

Applying Quality by Design Principles to Analytical Methods Associated with Orally Inhaled and Nasal Drug Products

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Summary

The advantages that may be gained by applying Quality by Design (QbD) principles to analytical methods are currently being discussed extensively within the pharmaceutical industry. There are particular benefits in applying QbD principles and tools to the analytical methods used to characterise inhalation products. These products are often complex and a greater understanding of method variability facilitates development of more meaningful product and process control strategies. This presentation elaborates how a high degree of confidence that the analytical method will meet its performance criteria (Analytical Target Profile) under all conditions of use can be achieved. A comprehensive approach for identifying all the method factors that need to be monitored or controlled, through the use of structured risk assessment tools and prioritised experimentation, is recommended.

Introduction

The development of precise, accurate and robust analytical methodology is a key part of the development of OINDPs and their appropriate control programmes. A quality by design (QbD) development programme uses a systematic approach that fully utilises designed experiments and multivariate statistical tools to assemble a product and process design space where critical parameters are defined and, where possible, linked to the demonstrated product safety and efficacy. Appropriate measurement systems will be required to gain greater understanding of the product and process and to establish this product and process design space. The increased understanding, enhanced knowledge and increased ability to control product and process more efficiently, will ensure consistent and high quality OINDPs.

One potential approach to applying QbD concepts to analytical methods is to establish an analytical target profile (what does the method need to measure? within what performance or operating criteria?), and develop flexibility around how this analytical target profile may be met. A full understanding of the capability of different analytical methods is key to this approach. A lifecycle approach to analytical method development and validation is recommended where a core set of initial development and validation information is augmented throughout the method lifecycle to demonstrate its continued fitness for purpose in all of the different environments and situations encountered in OINDP manufacture and control. A comprehensive assessment of robustness and ruggedness factors is a major activity in gaining this understanding. The approach will facilitate continual improvement by establishing a systematic framework to scientifically assess the impact of any proposed changes.

Therefore, a comprehensive method development programme that generates the required analytical knowledge to support the quality management system and design space establishment for products and processes is an integral part of a quality by design development programme.

This presentation is intended as a discussion of the points to consider when embarking on the development of analytical methods for use with OINDPs and where these points might fit in to a quality by design development programme. The employment of statistical tools such as design of experiments and measurement systems analysis, in tandem with suitable risk management techniques, is highlighted.

A QbD approach to OINDP analytical methods

A potential QbD approach to analytical methods can be exemplified as follows:

1. Understanding Measurement Requirements

- Start with the Patient (Safety, Efficacy and Quality requirements)
- Understand what needs to be measured (i.e. which material and component attributes are critical to process and/or product performance)

- Use prior knowledge, compendial considerations & analytical validation targets (for example, the level of precision required to demonstrate safety and efficacy requirements are routinely met)
- Understand the operating arena for the method, including physical environment, desired cycle time
- Based on the above requirements, develop an analytical target profile (ATP).

2. Selecting and developing the optimum analytical method

Based on an understanding of the analytical target profile, evaluate traditional methodologies alongside alternative methodologies and control strategies (such as on-line, at-line methods) to select and design an appropriate method to achieve the ATP. It may be useful to consider the method as a series of analytical modules and consider different analytical approaches to developing and validating each specific module.

3. Evaluate method performance and determine any critical analytical method factors

Use suitable evaluation tools, designed experiments and structured risk assessment tools to identify the factors that impact the performance of the method.

4. Develop the method control strategy

Ensure the method requirements are consistently met via control of the critical analytical method factors so that the method continually performs within its operable design region.

5. Monitor method performance and continually improve

- Confirm continued method performance.
- Use knowledge base to assess the impact of any changes and use the established Quality Management System to oversee them, including method improvements and technological advances.

Points to consider when applying this process to OINDPs

1. Understanding method requirements and developing the Analytical Target Profile

On identifying the need to develop an analytical method to measure an OINDP attribute or process parameter, target operating criteria embodying the intended use of the analytical method should consider the following points

- The type of sample to be tested, for example in-process samples, formulation intermediates, raw materials, packaging components, completed OINDP devices and their known critical quality attributes.
- The proposed operating environment such as in-line or at-line on the manufacturing line or off-line within Quality Control and/or Development laboratories
- The desired method cycle time
- Any target criteria or specifications available from Pharmacopoeial or regulatory guidance.
- Prior knowledge of the capability of the delivery platform and formulation characteristics that form the OINDP.
- Any available knowledge about the clinical implications of measured variability.

Once finalised, the target profile informs the selection of the analytical method and its subsequent validation.

2. Selecting and developing the method

The analytical principle covers the 'analytical unit operations' that will form the basis of the procedure for the OINDP method, these operations may include:

- Collection of the sample (for example, the delivered dose or aerodynamic particle size fraction).
- Sample preparation (for example, using volumetric apparatus to form an analyte solution).
- Analyte quantification, for example using chromatography or spectroscopy.

These processes can be considered further:

Sample Collection

For OINDPs, sample preparation, for example dose collection, should be performed in a way that produces data that are relevant to normal patient usage. Points to consider are:

- Device handling such as shaking dynamics (type, duration and intensity), device priming, firing/actuation (force, frequency)
- Airflow characteristics for dose collection apparatus (flow rate, acceleration)
- Environmental conditions (temperature, humidity, vibration)
- Orientation of the OINDP during storage and dose collection
- Apparatus (for example, specific sample collection apparatus for use with OINDPs are detailed in the Pharmacopoeias)

Understanding how device handling effects performance is a fundamental goal of the extensive product characterisation studies performed during development. Preliminary aspects of this work help to define any dosing instructions described in the method. For example the number of priming shots required for optimum dosing characteristics should be determined and stated in the analytical method. Cause and effect analysis, risk assessment tools and designed experiments may be used to understand the impact of device handling and how it influences sample collection variability at this stage.

Sample Preparation

The preparation of the analyte solution will involve solution transfer steps, wash down of apparatus and volumetric dilution. These operations are common with other product types and should be as simple as possible to minimise variability.

Quantification

Selection of the quantification principle will be based on the nature of the sample and the required selectivity, precision, sensitivity and accuracy.

When considering analytical methods associated with different formulations and/or delivery platforms some common attributes may exist. For example HPLC is widely used to quantify active species and associated impurities and degradation products. A large body of literature exists on using design of experiments to develop robust HPLC separation of multiple analytes using multivariate optimisation modelling software. The experimentally derived resolution maps will underwrite the method selectivity and help to define the operable design region for the analytical method.

3. Method evaluation and identification of critical analytical method factors

As it is desirable to reach a high degree of confidence that the analytical method will meet all method performance criteria under all conditions of use as it progresses through the method lifecycle. This can be achieved by identifying all the factors that can potentially affect method performance along with risk assessment tools to guide prioritised robustness and ruggedness experimentation. The goal is to identify analytical method factors that will require monitoring or control and eliminate any that introduce a high degree of variability.

Analytical method robustness testing typically involves evaluating the influence of small changes in the operating conditions on the variability of the measurement. Typically design of experiments (DoE) is used. Ruggedness testing identifies the degree of reproducibility of test results obtained by the analysis of the same sample under various normal test conditions such as different laboratories, analysts, and instruments. This may involve failure mode effect analysis (FMEA) and/or measurement systems analysis (MSA)

The process for discriminating between Robustness and Ruggedness factors during the process of structured risk assessment is particularly pertinent for OINDPs because of the nature of the analytical matrix and the influence that a variety of product components and external factors may have upon the analyte.

Robustness and Ruggedness factors can be established by generating a comprehensive list of all the potential factors that might influence analytical method performance. These may include human factors, environmental factors, material properties, instrumentation and method or measurement factors. In addition to the typical parameters associated with sample solution quantification, factors linked to sample handling and preparation are often additional critical aspects for OINDPs. Cause and effect analysis may aid in compiling this list.

The factors are then grouped according to their influence on the method:

Factors that should be routinely controlled as part of the analytical method. These factors will become part of the method control strategy.

Potential noise factors that can influence the ruggedness of the method. Failure mode effect analysis may help to identify these factors and further measurement systems analysis can then be used to assess their impact on overall method variability.

Factors for which acceptable table ranges should be established via appropriate experimentation designs. These parameters should be listed and prioritised before performing appropriate design of experiments to assess the effect of each factor and determine appropriate operating ranges. These experiments should explore interaction (interdependency) amongst the factors to understand all aspects of method performance and establish a comprehensive operable design region for the method.

The output from this exercise results in a thorough understanding of the different factors that can influence method variability and the development of a sound control strategy and knowledge base.

4. Developing the control strategy

The evaluation of the method will identify critical method factors along with their operable region that has been demonstrated meet the method performance criteria. This may be a multidimensional region including combinations and interactions. Suitable controls for the critical analytical method factors should be established such as instrument performance checks, run qualification procedures and method system suitability criteria.

5. Monitoring Performance and continual improvement

The use of formalised tools throughout development should facilitate effective knowledge management allowing any impact and assessment of changes to be performed in a structured way, relating back to the analytical target profile. Continual monitoring of analytical methods factors via control charts or other tools may be appropriate. As the methods are established in their different working environments, lean tools may be applied to optimise workstations and yield reductions in the cycle time for the method.

Conclusions

Measurement systems form an integral part of a quality by design development programme and the application of science and risk based approaches to analytical methods will result in better understood, more robust, methods with better control of critical analytical method factors. Sharing this increased knowledge with regulatory authorities should result in a decreased need for pre-approval of non-critical method changes and increased incentive for continual improvement.

Further discussions on the best way to share the increased knowledge associated with analytical methods in regulatory filings, exemplified via case studies, will be part of future industry efforts.

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