Quality by design: Considerations for inhalation product development

Concepts to simplify the complexity

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Getting a drug onto the market is a long, complex and costly process. Companies developing new therapeutics and formulations must be able to make the process as simple and efficient as possible. Quality by design, or QbD, is an approach that could help, by putting the focus on commercialization right from the early steps of the product development process, and ensuring that it is maintained and monitored throughout.[1] However, QbD also brings the challenge of securing a budget, and planning for more extensive and earlier product and process experiments than might have typically been considered in a more traditional approach to product development. While any additional development costs may be offset by a smoother and quicker review of regulatory filings and the increased reliability of the manufacturing process bringing reduced costs post-commercialization, the movement of cost from post-registration batch product learning and process refinement to pre-approval product development may be challenging in light of the uncertainty of a successful clinical program.

While the QbD process has already been used in the development of a wide range of dosage forms, there has so far been little focus on its use with inhaled drugs and their associated devices, including pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).

This article will look at how QbD can be built into product development to ensure the end results are a drug and device that are both safe and effective. It will also show that the process of building in QbD has the potential to improve a product's success.

What is quality by design?

Quality by design was a concept developed by the engineer Joseph M. Juran, who believed that quality could be planned.[2] It is a concept that can be (and is) built into the design and manufacturing process in many different industries, including pharmaceutical manufacturing. The QbD process includes elements such as target product profiles, control strategies built on assessment of quality attributes and risk assessment, and experimental design space which supports continuous improvement and lifecycle management.[3-5]

The European Medicines Agency (EMA) defines QbD as "an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines."[6]

One of the drivers behind the introduction of QbD was the FDA's observation that manufacturers were becoming increasingly wary of using new processes and technologies that had the potential

to improve quality and decrease cost to the consumer. In order to improve reliability and thus the efficiency and cost-effectiveness of manufacturing through the use of innovative technologies, the FDA started to move towards a "risk-based orientation" incorporating risk management, through its pharmaceutical cGMP (current good manufacturing practice) initiative, as well as by guidelines laid down by the International Conference on Harmonization (ICH) (see sidebar).[5, 7, 8] This provided the industry with a framework to apply to both the understanding of new products and the regulatory requirements for both new applications and managing change.

Benefits of quality by design

QbD has a range of benefits in trial design and product development[8] that include:

- Better-designed products
- Enhanced mitigation of risk
- Improved manufacturing processes, with fewer issues
- More streamlined introduction of new manufacturing technologies
- Opportunity for continuous improvement in manufacturing processes without costly post-approval change processes
- Lower-cost, or more cost-effective, manufacturing
- Less waste
- Faster and/or more flexible approval process based on enhanced knowledge
- Better understanding of processes

In addition to receiving encouragement from regulatory authorities, the biopharma industry has been positive about the adoption of QbD. The approach has enabled the industry to: reduce the risk of attrition due to manufacturing issues during the product development process, especially at later stages; increase flexibility; and add the potential for cost savings. Indeed, the first QbD approval was of a biologic license application (BLA) from Roche for Gazyva (obinutuzumab), an immunomodulator for the treatment of lymphoma.[9]

Doing quality by design step by step

The overall QbD approach is based on the risk assessment/management process,[5,7] which involves:

- Initial risk assessment of the effects of those discussed variables on the CQAs, based on the experience with similar products
- Study design and execution to evaluate the effect of the input variables on the CQAs
- Data analysis and trending to understand the correlation between the input variables and CQAs over the design space
- Finalizing the risk assessment and defining the operating space based on the outcomes of the experiments.

Understanding these variables is based on a combination of prior knowledge of all these criteria, along with risk analysis and experiments that have been statistically designed, and helps keep the objective—successful commercialization—in the mind of all concerned in the development process.[8,10]

The first step of the QbD process is to define the quality target product profile (QTPP), which the ICH guidelines describe as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."[5] For an inhaled product this might include a range of elements such as target dose range, frequency of dosing, delivery time, portability, shelf life and storage conditions.

The next step is to identify the critical quality attributes (CQAs) that drug developers and manufacturers will need to achieve the quality target product profile. A CQA is described by the ICH guidelines as "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."[5, 8] Ensuring that the right CQAs, such as aerodynamic particle size or air flow rate to trigger dose delivery, are selected is a vital part of the QbD process.

Pivotal to these two steps is an understanding of how components can vary. These components include active pharmaceutical ingredients (APIs), excipients, formulations and delivery devices (especially in inhaled therapies). The developer will evaluate how the properties of the end product will be affected by changes in the CQAs, and will look at how the CQAs are related to each other.[1]

Once the quality target product profile has been decided, and the critical quality attributes defined, the drug developer's next step is to create the design space. Again using the ICH guidelines definition, 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." These variables include in-process, drug substance and drug product attributes. The determination of the process design space includes the use of risk analysis, mathematical models where available and design of experiment (DOE) techniques.[5,8]

The role of the design space in QbD is to provide a place to define the range for the process variables. Provided that these variables remain within the pre-determined ranges, process developers can be assured that the performance of the drug product and device will be as expected. Each step that links

ICH GUIDELINES ON QBD

The ICH guidelines[5] include a number of suggestions for companies developing pharmaceuticals, using a process 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 define a control strategy, in order to ensure that products of the proper quality are produced consistently

to the manufacturing process for the drug product will need its own design space. Examples would be the processes that control the physicochemical properties of the APIs and excipients, or that affect the form and function of the delivery device. Separate design spaces will also be needed for the functional packaging components and secondary packaging.

The risk assessment allows definition of a more limited design space based on an assessment of Quality Attributes and Processes in light of previous product and process knowledge. A DOE approach may be applied at this stage to identify the critical process and material attributes. This approach has been used to define the design space for successful filling of capsules for inhalation, where the effects of Critical Process Parameters such as dosing chamber length, powder layer depth, capsule fill speed and the diameter of dosators (frequently used in dry powder filling), have been evaluated with critical material attributes.[11]

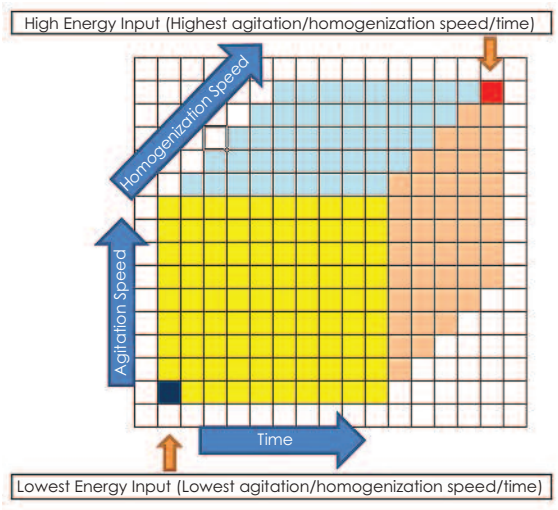
Using factorial design to develop quality by design experiments

Full factorial design is a powerful tool to capture all elements for QbD experiments, but the process can be labor intensive, lengthy and not very cost-effective. Taking a partial factorial design approach can help developers understand the design space better, yet be more time- and cost-effective. As part of the factorial design process, drug developers may need to carry out additional experiments to gain a fuller understanding of any interaction effects identified in the initial designs. Application of this type of design at small scale can be used to define a more limited sub-set of parameters for evaluation at-scale in process development.

Another approach is that of study design based on the extremes of the combination effect (Figure 1). For processes such as suspension preparation for pMDIs, this approach may be more practical than preparing a series of batches at-scale to explore input energy using a factorial design. In the example below, a range of dispersion/mixing input energies may be assessed in a time trial basis using a single batch with a subsequent confirmatory batch rather than multiple batches.

Figure 1

Study design based on the extremes of the combination effect



Once the effect of the process variables on the CQAs is understood, it is possible to evaluate the extremes of the combination effect. As shown in Figure 1, 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/homogenization speed, time and energy (ranges between the lowest energy and highest energy input points).

Quality by design for inhaled products

As with other dosage forms, creating a QbD-based process for inhaled product development is a

complex process, as there are many different variables in the drug development and manufacturing process. To be effective, QbD for an inhalation product (or indeed, for any type of drug product) must be based on an understanding of the ways materials, formulations, container closure systems, packaging, processes and other variables can affect the performance of the drug and device, both separately and in combination. While many of these variables are common to processes for most drug products, some are specific to designing clinical trials and manufacturing steps for inhalation product development and need to be assessed to consider their impact on the overall performance.

Table 1 highlights a list of potential variables applicable to inhalation dosage forms; other variables are likely to be involved and these need to be considered on a case-by-case basis.

Inhalation products such as pMDIs and DPIs will need multiple design spaces for API manufacture, formulation processes, filling and finally packaging, each requiring definitions and background knowledge.

As an example, when developing a suspension MDI or DPI product, one of the input variables is the particle size distribution. The required particle size is a critical quality attribute, and controlling this within a specific range (design space) is vital to the performance of the finished product. In order to do this, the drug developer and/or manufacturer needs to understand the size reduction and control processes and the post-manufacturing conditioning procedures, and have an awareness of the impact that these will have on the other physicochemical properties of the drug.

All of these properties and variables can have a significant effect on the stability of the finished product, and on its performance. Dry particle size reduction by micronization using an air jet mill is primarily dependent on the Critical Process Parameters (CPPs) of feed rate of the API into the milling chamber and the venturi and mill pressures utilized during the micronization process. The optimal operating ranges and design space can vary based on the size and type of mill (i.e., loop versus pancake mill) wherein a separate DOE would be needed during the validation stage of a scale-up or a technology transfer.

The Critical Material Attributes (CMAs) of the unmilled material can also affect the optimal operating ranges and resultant design space. As an example, variability of the unmilled material's particle size distribution could result in a shift of the optimal operating range. Changes to the CPPs may be needed in order to achieve the desired final particle size. The developer of processes for spray drying of materials for use in inhalation delivery can apply DOE to define operating ranges for feed rate, drying temperature, solution composition and nozzle design.[12]

The formulation team also needs to evaluate formulation variables, such as the mixing speed and time required for blending the components of the

Table 1

Input variables applicable to inhalation dosage forms

Inhalation dosage form	Input variable
All inhalation dosage forms	• Particle size distribution of the API • API State (crystallinity, polymorph, etc.) • Size reduction or particle engineering process • Material conditioning • Environmental control • Process duration/disruption
Pressurized 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/homogenization/recirculation time • Process temperature/filling to exhaustion
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
Inhalation suspensions	• Order of drug/excipient addition • Excipient functionality • Suspension agitation/homogenization/recirculation time
Inhalation solutions	• Order of drug/excipient addition
Soft-Mist product	• Order of drug/excipient addition • Container closure integrity • Device assembly • Device functionality

dry powder, and understand how these affect the key product performance needs. These requirements include consistently-delivered doses and correct aerosolization performance parameters, which are generally determined by the fine particle dose/fraction and mass median aerodynamic diameter (MMAD) of the dry powder particles.

The scale-up process also needs to be built into the quality by design thinking, in order to create a well-defined and robust process design space. The evaluation of formulation parameters such as the percentage of fines or types of lactose can often be assessed at smaller scale, thus controlling cost and potentially limited API supply, using partial factorial designs to explore formulation design spaces.[13] For solution pMDIs, the desired droplet size distribution may be predicted using mathematical models of the effect of non-volatile component concentration, metering volume and actuator dimensions on droplet size.[14] These models may influence the weighting of factors in the risk assessment phase.

All of these variables need to be evaluated in the QbD studies during the product development phase in order to create and populate a robust database. This will help increase understanding of the design space and justify the selected operating range.

Quality by design: Focusing on commercialization from the outset

The QbD process helps inhalation product developers and manufacturers focus on commercialization from the start of the clinical trial design and product development process, improving the safety, efficacy and cost-effectiveness of therapeutics and devices, as well as shortening the time to market and even smoothing out the regulatory process.

For a successful QbD process, developers need to have a full and in-depth understanding of the impact of the different variables from input materials, formulations and container closure systems, as well as the effects of different process variables. While it might seem a painstaking and detailed process, the end result is a drug and device that are safe and effective with quality built in, and therefore have the potential for success.

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