Taming the Demons of OINDP Development with Quality by Design

How to Bring your Nasal or Orally Inhaled Drug Product to Market Faster

proveris SCIENTIFIC

Photo courtesy of DPT Laboratories

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Executive Summary

The global market for orally inhaled and nasal drug products (OINDPs) is projected to double between 2011 and 2016 to $44 billion – a tempting and immense opportunity for pharmaceutical companies[1].

But expertise with tablets, capsules, or liquid formulations does not necessarily translate to success with OINDP development. In fact, most OINDP projects suffer from significant delays and cost overruns. Every day that a new OINDP introduction is delayed costs between $91,000 and $200,000 or even more[2].

Four approaches pharmaceutical organizations often use for OINDP prototype testing are manual testing, self-assembled systems, outsourcing to labs, and imitation systems. But none of these methods can generate the rigorous test data required for a timely FDA approval.

Fortunately, a better method is available that can avoid unnecessary costs and delays. Quality by Design (QbD) is a more modern, scientific approach that formalizes product design, automates manual testing, and eliminates troubleshooting by trial-and-error.

Companies using QbD benefit from:

- Faster and more reliable spray product testing.
- Fewer queries and faster FDA approvals.
- More scientific, less costly solutions to any OOS problems.

The FDA is strongly encouraging all pharmaceutical organizations to use QbD by the start of 2013. But not everyone understands the concept of QbD, appreciates its value, or knows how to implement it effectively especially for OINDPs.

This white paper addresses the challenges pharmaceutical organizations face when developing OINDPs, introduces the concept of QbD, explains how QbD improves on traditional processes, and then describes Proveris by Design, a proprietary QbD process that's been field-proven in over 100 spray product development projects.

After reading this white paper, you will be in a better position to make a decision about how and when to implement QbD in your operation. At this point, you may be ready to rethink your development process and to seek help from the industry-leading OINDP development partner, Proveris Scientific.

Getting to market with an OINDP: Easier said than done

The global respiratory drug delivery market is projected to double from $22.5 billion in 2011 to $44 billion by 2016[3] and many pharmaceutical organizations are tempted to enter this lucrative market. Successful pharmaceutical organizations with expertise in single dose solid or liquid formulations, e.g. tablets, capsules, caplets, and orally ingested liquids, often assume that their expertise in these formulations will translate to success in OINDP development.

Unfortunately, this assumption is flawed. And with this flawed assumption come the demons of cost over-runs and significant delays.

Each OINDP includes a miniature "machine" or medical device packaged with the formulation to create a complete drug-delivery system. The fact that an OINDP is a complete drug-delivery system rather than a simple dosage form adds more complexity at every stage of development.

Most OINDP development projects require far more time and money than their sponsors ever expect. For example, after tracking 298 FDA approvals from 1996 through 2006, two academics from the Tufts Center for the Study of Drug Development concluded that the average OINDP:

- Takes 7+ months longer to get approved than other categories[4].
- Requires more than one FDA submission[5].
- Demands more time responding to queries from the FDA[6].

All these delays inflict significant avoidable costs. Every day that a new product introduction is delayed—or every day that an existing product is not on the market—costs a typical pharmaceutical organization between $91,000[7] and $200,000[8] or higher, thereby challenging the feasibility of the project entirely.

Instead of moving forward toward a product, ambiguity injects a demon into your operation that will fight relentlessly to keep an OINDP from getting to market.

Traditional approaches and why they fail

Pharma companies traditionally use one of the following approaches to test their OINDP prototypes and achieve FDA approval:

- Completely manual testing.
- Self-assembled systems.
- Outsourcing to third-party labs.
- Imitation systems.

Unfortunately, these approaches most often lead not to approvals, but to a long, dizzying battle against a demon that will run your team in circles. The rest of this section explains why.

Traditional approaches are resource intensive, costly, and unreliable

Completely manual testing

This century-old manual method of testing spray prototypes uses thin-layer chromatography (TLC) plates and requires a small army of technicians to measure them.

Yet, as shown in **Figure 1** below, no two people actuate a spray product exactly the same. Manual actuation of prototypes introduces a vast range of variability that makes test results unreliable and unrepeatable. Thus, completely manual testing cannot generate data suitable for timely FDA approval and routine release testing.

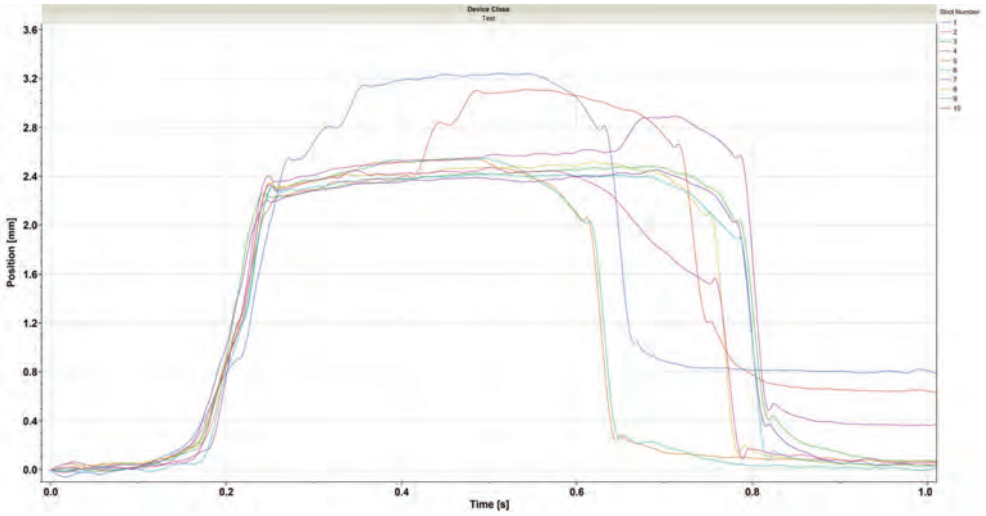

Figure 1 Example of variability in manual actuation of an OINDP – shots from multiple people.

Source: Proveris Scientific

Self-assembled systems

Well-meaning team members often volunteer to create a homegrown test rig, thinking, "How hard can that be?" Like most things in life, the devil is in the details – in this case, making a system that can easily produce clear, accurate data.

First-time system builders inevitably make mistakes, miss nuances, waste time and materials, and disappear into a multi-year instrument creation project. After all, inventing analytical instruments is not the core competency of most drug development firms. Even more important, how will these results be seen by the FDA when it reviews a submission or makes an on-site visit to the QC lab and sees a homegrown system? They might ask, "What will the next test system look like?"

Outsourcing to third-party labs

A handful of consulting firms advertise services such as analyst training, analytical trouble¬shooting, automation of device testing, and test method development. Contract researchers are generally fine for routine testing, where all the parameters are already known in advance. But very few are prepared to do the experimental design work required to create and implement a valid spray test suite. Despite their limited skill sets, contract research firms bill a staggering amount: as much as 10x the cost of your entire project team for up to 6 months.

Imitation systems

Similarly, imitation systems are available from certain vendors that are no better integrated than a self-assembled system. These systems are characterized by:

- Components rigged together without any quality-based procedures
- Prototype spray bottles actuated with little precision
- Plume geometry and spray patterns processed manually with image-analysis software
- Test data stored in a spreadsheet with no 21 CFR Part 11 compliance.

Among other drawbacks, traditional threshold-based image analysis requires manual adjustment of the algorithm whenever the camera is moved, takes up to 100 times as long as automated machine vision, and generates less reliable results with little traceability.

All these traditional approaches are resource intensive, costly, and unreliable. The truth is that any of these traditional approaches can produce numbers, but will they tame the demons of cost over-runs and significant delays?

What is Quality by Design and why should you care?

Quality by Design is a systematic approach that embeds quality within the process

Quality by Design (QbD) is a modern, scientific approach that formalizes product design, automates manual testing, and streamlines troubleshooting. A QbD approach is currently the most effective way to tame the demons of cost overruns and unproductive delays during OINDP development.

Conventional process development is often an empirical approach that relies on frequent end product testing and inspection to determine quality. The processes that create the end product are seen as fixed, any changes are disallowed, and the focus is on process reproducibility. This approach ignores most real-world variability in materials and processes along the way. As a result, any future efforts to discover the root cause of an OOS event either devolve into a trial-and-error hunt for clues, or result in a late-stage attempt at QbD for a product that is already being manufactured.

QbD on the other hand, is a systematic approach that ensures quality by developing a thorough understanding of the sensitivity of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the process. As a result, any quality issue can be deciphered and its root cause quickly identified.

QbD calls for identifying all critical formulation attributes and process parameters, and determining the extent to which any variation can impact the quality of the end product. The more information on the sensitivity – or insensitivity – of a process on a product's quality, safety or efficacy, the more business flexibility QbD provides[9].

The Benefits of QbD

Companies using QbD benefit from:

- Simpler and more reproducible spray product testing
- Fewer queries and faster FDA approvals
- Streamlined scientific, solutions to any OOS problems.

A high-ranking official at the FDA recently stated that all ANDA applications must use QbD by the start of 2013. At that point, deficiency letters will begin to explicitly cite the lack of QbD[10]. In exchange for successfully employing QbD, the FDA will reduce the amount of regulatory oversight of a company. Additionally, the FDA's own internal analysis has shown that QbD-based applications are processed 63% faster than traditional submissions[11].

Despite clear benefits to using QbD, many companies don't seem to appreciate its value and know how to implement QbD effectively. The rest of this section describes QbD in more detail.

Key Components of Quality by Design

The systematic approach of QbD contains four key components, which are performed as a series of steps:

1. **Defining the goal.**
2. **Discovering the Design Space.**
3. **Understanding the Control Space.**
4. **Targeting the Operating Space.**

After defining the product goals, each following step creates a progressively more exclusive set of statistically defined parameters that can be visualized as a multidimensional "space."

1. Defining the Goal

In this step, your team identifies all the critical quality attributes ("CQA") for your OINDP. CQAs and process control variables can be determined using:

- Literature directing the CQA's Design Space.
- Experimental results that discover variables that can be controlled.

In the case of an OINDP, actuation matters. Inhaler and spray devices are miniature "machines" or medical devices operated by human hands. Regulators provide the following guidance:

- Drug products administered by devices should be tested in a manner that mimics the intended use.
- Automation is the preferred method of testing[12].

Therefore a goal for an OINDP development project using QbD could be, "How do we mimic human actuation with an automated system?"

Literature from the FDA and major manufacturers has established that both actuation parameters and formulation properties influence critical quality attributes. Four CQAs controlled by actuation are:

- Shot weight;
- Spray pattern;
- Droplet size; and
- Plume geometry.

Defining the goals for a product forces a development team to deeply study and understand its processes and CQA's. This understanding ultimately eliminates the multi-year process of endless corrective action/preventive action ("CAPA") and out of specification/tolerance ("OOS/OOT") observations.

2. Discovering the Design Space

The key to understanding your processes is in discovering and defining the design space for the product. Critical formulation attributes and process parameters are identified by determining the extent to which any variation can affect the quality of the OINDP[13]. The ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality."

By accurately defining a design space, your team anticipates the issues, and plans for controlling the manufacturing process – rather than reacting to OOS/OOT observations on poorly defined specifications. Actual measurements or literature guidance are used to define the extremes of the parameter sets to be refined. Since actuation parameters are known to influence the dose delivery and spray characteristics, the design space for an OINDP should include measurements of hand actuation and the effect on outputs, as shown in **Figure 2**, below for example.

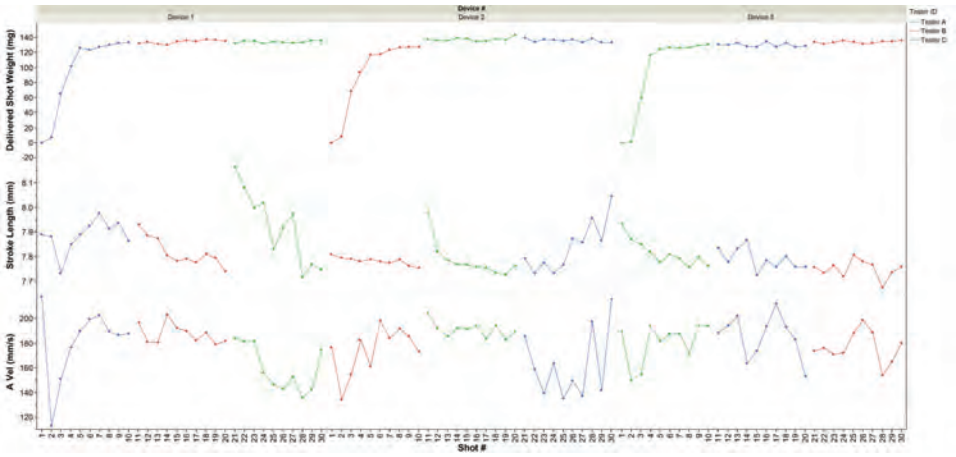

Figure 2 Example design space for a nasal spray product showing measured shot weight performance with corresponding stroke length and actuation velocity levels from consecutive actuations collected from three devices and three testers. The outer bounds of this data (i.e. the maximum and minimum value for each parameter excluding priming shots) defines the design space. Source: Proveris Scientific.

It is also useful to assess formulation choices along with the device selection. A matrix of devices, formulation choices, and actuation parameters can serve as the basis for development across a range of nasal or MDI products. With this design space envelope defined, you are ready to understand the sensitivity of your CQAs to changes in process variables, e.g. formulation, actuator design, pump or valve design, actuation, and so on.

Most importantly, if a manufacturer understands the product control space, method changes can then be handled by reporting them to the FDA in an annual report. The guidance is clear that the manufacturer must know if "the proposed change would present a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product." The simplest way to obtain this knowledge is through QbD during the development process. A QbD control space provides a scientific basis to identify any non-critical variations in input materials or processes that can be safely accommodated within the stated goals for the product[14].

3. Understanding the Control Space

Using the design space as a starting point, a set of control space scenarios can be defined and executed. The results of these experiments enable your team to understand your processes in a way that shields product quality from the ordinary variability in the production process. This disciplined approach finally tames all the demons that otherwise haunt complex production processes.

Figure 3, below illustrates the difference between a test product (blue symbols) and a reference product viewed from a control space scenario analysis. Clearly, there are significant differences between the products, especially with regard to stroke length. Additionally, the reference product data are tightly clustered, representing very consistent performance (i.e. consistent performance is normally the result of a consistent manufacturing process). The test product data are dispersed widely, representing very low consistency (i.e. low manufacturing process control). Clearly the demon is on the loose!! If a QbD study had been performed on the reference product to begin the process, a better matching test product design could have been selected and much wasted effort could have been eliminated.

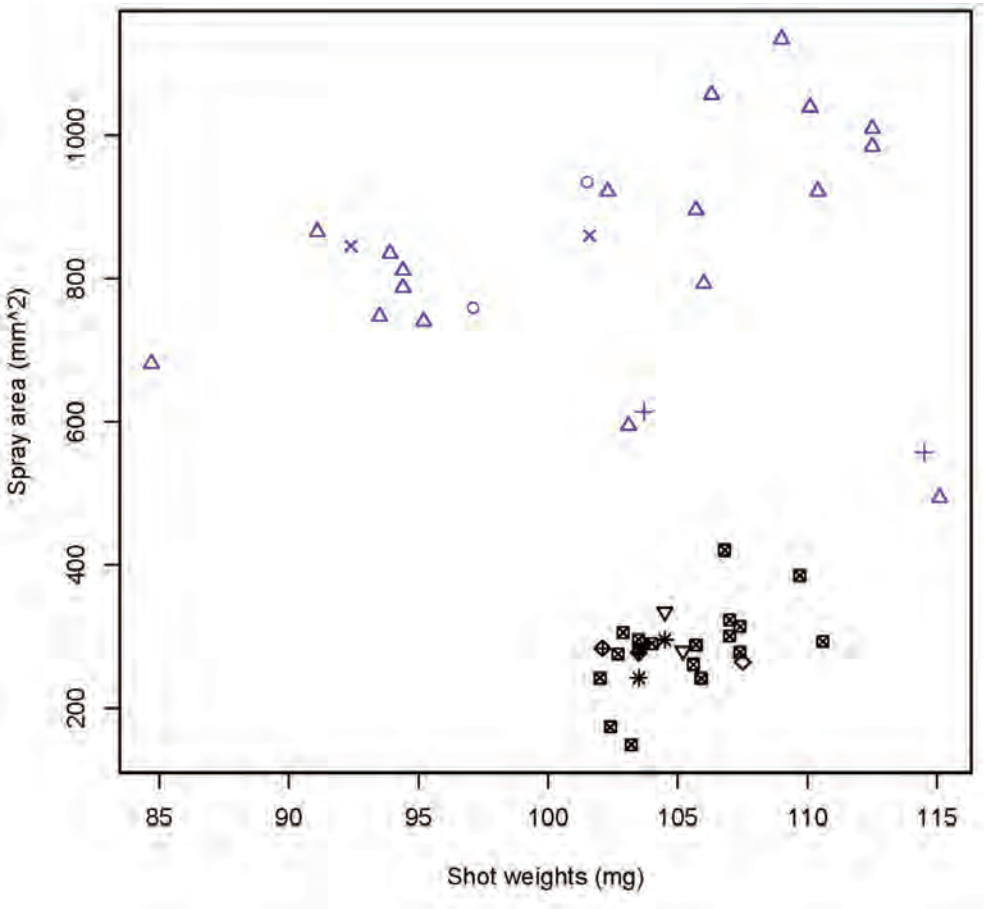

Figure 3 Example of two non-equivalent products that were developed independently, and only prior to filing was a QbD study undertaken. This represents a multimillion dollar mistake. Test results in blue and reference results in black collected at different actuation velocities.

4. Targeting the Operating Space

The operating space is the statistically best set of parameters that enable you to accommodate any natural variability in processes and formulations.

For generic products, the operating space should be within the control space and should allow the reference product to be tested with the same set of actuation parameters.

For innovator products, the operating space should be within the design space and compliant with FDA and EMEA guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product and make it difficult to reproduce.

Figure 4 below shows the through life performance of a reference nasal spray product using the operating space actuation parameters derived using a QbD approach. Notice how the natural variation in the shot weight performance is clearly identified through the use of automation.

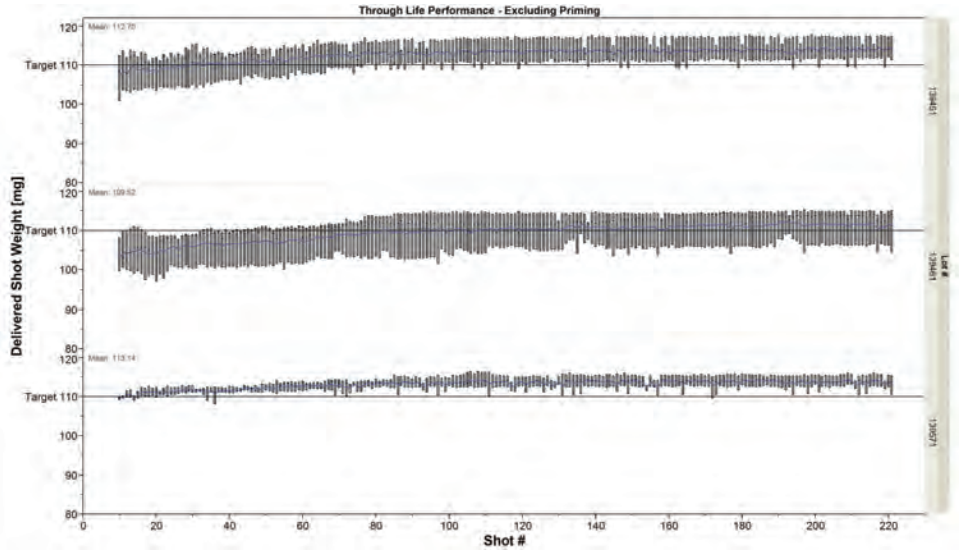

Figure 4 Operating Space confirmation of through-life shot weight performance for 3 devices from 3 lots of a Reference nasal spray product. Data is shown in box plot and includes the target shot weight of 110 mg. Data count was 660 shot weights per lot (1,980 total data points) and was collected in a completely automated manner (machine run time was time approx. 16 hours, unattended).

Obstacles to Implementing QbD

Despite the many financial and operational benefits of QbD, and even with the looming FDA deadline and enticements, not all pharmas involved in spray product development have yet adopted this approach. Some of the most common barriers to adoption include[15]:

- Insufficient understanding of the process and its benefits
- Organizational resistance to change
- Denial of the need ("Our process is under control")
- Competing priorities
- Lack of resources and expertise in QbD.

Weighed against the tremendous financial gain, faster time to approval, process improvements, and quality boost generated by a successful implementation of QbD, these obstacles seem rather insignificant. One way to overcome these objections is to join forces with a knowledgeable partner who can help your team begin to benefit from QbD with minimal disruption.

Photo courtesy of DPT Laboratories

Finding the Right Partner

A knowledgeable partner can synthesize multiple sources of information with their expert opinions. The right partner can also access a database with multiple product control spaces to yield deep, pragmatic insights into any issues with your product prototype. The right partner's familiarity with FDA submission guidelines can help you cut your opportunity losses and get moving toward your goal of launching your valuable OINDP. You should consider the following questions when evaluating prospective partners:

- How do you know when you've located a testing partner who can achieve all this? The key attributes to look for are listed in Table 1, below.
- Are you ready to tame the demons?
- Is there a vital partner missing from your team?
- Can you visualize how the right partner can help you succeed?

The right partner can help you reach your goals for a reasonable cost

ATTRIBUTES TO LOOK FOR IN AN OINDP PARTNER
Maintains a full-featured automated testing lab
Provides a full range of automated testing hardware, software, and professional services
Experienced at creating design spaces and test suites using Quality by Design approach
Generates unique and innovative intellectual property
Maintains strong financial stability
Has a track record of success with experience on scores of OINDP development projects
Contributes to the field through ongoing scientific research and publications

Table 1 Attributes of an ideal OINDP partner.

How does Proveris use QbD to help an OINDP development project succeed?

The patented Proveris by Design™ process yields better spray and aerosol drug products that reach patients faster than ever before. Proveris by Design has helped dramatically reduce development time – 12 to 18 months is typical in over 100 projects to date – and saved millions of dollars in development costs.

What is Proveris by Design?

Proveris by Design is a patented, step-by-step testing protocol that takes pharmaceutical spray and aerosol drug developers from pump selection to release testing for the life of an OINDP. The process employs Proveris' deep understanding of regulatory guidelines and vast experience helping global drug developers improve the quality of their regulatory submission packages.

The Proveris by Design process leverages QbD principles by:

- Establishing an optimized range of actuation parameters that can be used to perform spray and aerosol tests for the life of the product
- Reliably determining the length of a spray drug's conical region and the plume angle, using precise machine vision
- Providing a scientific basis for distances employed for spray pattern and droplet/particle size distribution by laser diffraction tests
- Measuring how representative people in the drug product's age and gender range use the product. These measurements are used as the basis for programming the actuation systems to ensure efficacy and patient safety as recommended by the FDA.
- Providing a solid, scientific basis for method establishment and assisting with regulatory requirement compliance.

Proveris by Design has been applied to more than 100 different development projects. The methods developed have withstood the rigors of method transfer, intermediate precision, and robustness. The high success rate of Proveris by Design-developed methods is testimony to the value of using high-quality instrumentation that relies on NIST and process control-derived benchmarks.

The success of applying QbD approaches to analytical method development was recently revealed in a paper by GlaxoSmithKline (GSK). The author cited six full analytical methods that were submitted with full QbD development data and accepted by the regulators with no questions, a feat unparalleled by any pharma company[16].

Using Proveris by Design can help you tame the demons and get your OINDP development project moving in the right direction toward regulatory approval.

Proveris by Design™ is a patented process that can help dramatically reduce OINDP development time

Conclusions

This white paper addresses the challenges pharmaceutical companies face when developing OINDPs, introduces the concept of QbD, explains how QbD improves on traditional processes, and introduces Proveris by Design, a proprietary QbD process that's been field-proven in over 100 spray product development projects. After reading this white paper you should be equipped with information to help you better decide how and when to implement QbD into your operation.

As pharmaceutical companies enter the lucrative OINDP market, they mistakenly assume their expertise with tablets, capsules, or liquid formulations will translate to success with OINDP development.

This assumption yields disappointing results. In fact, most OINDP projects suffer from significant delays and cost overruns. Every day that a new product introduction is delayed costs between $91,000 and $200,000... or even more.

Fortunately, these costs and delays can be avoided by using Quality by Design (QbD), a more modern, scientific approach that formalizes product design, automates manual testing, and eliminates troubleshooting by trial-and-error.

The FDA is strongly encouraging all pharmas to use QbD by the start of 2013. But not everyone understands the concept of QbD, appreciates its value, or knows how to implement it effectively.

After considering the benefits QbD can bring to your OINDP development project, you may be ready to seek help from the industry-leading OINDP development partner, Proveris Scientific.

For more information on how Proveris can help with your OINDP development, including gaining timely FDA approval and dealing quickly with any OOS events, call +1 508 460-8822, email **info@proveris.com**, or visit **www.proveris.com**.

Are you ready to rethink your spray product development process with help from Proveris?

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Proveris Patent and Trademark Information

Proveris provides the following information as a guide. Please speak with your legal counsel regarding any particular questions you may have related to Proveris's patents.

One or more patents have been issued in the following countries covering Proveris's SprayVIEW and or the use of Proveris's SprayVIEW: USA, Japan, Taiwan, Canada, Belgium, Denmark, France, Germany, Great Britain, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland-EP/CH

One of more patents have been issued in the following countries covering Proveris's actuators: USA, Taiwan, India, Belgium, Denmark, France, Germany, Great Britain, Ireland, Spain, Sweden, Switzerland-EP/CH

About Proveris Scientific

Proveris Accelerates Success

Proveris Scientific streamlines complex development and release testing processes of pharmaceutical OINDPs by providing complete solutions that reduce overall lab testing time by at least 100-fold compared to manual analysis. Proveris has deployed its complete solutions globally at 100+ pharmaceutical development and manufacturing sites. Proveris's complete solutions are used by the FDA and the pharmaceutical industry to set testing standards and generate robust data for their applications.

Proveris is certified to ISO 9001:2008 by TUV Rheinland of North America and has 17 patents on its technology issued in United States, Europe and Asia.

For more information please visit **www.proveris.com**
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