Developing OINDPs using Quality by Design

Providing key information to regulators may reduce costs and speed approval

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Introduction

Recently, regulatory agencies have put greater emphasis on the need to understand pharmaceutical process, product quality and risk management to ensure that patient needs continue to be met. The United States Food and Drug Administration (FDA) Quality by Design (QbD) initiative encompasses these considerations, building on previous concepts covered in the International Conference on Harmonization (ICH) Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality Systems.[1]

The QbD approach is meant to drive the drug development process to a proactive and holistic approach based on sound science, while managing risk. This is a deliberate design effort from initial product concept to commercialization, meant to provide patients with a safe and effective drug product. As a result, product and process performance characteristics are scientifically designed to meet specific objectives, rather than being derived empirically from performance of test batches.[1] Therefore, the opportunity exists to make changes within the established design space without the need for prior regulatory approval, ultimately reducing the overall approval time and number of product failures.

With that in mind, this article describes how understanding and applying the principles of QbD to analytical methods can ultimately save OINDP manufacturers time and money. This savings comes as a result of gaining a deeper understanding of the critical parameters that affect drug quality and performance, led by an appreciation of the contribution that method variability makes to the overall variability of the product and the process.

QbD for OINDPs

Benefits

While the primary benefit of utilizing a QbD framework is the resulting improvement in patient safety and product efficacy, this approach also enables improvement of the overall product development process. A QbD approach to developing OINDPs means that critical quality attributes for materials, products and critical process parameters are better understood. Once end-use performance criteria are

established, controls are designed within the process to fit these criteria. As a result, the entire manufacturing process is more flexible because the manufacturer can now account for and respond to variability in materials, environment and process within a predefined design space. By utilizing this framework, manufacturers may receive more regulatory flexibility and see a resulting reduction in overall approval time. In addition, this framework can also set the stage for a reduction in the number of post-approval product failures associated with variability in materials and process.[1]

Challenges

While the benefits of following a QbD framework may theoretically make sense, manufacturers of OINDPs face a number of challenges due to the complexity of this specific dosage form. While more manufacturers are beginning to develop OINDPs, many are wary of such endeavors as a result of high profile failures, lack of experience, and additional time and financial investment required to bring such products to market.

One of the biggest challenges comes from the need to assess the overall performance of the formulation and the delivery device in combination. Associated with this performance testing is the influence of the patient; for example, the force which is applied to actuate the device. Second, the lack of real-time analytical tools can add challenges to the manufacturing control. In general, characterization of these products occur post-manufacture as opposed to on-line. Lastly, the lack of clear *in vitro-in vivo* correlations (IVIVC) has made interpretation of analytical data and clinical performance difficult.[2]

Controlling costs and improving quality of OINDPs by outsourcing

Considering the benefits of utilizing a QbD approach and the challenges of developing OINDPs, the industry is turning to experts in the field who can provide regulatory consultation, as well as expertise in analytical testing and characterization of these drug products.

Numerous variables can affect product performance, adding to the complexity of developing OINDPs and placing major demands in both scientific knowledge and equipment requirements on pharmaceutical companies. Significant delays in product development can occur during the characterization process due to the need to troubleshoot unexpected scientific problems. As a result, pharmaceutical companies can benefit from working in partnership with a qualified analytical testing laboratory to help address these issues and supplement basic, internal analytical skills.

In addition, specialized equipment may be needed to perform required or supporting analytical tests. In some cases, cost of acquiring equipment may be significantly higher than the cost of outsourcing low-quantity characterization tests. In this case, working with an external partner as an extension of an internal laboratory may provide a cohesive path to navigate the complexities of developing and manufacturing OINDPs.

Analytical testing and characterization of OINDPs

The types of testing required for an OINDP are described in regulatory and pharmacopoeial guidance.[3-7] Analytical testing begins with the characterization of the drug substance and continues through product release testing.

Characterization of the drug substance may include tests for moisture content, polymorphic form, surface morphology, particle size distribution (PSD) and other parameters. See Table 1 for a list of recommended drug substance tests for OINDP development.

Analytical methods generate data that determine the selection of the drug substance, as well as the screening and selection of suitable excipients and container closure systems that form the OINDP.[7] Based on the QbD approach, early phase data are used to define desired product characteristics and performance. During formulation design, for example, characterization of the drug substance is important to identify polymorph forms and the drug's particle size distribution, as these attributes may affect product performance, such as delivered dose uniformity (DDU).

Table 1

Routine control tests of drug substances for OINDPs

Physical/chemical parameters
Color
Appearance (visual and microscopic)
Identification
Moisture
Residue on ignition
Specific rotation
Assay
Impurities
Microbial limits (USP 61)
Melting range
Particle size distribution
Crystalline forms
Amorphous content
Residual solvents
Heavy metals

Characterization of the drug/device combination is a key part of developing an OINDP. Analytical tests and characterization studies include delivered dose uniformity, aerodynamic particle size distribution (APSD) measurements, foreign particulate identification, impurities testing and much more. See Table 2 for a list of the FDA's Chemistry, Manufacturing and Control (CMC) tests for nasal and inhalation drug products.

Application of QbD principles to analytical techniques and characterization studies for OINDPs offers the benefit of more meaningful product and process control strategies. As a result, pharmaceutical companies have improved control of product quality and reduced the amount of time spent performing deviation investigations.

Table 2

FDA CMC analytical techniques and drug product characterization studies for OINDPs

Physical/chemical parameters	Drug/device characterization
Appearance and color†‡	Pump delivery reproducibility*
Identification*†‡	Spray content uniformity (SCU)*
Assay for drug, excipients and preservatives*†‡	Spray pattern and plume geometry*†‡
Impurities and degradation products*†‡	Droplet size distribution*
Drug particle size distribution (Suspensions only)*	Net content*†‡
Particulate matter*	Weight loss*
Microbial limits*†‡	Leachables and extractables *†‡
pH*	Particle size distribution*†‡
Osmolality *	Prime and reprime*
Viscosity*	Profiling*
Water and moisture content†‡	*In vitro* dose proportionality*
Dehydrated alcohol content (if used)†	Effect of dosing orientation*
Microscopic evaluation†	Dose content uniformity†‡
	Leak rate†‡
	Pressure testing†‡
	Shot weight†‡

** Indicates tests required for nasal spray suspension and aerosol products*
† Indicates tests required for metered dose inhalers
‡ Indicates tests required for dry powder inhalers

Case Study: Relating quality attributes to product performance

A key component of OINDP development includes particulate matter characterization and identification of the drug/device combination. The understanding of particulate matter as it relates to pharmaceutical products is critical. The formation of agglomeration, polymorphism and product contamination all have a direct affect on patient safety and product quality. Understanding the most efficient methods for characterizing particulate matter and determining mechanisms for dealing with deviations is vital to this end. The introduction or formation of particulate matter can be introduced through either the product or manufacturing process. The ability to understand and interpret this information allows a company to leverage analytical science to make safer products for patients.

Most pharmaceutical labs are not equipped or experienced to do this type of testing. However, they can turn to a qualified analytical testing laboratory to perform this service. Equipment such as scanning electron microscopes (SEM), high accuracy (HIAC) particle counters and automated particle imaging systems, can be costly to purchase, especially for a single or low-quantity characterization study. However, an analytical lab can create a cost effective structure to perform this test for multiple clients, leveraging equipment, regulatory experience and technical knowledge.

For example, while regulatory guidelines recommend some characterization of particulate matter, an analytical testing lab can provide consultation regarding the ways a pharmaceutical company can provide defensible information to receive approval, in order to move forward with development and manufacturing. Such information may include foreign particulate matter identification, source determination and process control efforts.

Particulate matter can be found and tested during various phases of OINDP development and manufacturing process. First, particulate matter can come from the device. Therefore, the device should be tested for shedding potential and all possible sources of particulates coming off the device into the product should be characterized. Second, particulates from the environment of the product, such as agglomerations, crystallized materials, raw material contamination, etc., should be characterized. Tests should be developed to determine the amount, size and speciation of the particulate matter that is present in the system.

Source determination tests should then be conducted to determine the source and evaluate its effect on the product. Acceptable species and limits should be determined and the appropriate risk reduction strategies developed. These tests and risk reduction strategies can then be implemented for later testing protocols of the product throughout the process.

Single particles can be characterized by typical particle characterization using various instrumental techniques, such as HIAC testing. By contrast, a new technique called Raman Chemical Imaging (RCI) can be used to obtain an overall characterization of the particulate matter, including particle size and species distribution. The complementary nature of adding a method such as RCI for organic components and automated SEM/EDS for inorganics can be used. This

combination of tests can provide information to determine if the particulate is from the product, device or testing environment.

By utilizing a forward-thinking approach as described in QbD principles, pharmaceutical companies can demonstrate a full understanding of the ways critical quality attributes relate to product performance. Therefore, by providing more complete information to regulatory agencies, these companies may receive increased regulatory flexibility while reducing overall operating costs and speeding up approval times.

Bibliography

1. Quality by Design Approaches for Orally Inhaled and Nasal Drug Products. Peri, Prasad. Paris: RDD, 2007.

2. Copley, Mark. Accelerating inhaled product testing. The Free Library. [Online] January 1, 2010. [Cited: August 26, 2010.] http://www.thefreelibrary.com/Accelerating inhaled product testing.-a0222507943.

3. FDA Draft Guidance: Metered Dose Inhaler and Dry Powder Inhaler Drug Products. s.l. : U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 1998.

4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry, Bioavailability and Bioequivalance Studies for Nasal Aerosols and Nasal Sprays for Local Action. April 2003.

5. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products: Chemistry, Manufacturing, and Controls Documentation. s.l. : U.S. Human Health & Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2002.

6. United States Pharmacopeia. Chapter 601. [Online] 2008. [Cited: Sept 2, 2010.] www.usp.org.

7. European Pharmaceopeia. Chapter 6.2. [Online] 2008. [Cited: September 2, 2010.] online.edgm.eu.

8. Quality by Design for analytical methods for use with orally inhaled and nasal drug products. Rignall, Andy, et al. 10, s.l. : Pharmaceutical Technology, 2008, Vol. 20.

9. Pharmaceutical Development. s.l. : International Conference on Harmonization, 2005.

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