



How to Get off the Merry-Go-Round and Get Your Spray or Aerosol Product to Market

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7 Questions to Ask
to Accelerate Spray or
Aerosol Product Development



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The Merry-Go-Round

Many pharmaceutical companies are considering creating an orally inhaled or nasal drug product (“OINDP”) or already have one under development. The market for these products is exploding: One report projected the global respiratory drug delivery market will double from \$22.5 billion in 2011 to \$44 billion by 2016.¹

Most OINDP development projects require far more time and money than any pharma company expects, because companies become stuck on a merry-go-round of out of specification (OOS) or out of tolerance (OOT) disruptions. These projects routinely take longer to gain FDA approval than other drug product categories, and 2 out of 3 submissions are sent back for more work (usually additional testing)—round and round the development goes.²

Most spray products consume far more time, money, and resources than any company ever expects.

Successful OINDP development—getting off the merry-go-round—requires three critical elements:

- Adequate in-house expertise;
- An automated system with many literature references; and
- The right partner to help transform test data into useful knowledge.

Without these elements, developing an OINDP can feel like riding a merry-go-round: While the lights flash and the horses bob, the clock is ticking, dollars are flying out the door, and the window of opportunity is closing.

7 Questions to Ask to Accelerate Spray or Aerosol Product Development

Here are 7 vital questions that every manager needs to ask to get off the merry-go-round and help ensure successful spray product development:

1. Are you experiencing delays in your program?
2. Do you know how winning companies succeed with OINDPs?
3. What are your goals, including FDA approval?
4. Are you working with a knowledgeable partner to help you transform raw data into useful knowledge?
5. Have you considered the risks of a self-assembled test rig or non-integrated equipment, and the benefits of an integrated test system?
6. Do you understand how Quality by Design can minimize OOS or OOT disruptions?
7. Can you meet the FDA guidance for Quality by Design?

After considering these questions, you will have a better understanding of the many challenges in developing a successful spray product. At this point, you may be ready to rethink your development process and to seek help from an industry-leading OINDP development partner, Proveris Scientific.

Question #1:

Are you experiencing delays in your program?

If so, you are not alone. In fact, most pharmaceutical manufacturers that undertake their first OINDP project seriously underestimate the complexity of these projects.

For example, at a 2009 IPAC-RS session, 135 industry professionals were surveyed on their experience with these products. In this well-seasoned group—more than half had 10+ years in the industry—almost half had experienced making a necessary product change after approval, and 78% of those professionals reported that re-testing and re-approval took more than a year—a costly ride on the merry-go-round.³

The key reason for these delays is that an OINDP is far more complex than any solid or injectable drug. Each OINDP includes a miniature “machine” or device packaged with the formulation to create a complete drug delivery system.

As shown in [Figure 1](#), a nasal device is a complete drug delivery system with many items: formulation, bottle, inside coating, pump with numerous moving parts, removable cap, and so on.

To gain quick FDA approval, all possible interactions between all of these components must be analyzed and rigorously tested.

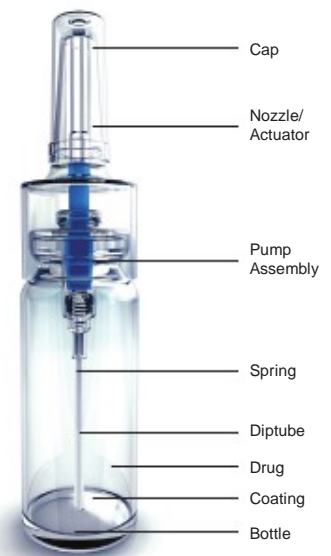
The fact that an OINDP is a complete drug delivery system rather than a simple dosage form adds more complexity at every stage of development.

For example, to dispense a spray dosage involves a chain of physical events with wide variations. Not everyone squeezes a spray bottle or presses the “puffer” button in the same manner.

Therefore, it’s not reliable to ask 20-year-olds to test a prototype spray bottle intended for senior citizens. Instead, the coordinated hand movements required to dispense one drug dose must be mapped and tested against the appropriate segment of the human population.

If your company has never developed an orally inhaled or nasal spray drug product before, can you be sure that your team understands the full complexity of the project? If not, is it any wonder you are riding the merry-go-round and experiencing delays?

FIGURE 1: Parts of a nasal spray product



Graphic used with permission from Aptar Pharma.

Not many companies have any experience developing a successful OINDP.

Question #2:

Do you know how winning companies succeed with OINDPs?

While the potential for OINDPs is huge, according to the FDA's Orange Book, only 75 or so products are on the market today. That means not many pharmas have experience developing a successful OINDP.

To ensure success, companies assemble large teams for spray product development. The majority of manufacturers for approved, branded OINDPs have device development groups of 40+ scientists and engineers, plus more people on their drug formulation teams.

To successfully develop an OINDP requires profound expertise in numerous domains, as listed in [Table 1](#). What's more, all of these skills may be in high demand and short supply, driving up labor costs.

Are you sure you have enough expertise in all these areas in-house?

TABLE 1: SKILLS REQUIRED FOR SUCCESSFUL OINDP DEVELOPMENT

SKILL OR KNOWLEDGE DOMAIN	KEY CHALLENGE
Ergonomics	To design a simple and convenient product for users
Experimental design engineering	To create a thorough and repeatable set of experiments that test all interactions between all items in the system
High-volume injection molding	To design and produce high-quality molded parts
Industrial design	To design an appealing and functional product
Machine vision	To create an automated system for precise, high-speed reading of spray test results
Materials science	To ensure that all chosen materials fulfill their intended purpose and do not interact in an unforeseen way
Mechanical engineering	To design and assemble an automated system for highly precise actuation and spray pattern analysis
Spray analysis	To quickly and accurately analyze test spray patterns
Statistical data storage	To ensure the integrity and availability of all test data
Validation engineering	To ensure the product can be tested in a reproducible way and that it remains within spec throughout the manufacturing process

Question #3:

What are your goals, including FDA approval?

Are you on schedule with your OINDP development?

Are you planning to develop more than one product in this category?

Are you confident that every product will hit all its milestones?

Does your team fully understand the control space such that you can implement a robust technology to help solve any production issues quickly?

To truly succeed in this category, an OINDP must:

- Achieve rapid FDA approval;
- Generate a large and profitable volume of sales; and
- Respond quickly to any OOS (out of specification) or OOT (out of tolerance) events.

Any delays in meeting any of these challenges can dramatically alter the profitability—and even the feasibility—of the product.

Bogged down in testing

Yet, OINDPs often get bogged down in development, testing, or regulatory approvals.

After tracking 298 FDA approvals of a variety of drug dosage forms 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 drug categories;²
- Requires more than one FDA submission;⁴ and
- Demands more time responding to queries from the FDA.⁵

Many pharma companies spend enormous periods of time—sometimes years—on the merry-go-round seeking valid test data for their FDA submissions. They may be testing spray prototypes using thin-layer chromatography (TLC) plates. Only a small army, using this 19th century manual method, can generate data suitable for timely FDA approval and routine release testing.

Some large QC teams have 16 people performing TLC for release testing, something that two automated systems could do.

Without a modern, rigorous testing protocol in-house, every time a prototype fails an incoming inspection, the team must go back to the pump manufacturer with its questions, and the merry-go-round turns.

Fluticasone
has a
demonstrated
opportunity
cost of
\$200,000
per day.

Can you afford these delays?

Calculate the impact that each unnecessary delay has on your expected revenue. For example, according to the 2011 Hi-Tech Pharmacal annual report, the Fluticasone Propionate Nasal Spray from Hi-Tech Pharmacal generated \$74 million in sales in 2011. Those sales equate to over \$200,000 a day.⁶ Other experts peg the “opportunity cost” for a new drug at \$91,325⁷ to \$107,000 a day.⁸

Have you calculated how any delays will diminish your projected profits or even push the break-even point past where the product is feasible? It is clear that for OINDP products, the opportunity cost for riding on the merry-go-round is very high.

Question #4:

Are you working with a knowledgeable partner to help transform raw data into useful knowledge?

Once your company is riding the merry-go-round—with manual, self-assembled test rigs, or non-integrated equipment testing that generates a stream of non-repeatable results—you have only a few options.

Option #1: Stay on the merry-go-round

This option is clearly unacceptable, since it wastes time and money, and does not further any strategic goals. The sooner you get off the carousel and back on solid ground, less money will be wasted and your window of opportunity will be restored.

Option #2: Outsource your testing

A handful of consulting firms offer OINDP testing as an outsourced service. These firms advertise services such as analyst training, analytical troubleshooting, automation of device testing, and test method development.

Contract researchers are generally fine for routine testing, where all the parameters are already known, but very few are prepared to do the thorough experimental design work that is required to create and implement a valid OINDP test suite. There are companies, like Next Breath, LLC, Melbourn Intertek, and Catalent, that work closely with Proveris and can streamline the implementation of spray analysis in your company.

Avoid buying a ticket for a more expensive merry-go-round: You can pay huge fees without making any progress toward your goals.

Option #3: Find a partner experienced in testing OINDPs

A cost-effective option is to find a knowledgeable partner who truly understands automated testing of OINDPs. The right partner can help you get off the merry-go-round and moving toward your goal, on time.

An ideal partner can help you organize raw test data into coherent information, and transmute information into useful knowledge with actionable insights that further your FDA approval process and streamline manufacturing.

These distinctions between data, information, and knowledge date back at least 40 years to the first use of the term “knowledge management.”⁹ The precise meaning of these terms has been debated ever since. Some of the relevant definitions are shown in [Table 2](#).

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

TABLE 2: DATA, INFORMATION, AND KNOWLEDGE IN OINDP TESTING

	DATA	INFORMATION	KNOWLEDGE
Definition	Discrete facts or observations with no context or meaning ¹⁰ , merely raw facts ⁸ , know-nothing ¹¹	Data organized or processed to be useful, meaningful and valuable ⁹ , the difference that makes a difference ¹² , data + context, know-what ¹⁰	A synthesis of multiple sources of information over time ⁹ , information + expert opinion + skills + rules + values + experience ⁹ , know-how ¹⁰
Example in spray product testing	Raw spray test results in CRO reports	Test results organized into a coherent control space or sensitivity map, reports formatted in an approved format enabling deduction.	Understanding root causes with a spray prototype, insights that direct any further testing and analysis, familiarity with FDA submission guidelines

A knowledgeable partner can synthesize multiple sources of information with their expert opinions, skills, and access to a database with multiple product control spaces to yield deep, pragmatic insights into any issues with your product prototype. This partner's familiarity with FDA submission guidelines can help you cut your opportunity cost losses and get back on firm ground, moving towards your goal of launching your valuable OINDP.

- How do you know when you've located a testing partner who can help you achieve your goals? Look for the key attributes listed in [Table 3](#).
- Are you ready to get off the merry-go-round?
- Is there a vital partner missing from your team?
- Can you visualize how the right partner can help you succeed?

TABLE 3: WHAT AN IDEAL OINDP TESTING PARTNER SHOULD OFFER

ATTRIBUTES TO LOOK FOR
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

Question #5:

Have you considered the risks of a self-assembled test rig or non-integrated equipment, and the benefits of an integrated test system?

You may be experiencing the risks of using a spray or aerosol test rig assembled in-house. Well-meaning team members often volunteer to create a homegrown test rig, thinking, "How hard can it be?"

Like most things in life, it's harder than it looks. First-time system builders inevitably make mistakes, miss nuances, waste time and materials, and step into pitfalls. After all, inventing analytical instruments is not an expected core competency for most drug development ventures.

Similarly, non-integrated equipment may be no better than a self-assembled test rig.

Such equipment usually includes these characteristics:

- Manufactured by a non-ISO certified vendor that has not committed to a quality regime
- Components from numerous suppliers rigged together without software or electromechanical integration
- Actuation machines lacking process control loops that make it hard to establish rugged and reliable methods.
- Plume geometry and spray patterns processed manually with image-analysis software or measured in a non-compendial manner
- Test data stored in a spreadsheet with no 21 CFR Part 11 compliance.

These approaches can produce numbers, but do they stop the merry-go-round?

For example, it has proven very difficult to reproduce a specific spray dose with manual actuation.¹³ Traditional threshold-based image analysis requires manual processing, takes up to 100 times as long as automated machine vision, and generates less reliable results with no traceability.

Many other questions spring up around any self-assembled test rig or non-integrated equipment:

- How precisely calibrated is the equipment?
- How valid are the test procedures?
- Are any components automatically verified?
- How accurate is the analysis?
- How long does the procedure take from data to decision?
- How repeatable are the results?
- What prevents any procedural mistakes?
- How carefully are the results organized, stored, and retrieved?
- Most important, what will the FDA think of these results when it reviews a submission or makes an on-site visit to the QC lab?

Since an OINDP is a complex drug delivery system with many variables, doesn't it make sense to get off the merry-go-round and test your OINDP with an integrated system that provides reliable, automated results in an approved format that accounts for all of these variables?

Table 4 lists the items that an integrated OINDP test system should include.

TABLE 4: WHAT AN INTEGRATED OINDP TEST SYSTEM SHOULD INCLUDE

ATTRIBUTES TO LOOK FOR
All required test equipment, validated, calibrated, and ready to use per ISO 9001:2008
A complete IT solution with an integrated 21 CFR Part 11-compliance enabling database, and automated workflow
System validation at instrument manufacturer's internal OINDP test laboratory
Demonstrated intermediate precision and robustness with real pharmaceutical products
Efficient, professional services to develop experimental design and test methods
Effective training, documentation, and knowledge transfer per ISO 9001:2008 SOPs

How accurate
are any results
from a self-
assembled
test rig?

Without QbD,
your team
will have to
use trial-
and-error
to resolve
OOS and OOT
events.

Question #6:

Do you understand how Quality by Design can minimize OOS-related manufacturing disruptions?

The FDA defines Quality by Design (QbD) as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding . . . based on sound science and quality risk management.”¹⁴

The same guidelines go on to describe the aim of pharmaceutical development as designing a quality product and manufacturing process that consistently delivers the intended performance. And they emphasize that “quality cannot be tested into products . . . quality should be built in by design.”¹⁵

Proper implementation of QbD provides three main benefits for OINDPs:

1. Saves time developing a product and preparing FDA submissions;
2. Reduces approval times and minimizes queries from the FDA; and
3. Provides rapid insights into any OOS or OOT disruptions to manufacturing.

Even after an OINDP has gained FDA approval, routine QC testing may detect an OOS result. For any pharma company that did not use a QbD approach, an OOS result can mean getting back on the merry-go-round of trial-and-error testing. Without a rigorous test system, all test results are suspect, questions are difficult to answer, and long delays are inevitable because of the absence of reproducibility and traceability. Without knowing where to look, your team will have to use trial-and-error to resolve any OOS occurrences.

A recent article presented several possible scenarios that add up to a 4- to 9-fold increase in testing to clear up an OOS investigation: a costly and time-consuming prospect.¹⁶ The impact of poor quality that spirals out of control into an OOS event can be horrendous.

“For manufacturers, there are potentially huge external costs for delayed product launches or approvals, or severe actions such as consent decrees,” notes one editor of an industry journal, plus “the internal costs of wasted raw materials, scrap batches, and the cost of investigation and remediation.”¹⁷

All of these costs add up to an enormous loss of money, not to mention the intangible damage to a corporate or product brand.

QbD minimizes these risks by mapping all of the possible variables of the product components into a known control space. This means that if any quality issues occur, your team can use scientific methods to quickly zero in on the specific variables that are most likely causing those issues.

The business benefits are significant, including:

- Fewer lost batches, typically costing \$250,000 to \$500,000 per batch
- Fewer manufacturing deviations, saving hundreds of costly hours and \$10,000 to \$15,000 per deviation
- Faster time to market and more reliable supply, when each day on the market could mean hundreds of thousands of dollars (or more)
- Fewer inspections of manufacturing sites
- A many-fold ROI through cost savings and increased revenue.¹⁸

Are you using Quality by Design to head off problems before they start?

Question #7:

Can you meet the FDA guidance for Quality by Design?

After two and a half years of advance notice, workshops, and consultations, as of January 2013 all ANDA generic applicants are now “strongly encouraged” by the FDA to use a Quality by Design approach, and deficiency letters will begin to explicitly cite the lack of QbD.¹⁹ Round and round your development will go.

The QbD components the FDA expects to see in all submissions include:

- Quality target product profile (QTPP)
- List of critical quality attributes (CQAs)
- List of critical material attributes of drug and excipients (CMAs)
- List of critical process parameters (CPPs)
- A control strategy that ensures the product reliability meets its predefined objectives.

The FDA clearly sees QbD as the way to enhance the quality of generic drugs for the benefit of everyone involved:

Manufacturers will save time and money developing and producing drugs, and gain better control of their supply chains with more rigorous scientific standards for incoming inspections.

Regulators will save time and resources approving drug applications, doing inspections, and troubleshooting any severe quality issues.

Patients will be assured of more consistent, high-quality generic drugs that perform as advertised.

In the eyes of the FDA and the many adherents of QbD, this approach truly represents a way to “do more with less” and gain a win-win-win outcome.

“When fully implemented, QbD means that all critical sources of process variability have been identified, measured, and understood.”²⁰

With the FDA now squarely behind QbD, how can you afford not to adopt it? And how will you adopt it with a minimum of cost and disruption? Why stay on the merry-go-round?

The only realistic answer is to have the proper combination of in-house expertise, integrated and automated testing systems that generate consistently repeatable results, and a knowledgeable partner to help guide you through your implementation of QbD principles.

The FDA has
“strongly
encouraged”
all pharma
companies to
adopt QbD.

Get Off of the Merry-Go-Round: Reduce Time to Market

This white paper presents 7 vital questions that every manager needs to ask to get off the merry-go-round and help ensure success with an OINDP development effort.

Any OINDP is a complete drug delivery system that includes a miniature medical device plus a formulation, making this drug category far more complex than a solid or injectable drug.

The device complexity routinely introduces delays in incoming materials inspection, finished product testing, gaining FDA approval, and dealing with any OOS events. In fact, most OINDP development projects require far more time and money than any pharma company expects.

Without proper in-house expertise, a rigorous integrated, automated testing system, and an experienced testing partner, developing an OINDP can feel like endlessly riding a merry-go-round.

After considering these questions, you should have a better understanding of the many challenges in developing a successful OINDP. You may also be ready to rethink your development process and to seek help from an 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 Scientific streamlines complex development and release testing processes of pharmaceutical OINDPs by providing complete solutions that reduce overall lab testing time in many cases by at least 100-fold compared to manual analysis. Proveris has deployed its complete solutions globally at 70+ 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.

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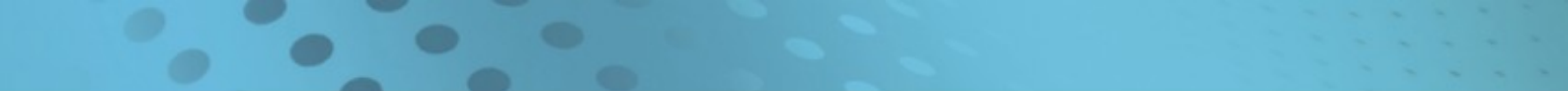
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About Proveris Scientific

Proveris® - Accelerating 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 70+ 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.

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