

Quality by Design for Analytical Methods for Use with Orally Inhaled and Nasal Drug Products

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BACKGROUND

A Quality by Design approach emphasises product and process understanding with appropriate application of manufacturing science, quality risk management and controls, resulting in higher assurance of product quality, regulatory flexibility and continual improvement.

Quality by design (QbD) thinking can also be applied to the development of analytical methods where a deeper understanding of method capability, alongside control of critical method parameters, can form an integral part of a robust quality management system.

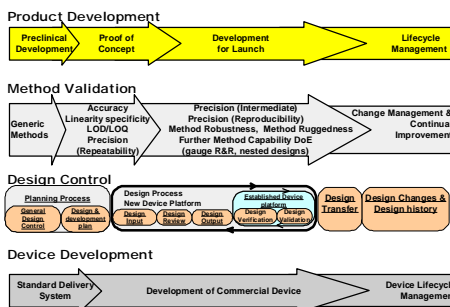
INTRODUCTION

The development of precise, robust, analytical methodology is a key part of the development of orally inhaled and nasal drug products (OINDPs) and their appropriate control programs. A QbD development program utilises risk assessment, designed experiments and multivariate statistical tools to assemble a product and process design space and, where possible, links any critical parameters to the product safety and efficacy. Appropriate measurement systems will be required to establish this design space. A comprehensive method development program is therefore an integral part of the QbD effort.

To gain full understanding of the capability of analytical methods, a lifecycle approach to their 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.

The development process for OINDPs integrates the usual proof of concept, safety and clinical efficacy development phases with medical device design control requirements. This can be illustrated in terms of a method development lifecycle (See Figure 1), where validation criteria are aligned with the typical product development phases and elements of the design control and device development lifecycle.

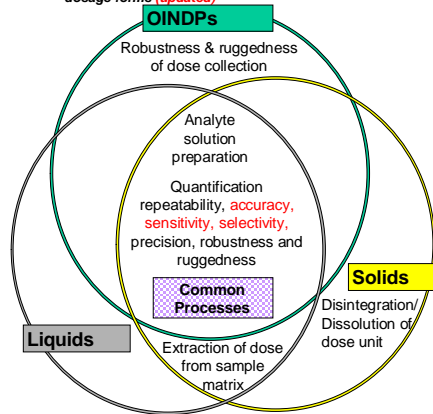
Figure 1. Linking together method validation, device design control and device development lifecycles



The design control aspects will ideally link to the critical development milestones but this may not always be the case. The entry point in the design control lifecycle is different depending on whether formulations use an established delivery platform design, or a new design where more than one iteration through design control process steps may occur.

Whilst there are many common analytical unit operations and processes associated with OINDP methods in comparison with other dosage forms, there are some additional points to consider, particularly those associated with sample collection (Figure 2).

Figure 2. Comparing OINDP analytical method processes with other dosage forms (updated)



DISCUSSION

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

Understanding method 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 environment for the method, including physical environment, desired cycle time.

Based on the above, develop an analytical target profile.

Select and develop the optimum analytical method

- Use the analytical target profile as guidance.
- Evaluate traditional methodologies alongside alternative methodologies and control strategies (such as on-line, at-line methods)

Determine any critical analytical method parameters

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

Develop the method control strategy

- Ensure the method requirements are consistently met via control of the identified critical analytical method parameters.

Monitor method performance and continually improve

- Confirm continued method performance.
- Use knowledge base to assess the impact of any changes and use the quality management system to manage them, including method improvements and technological advances.

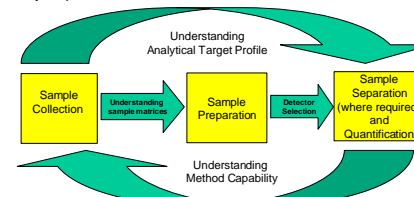
Understanding method requirements - Developing the analytical target profile for OINDPs

On identifying the need to develop an analytical method to measure an OINDP attribute or process parameter the following points should be considered:

- The type of sample to be tested, eg. in-process sample, formulation intermediate, raw material, packaging component, completed OINDP device and their known critical quality attributes.
- The proposed operating environment such as in-line or at-line on the manufacturing line of 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 clinical implications of measured variability.

Selecting and developing an optimum analytical method

Once finalised, the target profile can be compared with knowledge of the capability of different techniques to inform the selection of the apparatus and optimum operating parameters for each element of the method (i.e., sample collection, preparation and quantification, see below). Alternative ways of achieving the analytical target profile may be possible.



For OINDPs, sample collection should be performed in a way that produces data that are relevant to normal patient usage. How device handling effects sample collection variability should be fully understood. Sample preparation should be simplified as much as possible to minimise variability. Selection of the quantification principle will be based on the nature of the sample and the required selectivity, precision, sensitivity and accuracy.

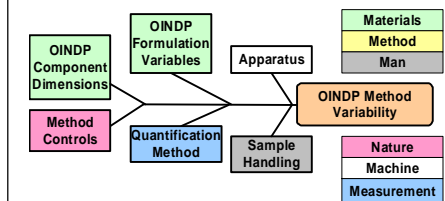
Determination of critical analytical method parameters

Critical method parameters are identified on the basis of prior knowledge of the method and the product, plus data generated during the extended validation program. A formal risk assessment, which identifies the parameters most likely to affect method performance, will provide a useful baseline and can be revisited in the light of any changes to the method, product, or process.

In addition to the typical parameters associated with sample solution quantification, parameters linked to sample handling and preparation, are often additional critical aspects for OINDPs. (see the related poster, "The Discrimination of Robustness and Ruggedness Factors during Evaluation of Analytical Methods for Orally Inhaled and Nasal Drug Products", for a detailed consideration of the delivered dose uniformity method's example). Furthermore, interaction (interdependency) among analytical parameters should be explored for establishing a comprehensive design space. Design of experiments (DoE) techniques may be used to assess the impact of multiple parameters.

Additional aids in the identification of critical method parameters are standard risk assessment tools and management tools, such as cause and effect analysis (see Figure 4) and Failure Mode and Effect Analysis (FMEA)

Figure 4. Factors influencing OINDP analytical method variability



Developing the method control strategy

Suitable controls for the critical analytical method parameters should be established such as instrument performance checks, run qualification procedures and method system suitability criteria to ensure the method requirements are consistently met.

Monitoring method performance and continual improvement

Suitable monitoring of critical analytical method parameters, for example via control charts, will reveal any long term shift in method performance. Any interventions or improvements should use the established quality system to manage the associated changes. Where technological advances result in new ways of achieving the established analytical target profile, again the quality management system should be used to manage the transition over to the new technology.

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 parameters. 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 by case studies, will be part of future efforts of the IPAC-RS Analytical Methods Working Group.

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