff from routine functions and potential ergonomic strain
- Elucidate and record actuations in documented fashion

The regulatory guidelines which are applicable:

- US (FDA) – Guidance for Industry: Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action, Draft 2003.
- US (FDA) – Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products CMC Guidance, Draft 2002.
- EU (EMEA) – Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, EMEA 2006.

A training programme is offered together with the instrument, which helps the user to understand its usage and our experts will help you get started understanding how to setup your measurement.



Configurable nasal spray actuator. Its simple and compact format makes it perfect for integration with optical instruments.



Control module for the nasal actuator

Rise-time Measurement Instrument Stig

RISE TIME – A Key Attribute of Dry-Powder Device Performance and Testing

Compendial methods of testing DPIs call for an abrupt start to the air flow through the inhaler and into the cascade impactor. This procedure is logical because real users do the same. It is recognized, of course, that this "in vitro" compendial testing cannot truly simulate real patient use. However, product developers will maximize the value of this quality control test if the drug product exits the DPI in a time frame similar to that of real users. It is the RISE TIME measurement accomplished by STIG that enables this evaluation to be made. This evaluation can lead to productive adjustment to devices still under development and can lead to better designed and controlled quality testing of registered drug products.

Experimental and computational studies of the RISE TIME in compendial testing are continuing to elucidate the relationship of device characteristics and the test system itself. These studies are critical because the device and the cascade impactor and connecting plumbing components together comprise a unique fluid mechanical system, one that does not exist in real patient use. The STIG instrument offered by FIA enables real-time experimental investigation of these important fluid flow dynamics, dynamics that can transpire in under 100 millisecond.

Now, more than ever, FIA's NEW Laminar Flow STIG enables millisecond response times, with no thermal lag, giving users unprecented accuracy in making this measurement.

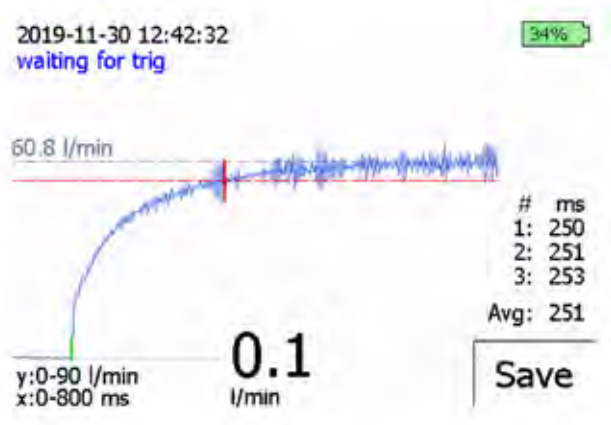


***Figure 1**. FIA's instrument, known as Stig, puts in users hands the most important measure of the time-dependent air flow start-up, namely, the rise-time.*

Key features of Stig:

- Rise-time measurement 0.1-1 s using a laminar flow element
- Average rise-time from a series of measurements
- Touch-screen which displays a graph of flow vs. time, rise-time and the final flow
- Printed records of the measurement with optional printer
- Rise-time profile saved to USB-memory
- Date and time
- Battery powered
- IQ/OQ and quality certificate for the regulated industry
- Training program and specialist support available

Trade Item Number: Rise-time Measurement Instrument Stig
Trade Item Number: Training and IQ Rise Time Equipment Stig

A training programme is offered together with the instrument, which helps the user to understand its usage and our experts will help you get started understanding how to setup your measurement.

Rise-time Measurement Instrument Stig

It is important that the rise-time is known and under control when testing inhalation devices. Russell-Graham and colleagues[1] showed that the fine particle dose increases as the rise time decreases. Previous and subsequent theoretical analyses point out reasons for this effect.[2,3] For established products, then, quality control (QC) testing requires knowing that the rise-time remains in a specified range…now possible with Stig. For GMP QC Stig can be locked to acquire and present the rise-time according to a defined and validated method.

Since patients do generate different inhalation air-flow profiles, it is also important during the development of a new drug product to adjust the prototype devices to exhibit a sensible rise-time, close to what will take place in patient use. This mindset is equally important for DPIs and for breath-actuated MDI devices.

Stig also makes possible the recording of air-flow profiles so that they can be reproduced on a breathing simulator (such as FIA's equipment F-SIG 6300) for studying nebulizers. Versatile, user-friendly, best-in-class – that is the Stig from AB FIA.



References

1. Russell-Graham, D., A. Cooper, B. Stobbs, E. McAulay, H. Bogard, V. Heith, E. Monsallier, "Further Evaluation of the Fast-Screening Impactor for Determining Fine-Particle Fraction of Dry Powder Inhalers," Drug Delivery to the Lung, December 8 to 10, 2010, Edinburgh, Scotland.
2. Roberts, D. L., M. Chiruta, "Transient Impactor Behavior during the Testing of Dry-Powder Inhalers via Compendial Methods," Drug Delivery to the Lung 18, The Aerosol Society, Edinburgh, Scotland, December 13-14, 2007.
3. Versteeg, H., P. Zhao, C. Blatchford, M. Copley, D. L. Roberts, J. P. Mitchell, "A Computational Fluid Dynamics (CFD) Model of the Start-Up Kinetics of the Andersen Cascade Impactor (ACI)," Drug Delivery to the Lung, Aerosol Society, Edinburgh, Scotland, December 9-11, 2015; pages 18-21.

Service and Training

Several of our products are pioneers and address an unmet need in the inhalable device test market. To get you started, we offer a fixed minumum price for training. For the regulated industry we also provide IQ/OQ packages. These services can be provided on site or remotely, depending on custom preference. We have a number of country-specific representatives, a number which is constantly growing.

Contact us at **i@fia.se** for more information.



Patient Realistic Inhaler Testing

Breathing Profile Generator F-sig 6300

The F-SIG 6300 by AB FIA is a breathing profile generator that is capable of replaying complex breathing patterns. Thanks to a novel multi-cylinder design, F-SIG 6300 enables generation of a number of clinically relevant patterns. F-SIG 6300 is not intended for clinical use on humans.

The areas of operation are for instance: testing of pharmaceutical inhalers and nebulizers with human breathing patterns, characterization of cigarettes (smokers profiles), rodent profiles and general respiratory research that includes very controlled breathing patterns.



The generator is easily movable and comes with a hand-held touch-panel.

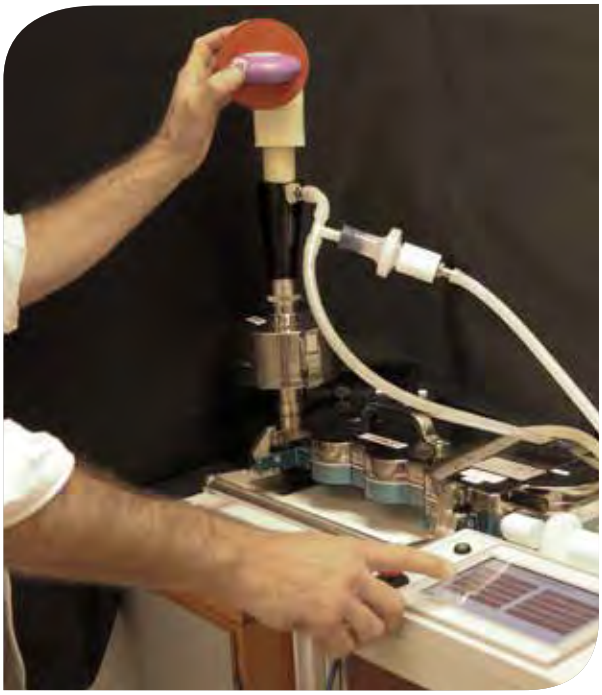


The user interfaces are simple and intuitive.

Equipment and Service

F-SIG 6300 consists of a breathing profile generator built into a box with transparent plastic covers and placed on wheels. The control system of the multi-cylinder package is configured and operated by the user through the touch panel. AB FIA can perform IQ, OQ and training. Also PQ and equivalence testing with anatomical throats if the customer has relevant target profiles. Extensive training can be offered at the customer's location.

Capacity large volume	0 – 6.3 liters
Capacity small volume	0 – 0.1 liters
Voltage	95 - 255VAC, 50 - 60Hz, 6.5A
Dimensions HxWxD	80x1036x480 mm
Dimensions Touch Panel	80x280x170 mm

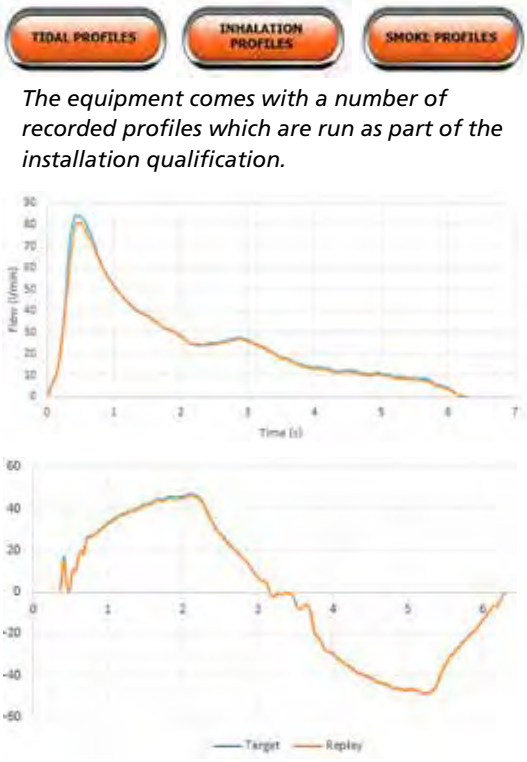


A typical application is the NGI with an anatomical throat and mixing inlet.

User-Friendly and Versatile

The F-SIG 6300 is operator-friendly and comes with a touch panel. Profiles, possibly recorded by FIA's Metivent software, are handled and modified in a spreadsheet (e.g. Excel) and the profile library is downloaded to the F-SIG 6300. The operator can thereafter, from the library of profiles, select desired profile on the panel and start the replay of the profile.

Trade Item Number: F-SIG 6300
Trade Item Number: Training and IQ F-SIG 6300

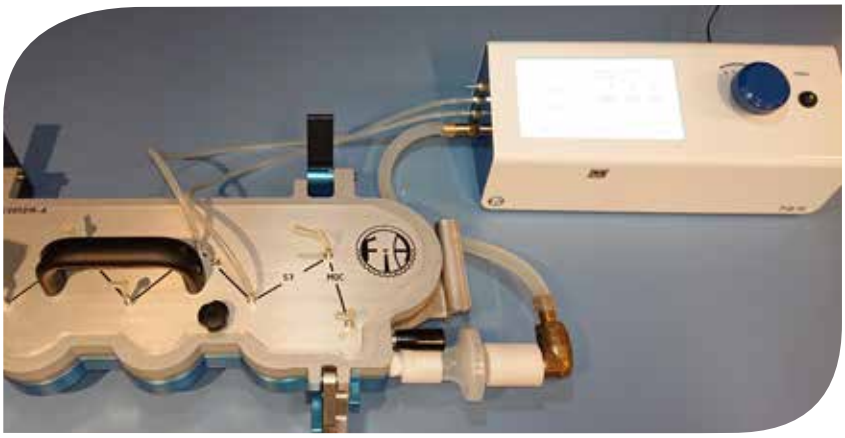


The equipment comes with a number of recorded profiles which are run as part of the installation qualification.

Breathing Patterns

- Forceful inhalation/exhalation profiles through e.g. dry powder inhalers.
- Replaying breathing patterns used in the characterization of Nebulizers as stated in e.g. USP <1601> and Ph. Eur. 2.9.44.
- Breathing patterns that comprise small air flows such as smokers' profiles or rodent nose breathing.





Adapters for Inhaler Testing

Adapters for inhaler testing are typically made of red or blue silicone. For inhaler mouthpiece adapters you need to send us your inhaler to make a mould of it at a fixed cost. For some RLD devices we have already moulds as will be evident in the quote from us. For more complex forms or functions we use 3D print or machined metallic components.
See **shop.fia.se** for more products and information.

Delivered Dose Uniformity Testing the FIA Way

Automated but Agile

The founders of AB FIA have worked with automation of the delivered dose uniformity (DDU) testing of inhalers for almost 30 years. No single system can fit every customer; factors such as flexibility, regulatory expectations and costs must be considered.

FIA's systems are customized for every project but are built on well-established modules[1] that have been implemented in bench-top, semi-automated and fully automated systems. The flexixble design allows the system to be designed for various devices, as exemplified in Figure 1A and 1B.



Figure 1A. *System configured for pDMI, with balance, canister separation, parallel shakers, and an integrated autosampler.*



Figure 1B. *Equipment for DDU of Novalizer inhalers.*

Summary

- An agile and compact system with a small foot-print but with a very high throughput
- Intuitive and simple methodology based on a fritted glass filter impinger
- Advanced solvent delivery and vacuum system
- At-line direct UV and H/UPLC analysis
- Fully automated DDU, waste and AIM and combinations thereof
- Semi-automated NGI, MSLI and ACI dosing
- Engineering and delivery according to GAMP 5 principles
- Project support from chemists and validation experts
- Well-proven software scheduler from Brooks Life Sciences

Techniques and Methodology

The most challenging part is to develop a sensitive but reproducible and robust method. Our solution for drug collection and recovery builds on a fritted glass collector, an impinger[2], inserted into a round-bottom glass flask (Figure 2).

This apparatus gives superior visibility for the analyst and has proven to be chemically compatible with most API's we have come across (other materials are available). The mouthpiece of the inhaler is inserted into the impinger's dynamic inlet which is activated during dosing to achieve a leak-tight fit (Figure 3). The impinger is connected to a highly advanced but compact vacuum system that helps attaining the critical flow condition (P3/P2 ratio with a sufficient vacuum source). During testing the system monitors the pressure drop over the device (P1). Additionally, the flow rise-time is maintained at patient realistic values by keeping the flow path distances at a minimum, something usually overlooked in other automated system designs. The volumetric air flow and P1-P3 of the dosing are recorded in the software and presented in reports. Since the air flow is sensed by a robust laminar flow element downstream of the impinger, the FIA systems minimize influences from evaporated solvents from previous work-ups.

The dose is collected on the glass frit of the impinger in the flask, which is connected to a solvent distribution system served by FIA's individually controlled dispensers. These dispensers give unsurpassed precision and accuracy, combined with a very long life-time. The forceful drive of the dispensers delivers solvents with high pressure through highly sophisticated nozzles for efficient recovery. To minimize explosion risks ATEX zones can be designed upon request. After solvents have been dispensed onto the glass frit, in portions and with different solvent composition, the solution is sucked through the filter and drug is automatically quantified by an at-line spectrophotometer or is injected into an on-board H/UPLC system. Collection of aliquots into vials is also possible for off-line analysis. Availability of several generic water- or alcohol-based analysis methods will help the customer get started with their own development. The collector station can optionally be combined with a waste station, with the benefit of dosing the device in essentially the same way as in the dose testing. The dosing is performed in a horizontal orientation, by rotating or lifting the collector of interest.

The system can also be configured for abbreviated impactor measurements (AIM).[3,4] The dosed aerosol is separated into two size-fractionating components by two standard Fast Screening Impactors (FSI) from MSP,[5] Figure 4, that are mounted above the impinger dose station (Figure 3) from which the drug product is collected on the impinger frit and worked-up in the same way as in the delivered dose example. By automatically alternating which of the two FSIs are aligned above the impinger and by the proper choice of the size-fractionating components, the recovered fine particle dose (FPD) can be either the large particle mass (LPM) or the small particle mass (SPM).



Figure 2. *Sampling apparatus for the delivered dose (principle described in reference 2).*

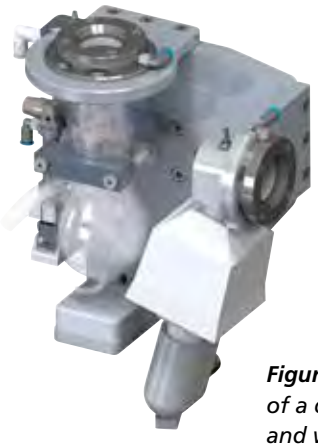


Figure 3. *An example of a combined dose and waste collection station.*



Figure 4. *Two FSIs used alternating on top of the sampling apparatus in Figure 3.*

Without human intervention, dosing can consequently be done for AIM, dose and waste on the same device throughout the full dosing regime, on all inhalers in the magazine! Such a system configuration is shown in Figure 5. Because of the efficient work-up and cleaning of the impinger, an astonishing cycle time of ONLY THREE MINUTES per dose is commonly achieved.

One additional option is to equip the system with a holder for an NGI, MSLI or Andersen impactor (ACI) for FPD, using the same dosing position as the AIM, which is removed when doing FPD. This semi-automated function brings the opportunity to dose the impactors automatically and get meta-data such as P1. The user manually replaces the NGI cup tray or impactor with a new one. Fully automated delivered dose or waste dosing can be performed with the next dosing regime or inhaler before the next impactor is dosed. Automation is the easy part; movement of the device is done by an overhead Gantry (on the right-hand side in Figure 1 and 5) or by an articulated robot arm, which collects and returns the device to a magazine. The overall storage capacity is between 60-240 inhalers depending on need and the device. Numerous DPI and pMDI actuators have been produced for customers with various levels of control and monitoring. The analytical quantification system is configured according to the customer's needs and positioned to the left of the dosing station in Figure 1 and 5. The system is surprisingly compact, with a length and height of roughly 2 m and a depth of 1-1,5 m, it fits into a standard lab room with little need for re-arrangements. The system is connected to a local or central vacuum, solvent and waste distribution system.

FIA testing systems now implement the widely recognized Sprint™ 6 Windows-based software in partnership with Brooks Life Sciences (www.brookslifesciences.com/products/sprint-6-throughput-software). This software underlies FIA's most recent success in full automation of total dose testing in a commercial GMP production facility, among others. Because of the numerous Sprint™ installations in commercial Life Science applications, FIA customers are assured of long-term, regulatory-compliant software support. The global reach of this FIA/Brooks partnership makes our combination of robust, proven hardware and software accessible to ALL major market participants.

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Figure 5. *Equipment for DDU of Novalizer inhalers. Here prepared for AIM analysis, as seen by the mounted FSIs. The empty space to the left is reserved for analytical instruments, such as direct UV or HIUPLC.*

What are the Key Factors for Success of Lab Automation?

We would stress simplicity and that the system should be intuitive to both the analyst and technician[6]. Our staff is available for technical and application support before, during and after the implementation. FIA has an outstanding track-record working according to GAMP 5 and having an integrated development team of engineers and analysts. Through FIA's membership in MVIC (www.mvic.se) we have direct access to world-leading expertise within inhaler performance testing, drug characterization, validation and regulatory advice, including writing automated analysis methods to be included in the submission file.

We have access to test laboratories where we can perform factory acceptance testing and method development with our own chemists, before delivery of the system to the customers! This service minimizes the long lead times often seen between system delivery and having an analytical method in place.

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FIA – Where the AIM is Quality Control

Successful inhalation products require rigorous quality control (QC) testing throughout the product life-cycle, including measurement of the total dose and fine particle dose (FPD) of the emitted aerosol. This long-term need for repeated measurements lends itself, in concept, to automatic equipment.

However, automation of the FPD has proven extremely challenging, successfully accomplished by only very few pharma companies and at a substantial expense. FIA is now changing that equation together with its partners.



Summary

FPD is typically the key quality measure for European regulatory authorities. LPM and SPM are the key measures for the so-called "efficient data analysis" that the US FDA is carefully considering as an adequate QC test for a registered drug product. Bringing together the engineering and quality assurance capabilities of FIA and combine that with the scientific and lab methodology support from APP and Emmace, the customer has the opportunity to implement the best AIM tools for individual customer drug products and to help customers explain to regulatory agencies the rigorous relationship of AIM to the QC necessary for product safety and efficacy. We can provide a manual lab set-up for AIM as well as a fully automated combined delivered dose and AIM equipment, engineered for each customer's inhaler and choice of cut-off.

"We think customers will be increasingly successful getting regulatory approval of the abbreviated measures of particle size, when it comes to routine quality control testing," says Kjell Fransson, managing director of AB FIA. "Our equipment will play a key role in the long-term success of these products."

Materials and Methods for AIM

"I was impressed when I first learned of FIA's proven approach to automated dosing equipment. The light bulb went on immediately – this is perfect for abbreviated impactor measurements (AIM)," says Dr. Daryl Roberts, co-inventor of the Next Generation Impactor (NGI) and now president of his own consultancy, Applied Particle Principles.

FIA's Automated Measurement System applied to the AIM concept has been worked out together with Dr. Mårten Svensson at Emmace Consulting and is based on established automation concepts.[1]

The dose aerosol is separated into two size-fractionating components by two standard Fast Screening Impactors from MSP, Figure 1, that are mounted above a fritted glass collector, Figure 2, from which drug product can manually or automatically be recovered and quantified. These components are part of a complete automated dosing and analysis station manufactured by FIA. With proper choice of the size-fractionating components, the recovered drug product can be either the FPD or the large particle mass (LPM) or the small particle mass (SPM). Here we present the scientific rationale behind the AIM concept applied to a QC situation.



Figure 1. *Two FSIs used alternating on top of the sampling apparatus in Figure 2.*



Figure 2. *Sampling apparatus for the emitted dose (principle as of reference 2); in the AIM concept the particles have passed through one of FSIs in Figure 1 before being collected in the apparatus.*

Technical Rationale for the Adequacy of Having Two Size Fractions for Quality Control of Newly Approved Inhalable Drug Products

A key element underlying the technical adequacy of an 'abbreviated' impactor measurement is the question of WHEN to introduce the abbreviated measurement. The proper time is during the late stage of development, AFTER full resolution impactor measurements have adequately characterized the size distribution of the batches released for clinical trials. These batches should be released with Full Resolution Impactor (FRI) measurements AND with properly chosen AIM, specifically having just two size fractions. That way, when and if the clinical trial results show the desired safety and efficacy, the most cost-effective analytical method for the routine quality control tests for the release of commercial product will be the abbreviated measurements with the two size fractions. The adequacy of measuring two size fractions alone to describe the safety and efficacy of an inhalable drug product was first articulated by Tougas, et al.[3]

These investigators show that the ratio of the LPM to the SPM produces a more sensitive measure of the mass median aerodynamic diameter (MMAD) than does the conventional method of grouping stages of a full-resolution impactor. The trick is to choose the definition of "large" and "small" so that the ratio of LPM to SPM ranges from approximately 0.8 to 1.2. The user is able, in fact, to make such a choice by examining the FRI measurements made during product development and is able to do so with only two size fractions (LPM and SPM must include only the "impactor-sized mass" – ISM – as discussed by Tougas, et al.). The math itself is quite straightforward for finding the appropriate split between "large" and "small," but surprisingly a graphical representation is also sufficient in many cases and can provide a more intuitive confidence in the chosen split.

Figure 3 displays a logarithmic bar chart of the mass of active drug product on each stage of an NGI for a commercial metered-dose inhaler.[4] The y-axis is the mass of active drug product on each stage (stages 1 to 7, right to left). Because of the unique logarithmic spacing of the NGI cut-points, each bar has the same width (same proportionality to the height). Therefore, the area of each bar is proportional to the mass on each stage. The proper split between "large" and "small" is therefore where the total bar area, less the area of the right-most bar (stage 1), is cut in half…and one's eye can see that this split takes place roughly at 4.5 microns.

So, the two size fractions needed for quality control testing of this particular product would be approximately at 14 microns (the cut-point of NGI stage 1) and 4.5 microns. These size fractions yield either ISM and SPM or yield LPM and SPM, depending on the method of making the measurements (ISM is equal to LPM plus SPM, so only two of these three quantities are independent). These measurements can be made with several commercially available devices, provided that the collective efficiency curves are sharp, such as in the Fast Screening Impactor offered by MSP Corporation.[5]

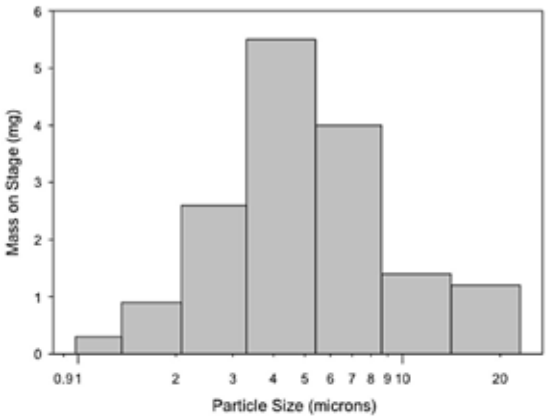

***Figure 3** – Logarithmic Bar Chart of pMDI Data Collected with the NGI Operating at 15 L/min*

Validation of any choice of two size fractionations will always need to be established, as described by Tougas et al.[3] But once accomplished, the quality control testing for the batch release of commercial product will require only two size fractions, allowing for substantial cost saving over the 20-year to 30-year life of the drug product compared to full-resolution impactor testing, and fully meeting the expected safety and efficacy requirements. Tougas and co-workers[6] have shown more recently that particle sizing with two size fractionations is far more able to detect differences in particle size distributions than is the simple measure of FPD (defined in Europe as the mass of active drug product residing in particles smaller than five micron aerodynamic diameter). The main reason for this outcome is that a large fraction of the total mass of active drug is smaller than five microns in a typical commercialized inhalable drug product. Consequently, the FPD dose test is not much different than a total dose test, and therefore the size distribution can change substantially and not be detected at all. The AIM approach is thereby shown to be more sensitive to changes in the size distribution and is therefore a better quality control test than FPD.

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Summary – Fully Automated GMP-Compliant Total Dose Testing

AB FIA has been involved in the design and construction of over 100 automated units built according to customer requirements. FIA has had the full project delivery accountability for several of these.

APPLICATIONS INCLUDE:

- **Delivered dose testing**, automated handling of device and applying dose collection principles of EP <0671> and USP <601>
- **Aerodynamic particle size distribution testing,** semi-automated concepts based on the Andersen and the NGI, possibly combined with fully automated delivered dose testing
- **Foreign particle analysis,** semi-automated concepts

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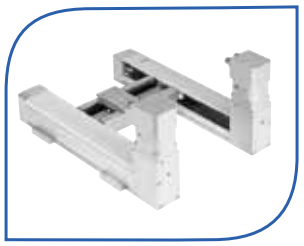

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