WHAT IS QUALITY BY **DESIGN** AND WHY SHOULD YOU CARE?

Quality by Design (QbD) is a scientific approach that formalises product design, automates manual testing, and streamlines troubleshooting. A QbD approach is an indispensable tool for successfully developing inhaled and nasal drug products as well as critical to creating effective manufacturing processes for released products. Proveris Scientific explains how this approach works.

Traditional 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 not allowed and the focus is on process reproducibility.

> "Instead of relying on finished product testing alone, QbD provides insights upstream throughout the process by identifying all critical quality attributes and process parameters..."

This approach ignores most real-world variability in materials and processes along the way. Consequently, any future efforts to discover the root cause of an out-of-specification (OOS) or out-of-tolerance (OOT) 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 the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the process by identifying all critical quality 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.[1] Therefore, any quality issue can be deciphered and its root cause quickly identified.

Getting to market with an orally inhaled or nasal drug product (OINDP) is a difficult and complicated undertaking. Each OINDP includes a miniature machine or medical device packaged with the formulation to create a complete drug delivery system. The fact that each product is a complete delivery system rather than a simple dosage form adds more complexity at every stage of development.

These complexities can result in longer approval times, multiple regulatory submissions, and more time responding to queries from regulators, such as the US FDA.[2] Following a well executed QbD approach helps to reduce the development complexity and get a product to market more quickly.

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Proper implementation of QbD provides three main benefits:

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

FDA GUIDANCE FOR QUALITY BY DESIGN

The FDA 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 outcome. When fully implemented, QbD means that all critical sources of process variability have been identified, measured, and understood.[3]

The FDA defines QbD as "a systematic approach to development that begins with predefined objectives and emphasises product and process understanding . . . based on sound science and quality risk management."[4] 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 emphasise that "quality cannot be tested into products . . . quality should be built in by design."[4]

Even after a drug product has gained FDA approval, routine QC testing may detect an OOS result. Without a rigorous test system, test results can be inconclusive, questions are difficult to answer, and long delays are possible due to the absence of reproducibility and traceability. QbD minimises these risks by mapping all the possible variables of the product components into a known control space.

This means that if any quality issues occur, scientific methods can be used to quickly zero in on the specific variables that are most likely causing those issues and not have to resort to trial and error. This will result in less frequent occurrences of lost batches, manufacturing deviations and inspections, and will result in a more reliable supply of product.

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.

KEY COMPONENTS OF QUALITY BY DESIGN

The systematic approach of QbD contains four key components that 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 of the following steps creates a progressively more exclusive set of statistically defined parameters that can be visualised as a multidimensional space.

1. Defining the goal

In this step, the development team identifies all the CQAs for an inhaled or nasal drug product. 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.

For these drug products, actuation matters. 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.[5]

Therefore, a goal for an inhaled or nasal drug product 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
- Plume geometry.

Defining the goals for a product forces a development team to study deeply and understand the processes and CQAs. This understanding ultimately eliminates the multi-year process of endless corrective action/preventive action (CAPA) and 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 drug product.[1] The ICH Q8 defines design space as an "established multi-dimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality".

By accurately defining a design space, a development team can anticipate the issues and plan for controlling the manufacturing process – rather than reacting to OOS/OOT observations on poorly defined specifications. Since actuation parameters (i.e. stroke length, actuation velocity and hold time) are known to influence the delivered dose and spray characteristics, the design space for a drug product should include measurements of hand actuation and the effect on outputs (i.e. delivered/metered shot weight), as shown in Figure 1.

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 pMDI 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).

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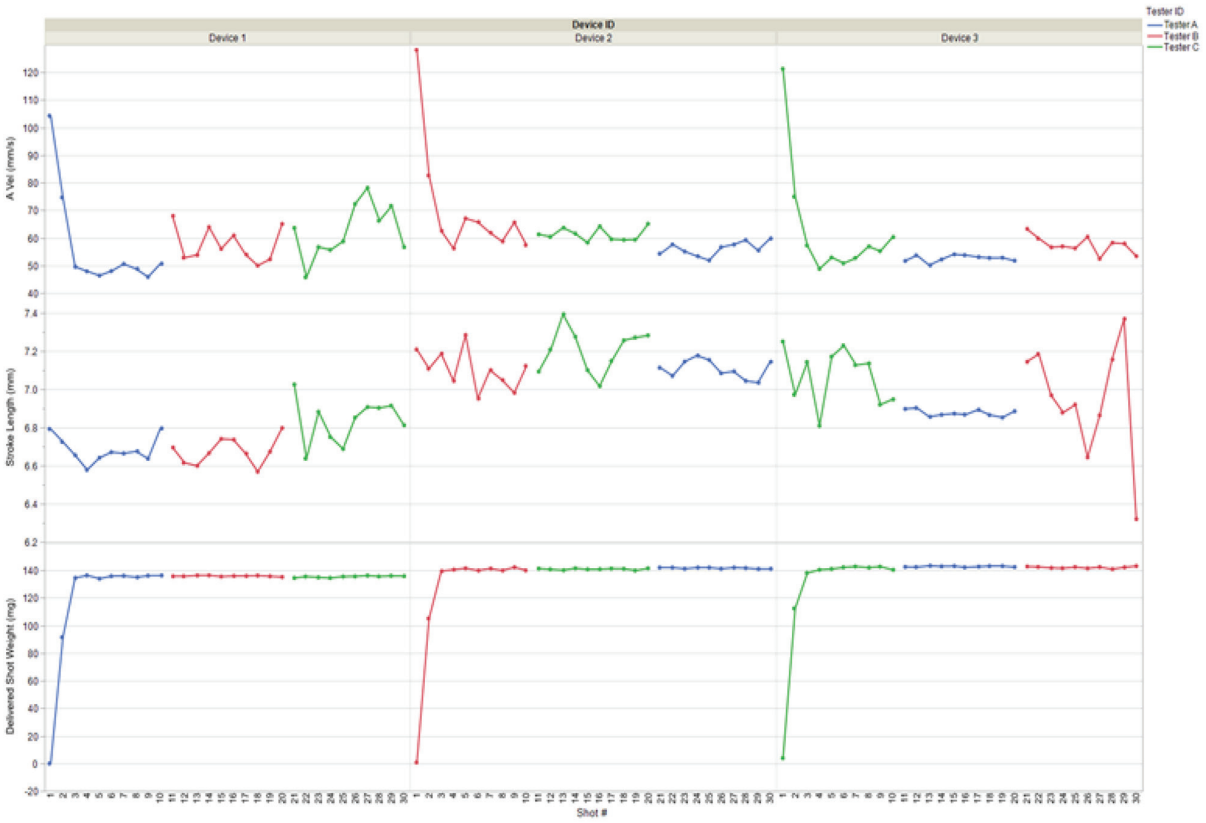

Figure 1: Example design space for a nasal spray product showing delivered shot weight performance with corresponding stroke length and actuation velocity ranges from consecutive actuations collected from three devices and three testers. The outer bounds of this data (i.e. the maximum and minimum value for each parameter excluding priming shots) defines the design space.

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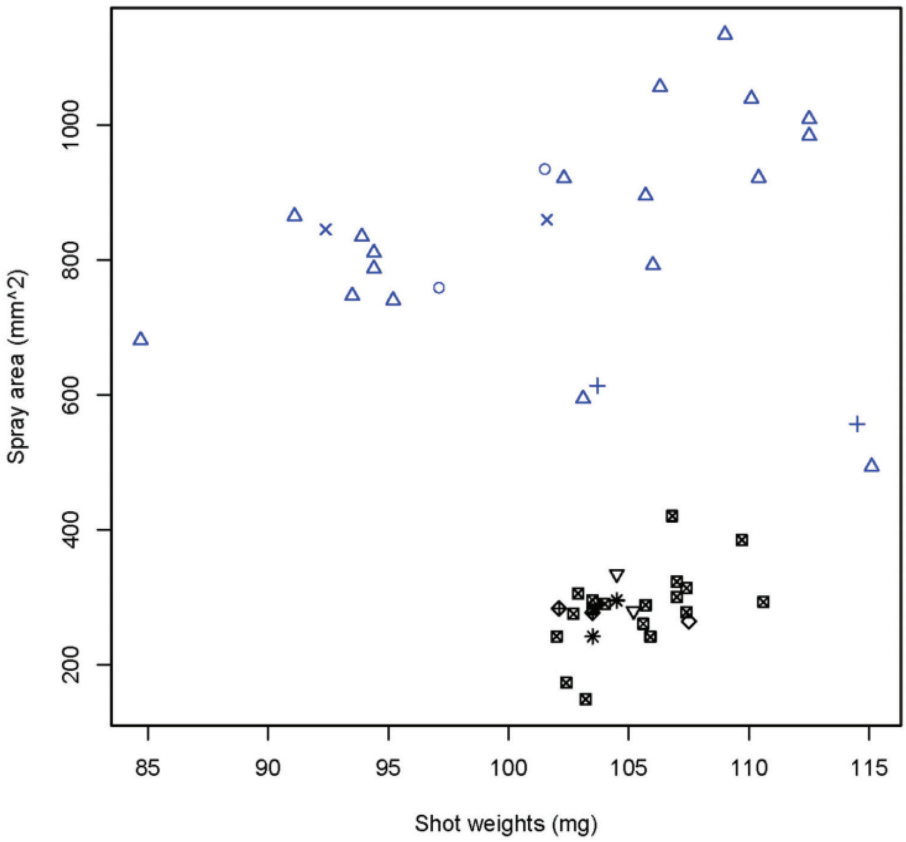

Figure 2: Example of two non-equivalent products that were developed independently – a QbD study was undertaken only prior to filing. This represents a multimillion dollar mistake. Test results in blue and reference results in black were collected at different actuation velocities.

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.[6]

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 a team to understand their processes in a way that shields product quality from the ordinary variability in the production process.

Figure 2 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. Additionally, the reference product data is tightly clustered, representing very consistent spray performance, which is normally the result of a consistent manufacturing process. The test product data is dispersed widely, representing low consistency (i.e. low manufacturing process control). 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.

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.

The Proveris by Design process leverages QbD principles by:

- Providing a solid, scientific basis for method establishment and assisting with regulatory requirement compliance.
- 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.
- Establishing an optimised range of actuation parameters that can be used in spray performance testing 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, plume geometry and droplet/particle size distribution.

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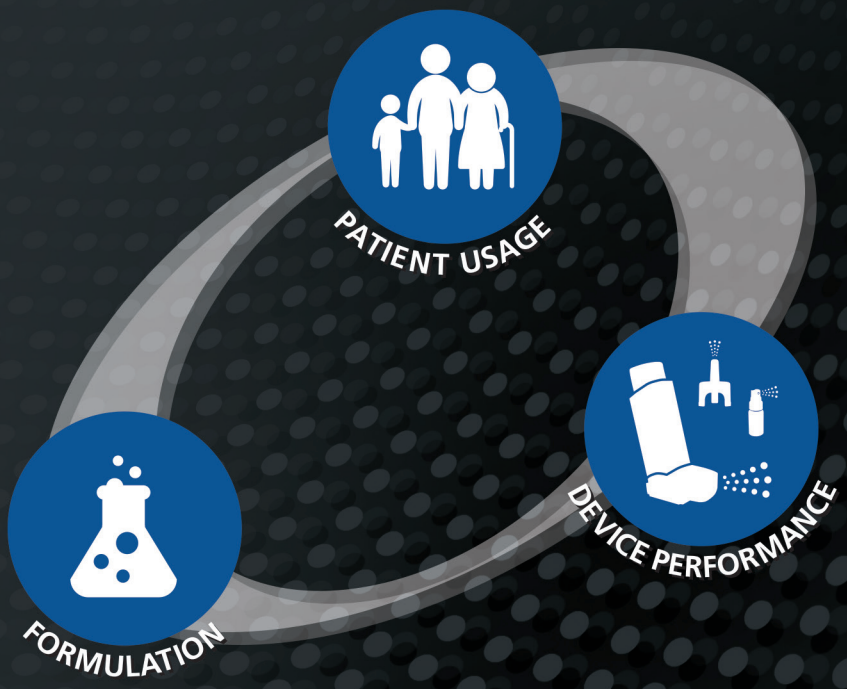
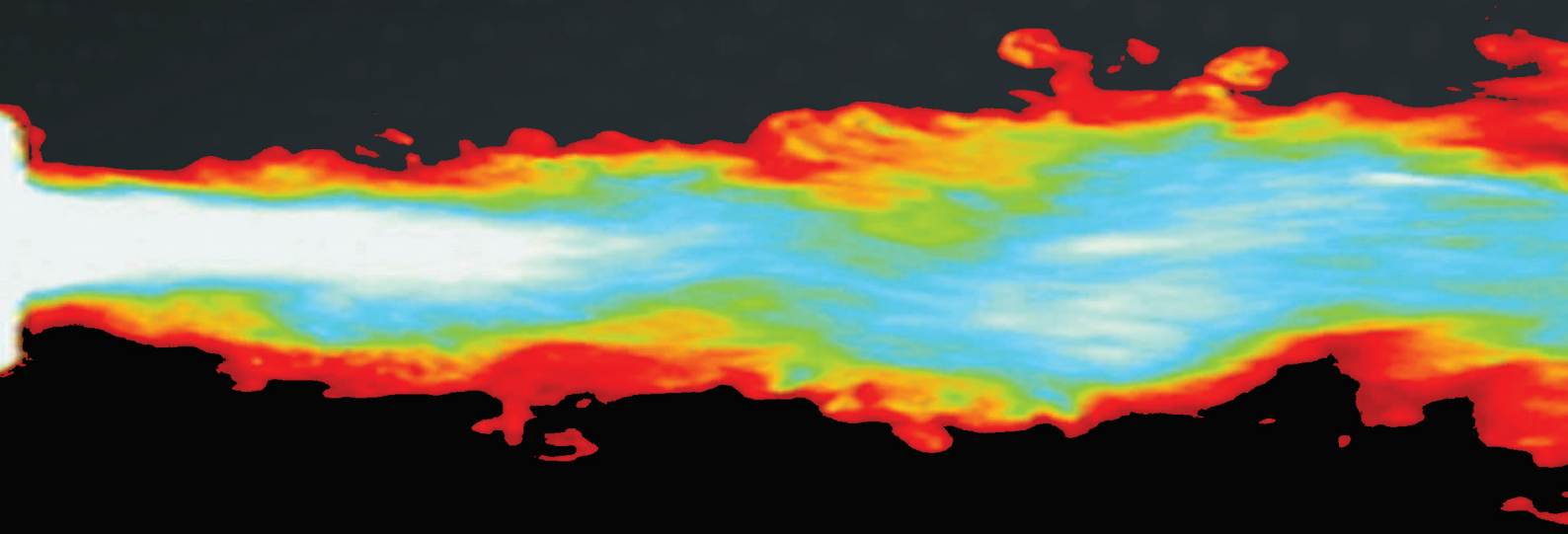


Bridging the Gaps between Patient Usage, Device Performance, and Formulation

Proveris by Design™ Lab Studies accelerate development by reducing the time and cost of optimizing the patient-device-formulation combination required for a successful drug product. Our expert lab scientists work one-on-one with customers to bring products to market more quickly utilizing the following services:

- Reference Product Characterization
- Method Development, Transfer, and Validation
- Patient Usage Ergonometric Studies
- Device Component Optimization



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