# QUALITY BY DESIGN IN INHALATION PRODUCT DEVELOPMENT

In this paper, Carole Evans, PhD, Director, Inhalation, and Lei Mao, PhD, Manager, Inhalation, both of Catalent Pharma Solutions, explore the application and principles of quality by design in the development, manufacture and commercialisation of inhaled pharmaceutical products. Compared with other dosage forms, QbD has not often been applied to inhalation products but, the authors argue, the potential benefits are significant throughout the process.

## INTRODUCTION

Quality by design, frequently referred to as QbD, is a buzzword not just in the pharma and other industries but also in design and development across a wide breadth of industries. The quality-by-design process builds quality in from the beginning of development and makes certain that this quality is maintained through statistical, analytical and risk-management approaches, rather than tested for it after the fact.[1] Quality by design requires that the drug developer begins to think about commercialisation right at the beginning of development.[2]

While there has been a lot of work and discussion of the application of quality by design to many other dosage forms, there has not been as much of a focus on inhalation dosage forms, e.g. pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).

## BUILDING QBD INTO THE DEVELOPMENT PROCESS

The implementation of quality by design has been a response to regulatory requirements and industry concerns in the pharma and biotech industries. The US FDA is working to put it in place, through its pharmaceutical cGMP initiative, and through international collaboration as part of the International Conference on Harmonization (ICH) (see Box 1).[3,4]

Quality by design has to start right at the very beginning of product development, by thinking about the quality target product profile (QTPP). This helps keep the objective of successful commercialisation in mind all the way through the development process.[2] The QTPP will capture the critical quality attributes some of which, such as dose, may be poorly defined early in development.

## BOX 1: ICH GUIDELINES ON QBD

The ICH guidelines [4] suggest the following steps for pharmaceutical development encompassing quality by design:

- Defining a quality target product profile (QTPP), relating to quality, safety and efficacy; this needs to consider factors such as the route of administration, dosage form, bioavailability, strength, and stability
- Identifying critical quality attributes (CQAs) of the drug product, active pharmaceutical ingredient and excipients, as decisions over these could have an impact on product quality
- Evaluating and refining the formulation and manufacturing process, including the attributes and process parameters that could affect the quality control attributes
- Combining the enhanced understanding of the product and process with quality risk management to defining a control strategy, in order to ensure that products of the right quality are produced consistently

**Dr Carole Evans**
Director, Inhalation

**Dr Lei Mao**
Manager, Inhalation
T: +1 919 481 4855
E: info@catalent.com

**Catalent Pharma Solutions**
160 Pharma Drive
Morrisville
NC 27560
United States

**www.catalent.com**

Quality by design requires drug developers to understand how input materials, formulations and processes can vary; how a product's critical quality attributes (CQAs – see Box 2) are related; and how the treatment's clinical properties are affected by any changes in the CQAs.[1] Selecting the right critical quality attributes is an important step in implementing a quality-by-design strategy. Defining the operation range or "design space" (see Box 2) of those variables to ensure consistent CQAs and control the product quality through lifecycle management is the ultimate goal for the quality-by-design concept. If the design space is large enough to encompass the input parameters that generate product not meeting the target product profile, an operation range may be defined in the design space that encompasses the range over which product may be reliably made. This can be evaluated by exploring a wide process range in order to establish the failure points.

## QBD IN INHALATION PRODUCT DEVELOPMENT

When looking at quality by design during the development of an inhalation product (or for any form of drug product), it is essential to start by understanding the input materials, formulation, container closure systems, and process variables, and how these affect the critical quality attributes and therefore the finished product's performance within the design space.

The operating space is used to define the range for the process variables in quality by design, so that companies can be comfortable that performance is assured when the variables remain within the range. Any processes that link to the drug product manufacturing process, such as those controlling the physicochemical properties of the input drugs / materials, or functional packaging components and secondary packaging, will also need to have their own design space. Typically, inhaled products such as pMDIs and DPIs will have multiple design spaces requiring definitions and knowledge spanning API manufacture, formulation processes, filling and finally packaging.

There are a number of variables and factors that companies wishing to apply quality by design to inhalation product development need to take into account, and these all need to be assessed to consider their impact on the overall performance. See Box 3 for suggestions. There are likely to be other factors involved and these need to be considered on a case-by-case basis.

## BOX 2: CQA, DESIGN SPACE AND QTTP

According to the ICH guidelines, a critical quality attribute or CQA "is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".[4]

A design space is the "multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality".[4]

The critical quality attribute is a subset of the quality target product profile.[2]

Using the input drug in a suspension MDI or DPI product as an example, the particle size distribution is critical and the finished product performance can only be assured when the drug particle size distribution is well controlled within a certain range (design space). An understanding of the size reduction/control processes and the post-manufacturing conditioning procedures, and their effect on other physicochemical properties of the drug substance, is equally important as these properties could have a significant impact to the finished product performance or stability. All these variables need to be evaluated in the quality-by-design studies during the product development phase in order to create and populate a robust database. This will help to understand the design space and justify the selected operating range.

Likewise, variables in the process, such as the mixing speed and time required for the dry-powder blend formulation manufacturing, need to be evaluated, and their impact on the key product performance needs to be well understood. This includes requirements such as consistently-delivered doses, as well as the desired aerosolisation performance parameters, which are typically determined

> "While there has been a lot of work and discussion of the application of QbD to many other dosage forms, there has not been as much of a focus on inhalation dosage forms."

## BOX 3: SELECTION OF SUGGESTED RELEVANT VARIABLES & FACTORS IN APPLYING QBD TO OIDPS

Input drug substances applicable to all inhalation dosage forms:
- Particle size distribution, size reduction process, material conditioning

Pressurised metered dose inhaler:
- Drug/surfactant/co-solvent concentration, propellant ratio (if required)
- Excipient functionality
- Container closure variants
- Order of drug/surfactant/co-solvent addition
- Suspension agitation/homogenisation/recirculation time
- Process temperature/filling to exhaustion
- Process duration/disruption

Dry powder inhaler:
- Drug/carrier ratio, ternary cleaning agent and ratio (if required)
- Excipient functionality
- Blending process – speed and time
- Bulk formulation holding/conditioning
- Filling process variables
- Environmental control


Figure 1: ICH Q8(R1) Pharmaceutical Development; ICH Q9 Quality Risk Management; and ICH Q10 Pharmaceutical Quality System, all contribute to the principle of QbD.

by fine particle dose/fraction and mass medium aerodynamic diameter (MMAD). Building quality-by-design elements into the scale-up process also allows better definition of a robust process design space.

## GENERAL APPROACH FOR QBD STUDY

Similar to other dosage forms,[3,4] creating a quality-by-design-based process for inhaled product development is complex, as there are many different variables in the drug development and manufacturing process. The overall approach is based on the risk assessment/management process, which involves:

a) initial risk assessment of the effects of those discussed variables on the CQAs based on the experience with similar products
b) study design and execution to evaluate the effect of the input variables on the CQAs
c) data analysis and trending to understand the correlation between the input variables and CQAs over the design space and
d) finalising the risk assessment and defining the operating space based on the outcomes of the experiments.

In terms of the quality-by-design experiments, a full factorial design is a powerful tool to capture all elements. This process, however, can be labour intensive, lengthy, and not very cost-effective. Partial factorial design approaches allows developers to understand the design space. Additional experiments may be required for a fuller understanding of any interaction effects identified in the initial designs. An alternative approach, such as an evaluation of the extremes of any combination effects could also be considered in the study design.

Once the effect of the process variables on the CQAs is understood, it's possible to evaluate the extremes of the combination effects. As shown in Figure 2, if the CQAs are affected by the energy input in mixing, the batches manufactured can be evaluated with the lowest and highest energy inputs. If both batches demonstrate consistent CQAs, a design space can be defined for all three elements, i.e. agitation/homogenisation speed, time, and energy (ranges between the lowest energy and highest energy input points).

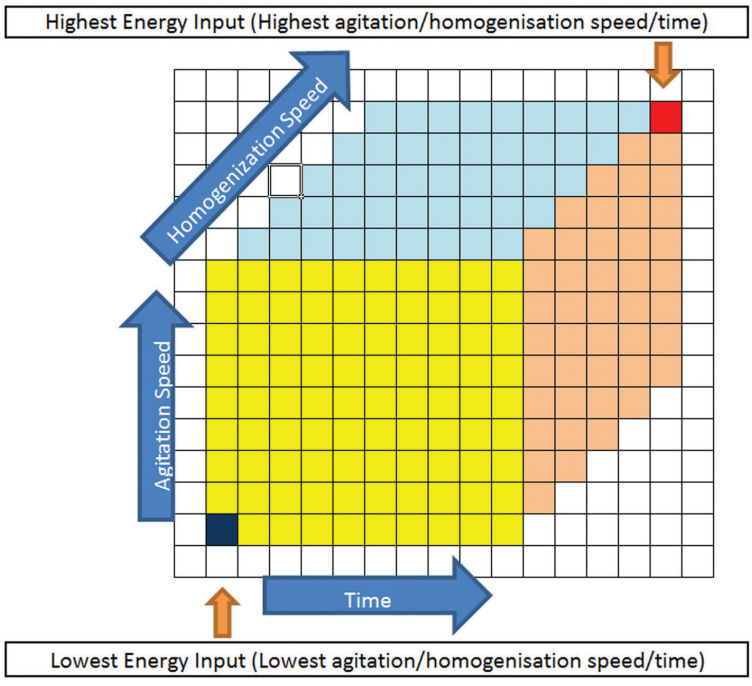



Figure 2: Study design based on the extremes of the combination effect.

## CONCLUSIONS

Quality by design builds quality in from the product development phase, making commercialisation a focus. This ensures that the inhaled products maintain quality, safety, and efficacy, and keeps the production process as cost-effectively as possible. Successful quality by design relies on a full understanding of the effects from input materials, formulations, container closure systems, and process variables on the CQAs of the products. Proper study design and execution allows us to define the design space of all variables that can be controlled during product manufacturing. Quality by design ensures product quality through data driven risk assessment and product lifecycle management.

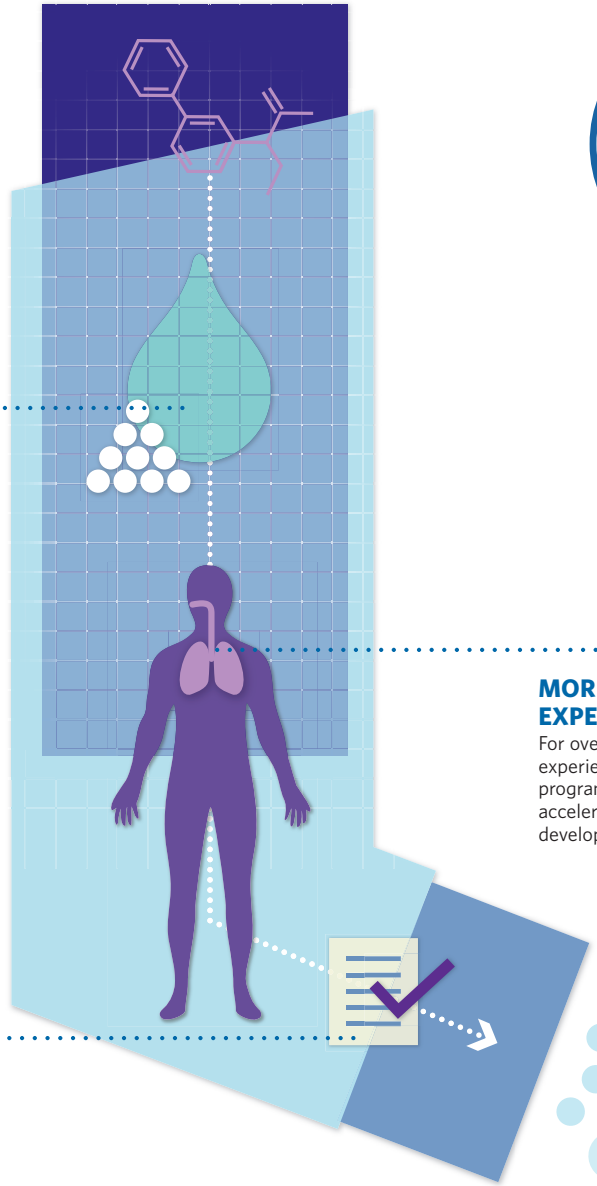
## REFERENCES

1. *Rathore, AS & Winkle H, "Quality by design for biopharmaceuticals". Nature Biotech, 2009, Vol 27(1), pp 26-34.*
2. *"Quality by Design for ANDAs: Immediate-Release Dosage Forms. An Industry-FDA Perspective FDA/GPhA Workshop Draft Example Product Development Report". US FDA, May 4-5, 2010.*
3. *"Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan". US FDA, August 17, 2009. (Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing.*

# broadest inhalation capabilities. proven results.

Catalent® inhalation

CTLT LISTED NYSE



**BROADEST DEVELOPMENT CAPABILITIES**
With our complete range of dosage forms and comprehensive, integrated services, we create customized solutions that ensure superior results.

**MORE INHALATION EXPERIENCE**
For over 20 years, our deep experience and effective program execution have accelerated inhalation drug development time to market.

**PROVEN TRACK RECORD**
Our global project and supply chain management capabilities and proven regulatory expertise ensure high quality service and on-time delivery.

**Breathe easier.** Whatever your dosage form—pMDI, DPI, nasal, solution/suspension, or nebulizer—we are the catalyst for your success. With our broad range of services and deep industry experience, we create customized inhaled drug development and filling/manufacturing solutions that improve the value of your treatments from early stages to launch. And, our thorough understanding of regulatory requirements and submission protocols ensure ongoing, reliable supply. **Catalent. More products. Better treatments. Reliably supplied.™**

DEVELOPMENT DELIVERY SUPPLY

**Discover more solutions with Catalent.**
Call: + 1 888 SOLUTION (765 8846) Europe: 00800 88 55 6178
Email: solutions@catalent.com Visit: www.catalent.com