NOVI
AUTOMATION SYSTEMS

A NEW, ADVANCED HIGH-THROUGHPUT SYSTEM FOR AUTOMATED INHALER TESTING

Two years ago, Novi Systems Ltd set out to shake up the inhaler automation market. On December 8th, 2015, at the Drug Delivery to the Lungs 26 Conference (Edinburgh, UK), after numerous iterations and months of testing, Novi is officially launching the DecaVertus ten-way shake-and-fire testing system for pMDIs. Here, Adam Smith, Director at Novi, introduces DecaVertus, describing its single-inhaler predecessor the Vertus, and how the DecaVertus design evolved using the Vertus technology.

If you manufacture (or are planning to manufacture) inhalers, then you know that regulatory bodies around the world require them to be thoroughly characterised – both at submission for approval and continuously through production. You also know that test results can vary greatly.

> "The technologies used on the bench-top systems are the same as used on large systems, meaning that the methods used are identical on both. This gives a pathway from small-scale R&D to large-scale production that minimises the requirement for revalidation of methods every time a new system is introduced"

Regulators including the FDA and EMA require inhalers to be tested using an impactor (Andersen Cascade Impactor (ACI) or Next-Generation Impactor (NGI)) and a dose unit sampling apparatus (DUSA) as part of the regulatory filing and, ongoing during production, as part of the batch quality control process. Inhalers must be tested at beginning and end of life, meaning that waste shots must be fired in between. The regulatory bodies expect that the actuation of inhalers is representative to some degree of patient use. For pMDIs, this means that they must be shaken prior to each actuation (including waste shots), and that the airflow through the collection device is controlled.

COMMON ISSUES WITH MANUAL TESTING

pMDIs are susceptible to variations in the method used to deliver a dose. Some pMDIs are more susceptible than others, and one or more of the following parameters can be critical for any pMDI type:

- Shaking speed, angle and duration
- Firing force, speed of force application and release, duration of fire down-time
- Time between end of shaking and actuation of the inhaler into the collection device. (The impact of this depends on how quickly the suspension settles. It has been known to be just a few seconds.)
- Speed of air-flow through the collection device
- Leaks in the ACI or NGI.

This inherent variation means that it is difficult to characterise and interpret results from manual testing. When these variations are possible, the question arises: "How do I know

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whether variations in my results are due to characteristics of the formulation and inhaler, or due to the test method?" This can be a very lengthy and costly question to answer.

Another time and cost consideration of manual testing is that it takes a lot of training effort to ensure that different analysts are delivering doses in the same way, and that they are doing so consistently over long periods. An additional risk is that the constant shaking and firing of inhalers can lead to repetitive strain injury (RSI).

BENEFITS OF AUTOMATION

A principle benefit of automating the testing process is that it eliminates the variation in how the dose is delivered, including variation within the shaking and firing steps, and the duration between the end of shaking and actuating the device into the collection device. Automation also greatly reduces the analyst training requirement and the set-up time as all the parameters you need to control are handled by the system.

With automation systems such as Novi's Vertus, there is no need for a pump as the system uses your pressurised air supply to generate the air flow required. Likewise, leak testing is fully automated, so there is no need to set up a pressure meter, create a vacuum and measure the leakage.

Improvement in productivity is another important advantage. As everything is automated, the analyst can start the system and leave it until finished. Methods to perform through-life testing are available. Health and safety is also improved since the risk of an employee suffering RSI from undertaking manual testing is completely removed.

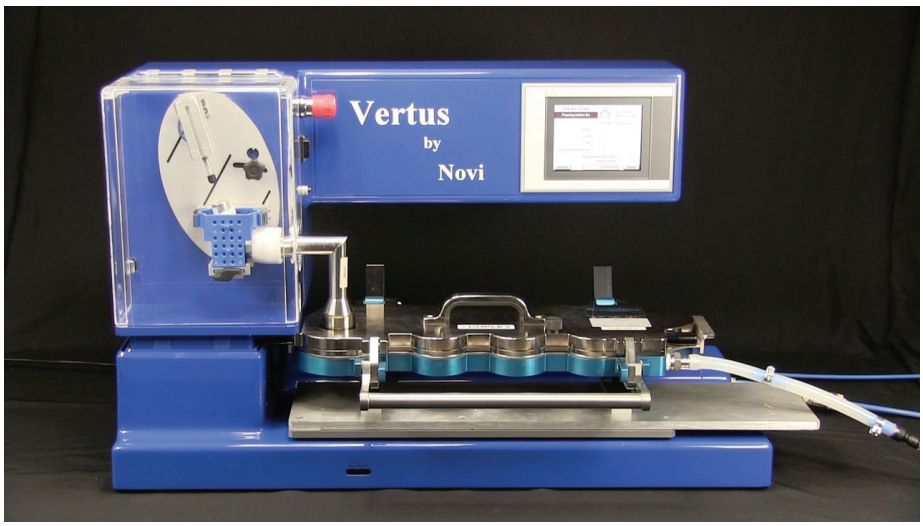


Figure 1: The Vertus can be used with a wide range of collection devices including NGI (shown here), ACI, DUSAs and waste filters.

THE VERTUS

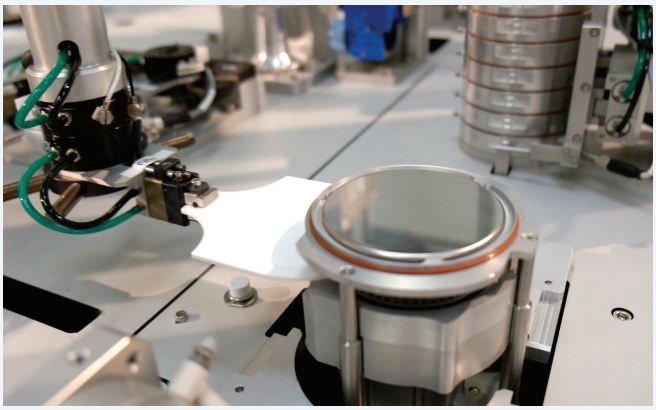
The predecessor to Novi's new ten-inhaler tester DecaVertus is the single-inhaler tester, the Vertus, shown in Figure 1. The Vertus has proven popular since its launch in 2010 and has been delivered

HISTORY OF NOVI SYSTEMS

Novi's first contact with the world of inhalers was more than 20 years ago when British multinational Fisons PLC asked it to create a system for automatically shaking an inhaler. This was the beginning of Novi's long association with the inhaler industry, which is now the entire focus of the company.

Novi's main technology platform is a fully automated ACI system called the Ictus (image below). The user loads up to thirty inhalers onto the system, presses "Go", and returns later to find rows of vials with drug recovered from ACI stages ready for HPLC analysis. Each Ictus is built according to the specification of the customer and over the years has incorporated all elements of inhaler preparation and drug recovery for ACI test methods.

Variants of Ictus have included, amongst others, MDI and DPI versions, force-actuation and breath-actuation, critical flow control, leak testing, waste shots, DUSA automation, weighing, actuator changing (to remove dirty actuators after waste shots), anti-static measures, plate coating and dose detection/verification.



Ictus fully automates ACI testing including shaking, firing, dose collection and drug recovery

INTRODUCTION OF BENCH-TOP SYSTEMS

Using the tried and trusted Ictus technology base, Novi has created a family of bench-top devices that can be used in more flexible arrangements in smaller scale R&D and production environments. These include the Flutus Air airflow generator and controller and the WaSC waste-shot collector, in addition to the Vertus shake-fire-flow control automated pMDI tester discussed in more detail in the main article.

Why does this matter?

The technologies used on the bench-top systems are the same as those used on the large systems, meaning that methods used are identical on both. This gives a pathway from small scale R&D to large-scale production that minimises the requirement for revalidation of methods every time a new system is introduced.

Figure 2: DecaVertus can shake and fire up to ten inhalers at a time.

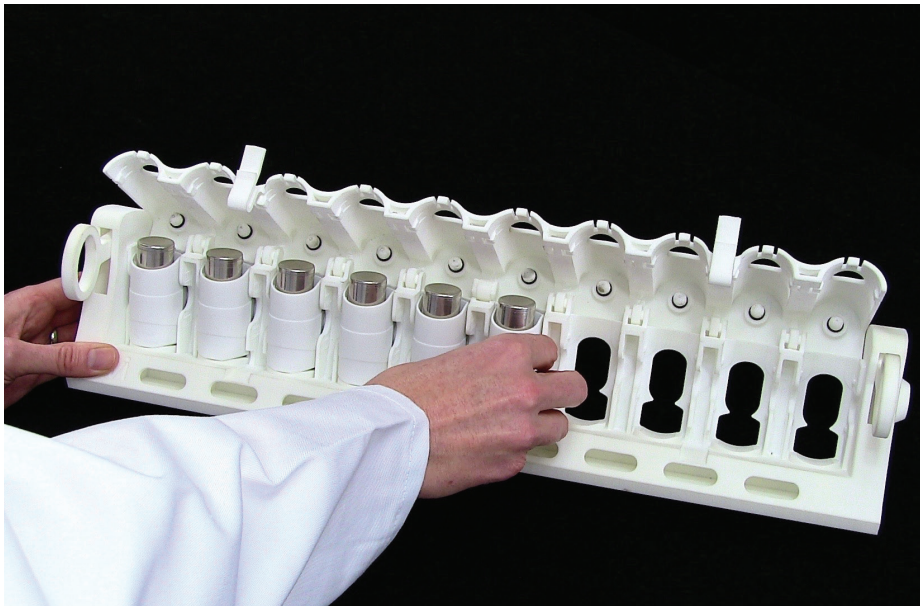


Figure 3: Loading inhalers into the DecaVertus is quick and easy.

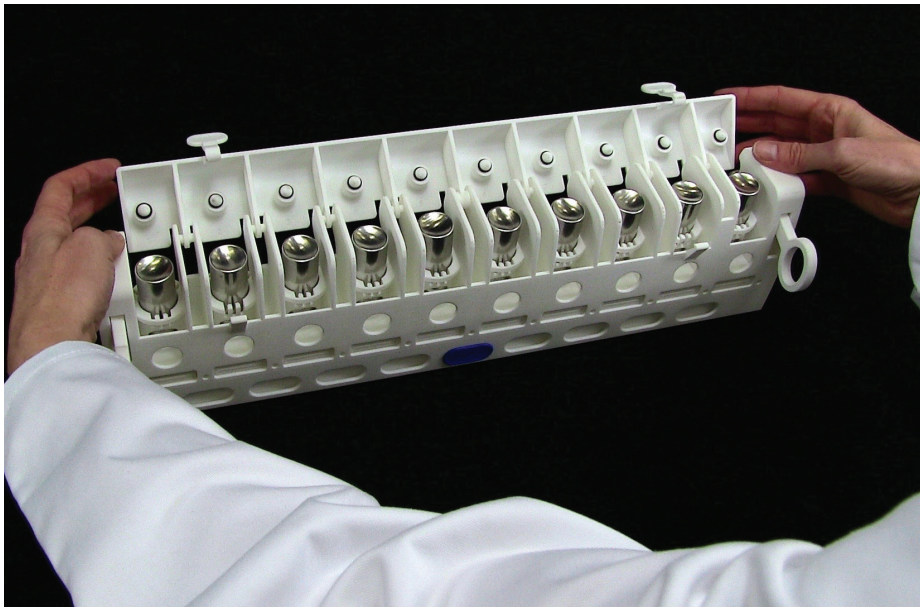


Figure 4: DecaVertus can test both cans on their own (shown here) and cans in actuators.

across the world. It automates all aspects of dose delivery of pMDIs to ACIs, NGIs, DUSAs and waste. The analyst simply fits a collection device to the system, fits an inhaler, selects the method to use and presses "Start".

Advantages

The collection device (ACI, NGI, DUSA or waste) is integrated with the system, which means that no manual intervention is required during the process. This reduces potential variation in the method (especially the critical time between end of shake and actuation) and improves productivity as the analyst does not have to be present

Airflow control is part of the system, which means that no separate pump, airflow meter or pressure meter is required and no measurements need to be recorded – these are all logged by the Vertus.

Other key features and advantages include:

- Automatic leak testing
- Log files may be copied to a USB stick or to your LAN
- Option for ER/ES compliance (e.g. 21 CFR Part 11)
- Option for printer
- Option to record temperature and RH
- Integrated touch-screen display with intuitive control. No separate PC required.
- Issues can be diagnosed and firmware updated remotely.

DECAVERTUS INTRODUCTION

Following the success of Vertus, Novi engineers set out to create a high-throughput version. Customers love the flexibility the Vertus gives in terms of the different collection devices that can be fitted to the system, but only one inhaler can be fitted at a time.

This is not so critical for impaction or dose uniformity tests because only a few shake and fire cycles are required and so the tests take a few minutes. Performing waste shots (to get from beginning-of-life (BOL) to end-of-life (EOL) for example) can take one to three hours or even more depending on the method. If you have a number of inhalers to test, this ties up the Vertus for long periods.

Given this clear need from customers to be able to waste-fire multiple inhalers at a time, the challenge to Novi engineers was to replicate the shake and fire technology of

Vertus on a system that can fit ten inhalers at a time for wasting.

Two years, three major system iterations, many mechanical and software iterations and months of testing later, the DecaVertus (see Figures 2-4) is being officially launched in December 2015.

DESIGN APPROACH

Novi engineers set out with a clear idea of what they wanted to achieve. Firstly, the DecaVertus must have identical shake and fire technology to Vertus to allow methods to be seamlessly transferred between the two. This also ensures that the range of movements, speeds, forces and timing settings that are available on Vertus are also available on DecaVertus.

Secondly, it must work with inhalers situated in their actuators just as the Vertus does; but it must also work with cans on their own just as effectively, as this is traditionally how wasting has been done.

Thirdly, the DecaVertus must give maximum assurance to the analyst that every inhaler experiences the same shake, fire and airflow on each and every shot.

Fourthly, the DecaVertus must require little cleaning, even given the quantity of drug that will go through it, and be easy to use and maintain.

ACHIEVING DECAVERTUS DESIGN OBJECTIVES

There are two cornerstones to the development approach at Novi. The first is risk management in which the risks of all aspects of the system and its functionality are listed and given scores of likelihood of occurrence, likelihood of detection and impact. This helps both to ensure that design effort is focussed on the most important areas and that every function provides a benefit that outweighs its cost to the customer.

The second is the purposeful use of iterations in all aspects of the design, both mechanical and software, in which each iteration is built and tested thoroughly and the resulting lessons are incorporated into the next iteration. In this way, early iterations can concentrate on the most important aspects of the design (as identified in the risk analysis) without unnecessary cost and delay in trying to finalise less important aspects at the beginning. This approach also ensures a body of testing throughout the development cycle and so issues are identified early on.

TESTING AND CUSTOMER TRIALS

After a year of checking functionality priorities with customers and going through the first design and test iterations of the system internally, the first fully-functional pre-production model became available in January 2015.

Three customers in two countries took delivery of this model in the first half of 2015 and significant testing has been conducted at these sites and internally at Novi. One of these customers is using the DecaVertus to test a new product in-actuator, one customer is using it to test a number of well-established products can-only, and the third is a CRO testing a wider range of inhalers in-actuator.

This means that the DecaVertus has already been subjected to a wide range of uses and experienced both light formulations (which have a low impact on the waste channels) and very heavy, hydrophilic formulations (which tend to clog waste channels extremely quickly).

This testing regime has been invaluable to the development of the DecaVertus. In collaboration with these customers, functionality has been added and performance issues have been identified and resolved.

ADVANTAGES OF DECAVERTUS

The DecaVertus has been designed from the ground up to set a new standard in pMDI dosing to waste. The primary advantages of the DecaVertus are:

- The entire inhaler is tested as it would be used by a patient (although cans can also be tested on their own)
- Gives a large range of programmable control over shaking, firing and airflow parameters
- Assurance that each inhaler is experiencing the correct shaking, firing and airflow parameters set
- Greatly reduced cleaning requirement and improved health and safety
- Flexible – any standard pMDI can be tested, in-actuator or can-only
- Independent airflow control at every channel
- Modern, slick and intuitive touch screen interface
- Fitting inhalers to the system is quick and intuitive
- Issues can be diagnosed and firmware updated remotely.

FULL COMPATIBILITY WITH THE VERTUS

The Vertus, which shakes and fires one inhaler at a time to ACI, NGI, DUSA or waste, uses identical technology to the DecaVertus to shake and fire the inhalers, and to control airflow through waste filters – which are again the same on both systems. This means that methods can be readily transferred from one system to the other.

The Vertus and DecaVertus can work alongside each other and waste shots may be conducted on either with the assurance that the results will be the same.

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CONCLUSION

After years of development, building on years of experience, many iterations, and thorough road testing by pioneer customers, the DecaVertus is officially being launched in December 2015 at DDL in Edinburgh, Scotland. If you are at DDL, be sure to visit the Novi Systems stand and take a look at the new standard in pMDI shake and fire to waste.

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new

10-WAY SHAKE AND FIRE TO WASTE

Setting the new standard in MDI wasting

Meet Novi at DDL26
Stand 148

- In-actuator and can-only wasting
- Control all aspects of the shake and fire cycle
- Less cleaning and no clogging
- Dedicated airflow control and filters on each channel
- Automatic alerts when the filters need changing
- No need for fume cupboard
- No pump required

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