

The Discrimination of Robustness and Ruggedness Factors during Evaluation of Analytical Methods for Orally Inhaled and Nasal Drug Products

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BACKGROUND

The development of precise, accurate, robust, analytical methodology is a key part of the development of orally inhaled and nasal drug products (OINDPs) and their appropriate control programs. Analytical methods are used to generate data that informs the selection of active ingredient and the screening and selection of suitable excipients and container closure systems that form the OINDP.

INTRODUCTION

A Quality-by-Design (QbD) development program uses a systematic approach that fully utilises designed experiments and multivariate statistical tools to assemble a product and process design space and, where possible, link any defined critical parameters to the demonstrated product safety and efficacy.

Appropriate measurement systems will be required to establish this product and process design space so it can be used to ensure consistent and high quality OINDPs, gain regulatory flexibility and facilitate continual improvement.

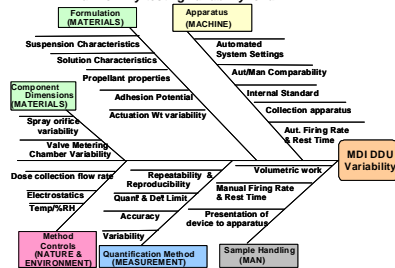
A comprehensive method development programme that generates the required analytical knowledge to support the quality management system and design space establishment is therefore an integral part of this quality by design effort.

DISCUSSION

The identification of critical method parameters, and demonstration of how changes in these parameters influence the method outcome, aids establishment of the analytical method design space (the boundary values for the combination of method parameters inside which the method performs as intended).

A useful tool for visualising all influences is an Ishikawa (or "fishbone") diagram. Such a diagram customarily includes several major categories of factors (e.g., Man, Machine, Material, Mother Nature) and the more detailed, specific causes that fall within each category. An example of a fish-bone diagram for delivered dose uniformity testing of a metered dose inhaler (MDI) is presented in Figure 1.

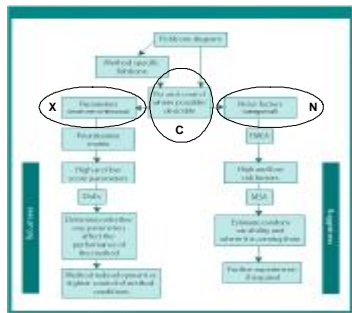
Figure 1. Ishikawa (Fishbone) diagram for delivered dose uniformity testing variability for an MDI



An understanding of the variability associated with an analytical method may provide insights into the contribution this makes to the overall variability of the OINDP. Key to this approach is distinguishing between analytical robustness testing and analytical ruggedness testing. (See Figure 2).

Figure 2. Determination of robustness and ruggedness as part of a risk assessment

Based on the figure from: Phil Borman, Phil Nethercote, Marion Chatfield, Duncan Thompson, Keith Truman: The Application of Quality by Design to Analytical Methods. Pharmtech.com. 2007



C = parameters to be controlled
X = parameters which acceptable ranges need to be established through experimentation (and which influence robustness)
N = potential noise factors (influence ruggedness)

Evaluation of an analytical method robustness typically involves experimentation (e.g., through designed experiments) to determine how changes in the operating conditions influence the variability of measurements.

Evaluating an analytical method's ruggedness involves identifying 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 process may involve failure mode effect analysis (FMEA) and a measurement systems analysis (MSA).

Because OINDPs combine medicinal formulation with a delivery device and therefore many characteristics of the "dose" measured by an analytical method depend on the device preparation and performance at the time of the test. Assessment of analytical methods for OINDPs are associated with special considerations, as highlighted in the accompanying poster entitled "Quality by Design for Analytical Methods for Use with Orally Inhaled and Nasal Drug Products".

For the specific example of Delivered Dose Uniformity (DDU) testing of MDIs and dry powder inhalers (DPIs), a large number of factors may potentially influence the measurement's variability and consequently the DDU method's ruggedness and robustness. These may be grouped into major categories as shown in Figure 3. A different representation, which focuses on the distinction between manual and automatic measurements, is shown in Figure 4.

Steps to Assessing Ruggedness and Robustness of an Analytical Method

- Determine all the potential parameters that might influence the performance of a given method using process flows and mapping. (See several commonly encountered parameters in Figures 3 and 4).
- Determine which robustness (X) parameters should be studied via designed experiments (DoE) and which parameters should be fixed as controlled (C) factors that do not need experimental evaluation. Finally, determine which noise (N) factors should be studied via a measurement systems analysis (MSA).
- For robustness testing, use Fishbone diagrams and CNX parameter allocation and ensure that "X" parameters are scored using an appropriate prioritisation matrix.
- For ruggedness testing, use Fishbone diagrams and CNX parameter allocation, and ensure that "N" parameters are scored using an appropriate FMEA tool.

Figure 3. Specific parameters influencing robustness and ruggedness of delivered dose testing. (Boxes color-coded to Figure 1)

Man	
MDI	DPI
Glassware cleanliness	Glassware cleanliness
Dilution technique	Dilution technique
Following procedures	Following procedures
Competency (training)	Competency (training)
Technique/precision	Technique/precision
Firing technique	Firing technique
Using correct sampling plan	Using correct sampling plan
Shaking technique	Checking flowrate every time

Machine	
MDI	DPI
Dose-collector (automated or auto-waste)	Dose-collector
Firing station	Firing station
Washing station	Washing station
Washing station	Diaphragm liquid pump
Drying station	Drying station
Pump	Pump
Flow meter	Critical flow control
Waste firing	Flow meter
	Waste firing

Measurement	
MDI	DPI
Weigh can pre test	Diluent composition (sample prep)
Weigh can post test	Volume of diluent (sample prep)
Actuation time (test)	Wait time (test)
Wait time (test)	Mixing time (sample prep)
Actuation time (waste)	Pump flow measurement
Wait time (waste)	Rise solvent flowrate measurement
Shake time (test)	Actuation time (test)
Shake rate (test)	Waste dose firing flow rate
Shake rate (waste)	Actuation time (waste)
Ram force (test)	Diluent composition (sample prep)
Ram force (waste)	Volume of diluent (sample prep)
Force rise/fall time (waste)	Mixing time (sample prep)
Release delay	

Method	
MDI	DPI
Incorrect volume used for recovery	Device/dose collector not sealed
Equipment clean (carry over)	Static charges due to firing
Valve stem wash	Sample blister not opened
Equipment wash	Incorrect change of parts used
Seating (firing)	Incorrect flow/pressure drop
Seating (waste)	Incorrect flow rate
	Wash station inverted early
	Incorrect volume used for recovery
	Maximum waste dose threshold for waste dose firing

Materials (Both MDI and DPI)

Water quality
Solvent (manufacturer, batch)
Glassware quality

Environment (Both MDI and DPI)

Procedures
Maintenance standards
Calibration/qualification procedures
Temperature (°C)
Humidity
Electrical supply

The parameters of potential influence will differ depending on whether manual or automatic methods are used. See Figure 4 for an example of DDU testing in dry powder inhalers.

Figure 4. Differences between specific parameters when manual or automatic methods are used for DDU testing of DPIs. (Boxes color-coded to Figure 1)

Man		Machine	
Manual	Automated	Manual	Automated
Preparation of testing system	Preparation of the device	Preparation of testing system	Preparation of the device
Glassware cleanliness	Glassware cleanliness	Glassware cleanliness	Glassware cleanliness
Dilution technique	Competency (training)	Following procedures	Competency (training)
Following procedures	Competency (training)	Technique/precision	Correct sample plan
Competency (training)	Technique/precision	Following procedures	Device cleaning between actuations
Technique/precision	Correct sample plan	Firing technique	Correct sample plan
Correct sample plan	Device cleaning between actuations	Competency (training)	Technique/precision
Device cleaning between actuations		Technique/precision	Competency (training)

Testing/Firing		Recovery	
Manual	Automated	Manual	Automated
Following procedures	Competency (training)	Following procedures	Competency (training)
Competency (training)	Correct sample plan	Following procedures	Competency (training)
Technique/precision	Testing sonic flow	Technique/precision	Competency (training)
Following procedures	Correct sample plan	Technique/precision	Competency (training)
Competency (training)	Device cleaning between actuations	Technique/precision	Competency (training)
Technique/precision	Device cleaning between actuations	Competency (training)	Competency (training)
Correct sample plan		Competency (training)	Competency (training)
Device cleaning between actuations		Competency (training)	Competency (training)

Machine		Materials	
Manual	Automated	Manual	Automated
Preparation of testing system	Preparation of the device	Preparation of testing system	Preparation of the device
Dose collector	Dose collector	Water quality	Water quality
Firing station	Firing station	Solvent	Solvent
Pump	Pump	Glassware quality	Glassware quality
Drying station	Drying station		
Critical flow control	Critical flow control		
Flow meter	Flow meter		

Testing/Firing		Recovery	
Manual	Automated	Manual	Automated
Stable pump performance	Waste firing	Manual	Automated
	Orientation device	Washing station	
	Stable pump performance		

Materials (Both MDI and DPI)

Man		Machine	
Manual	Automated	Manual	Automated
Preparation of testing system	Preparation of the device	Preparation of testing system	Preparation of the device
Water quality	Water quality	Water quality	Water quality
Solvent	Solvent	Solvent	Solvent
Glassware quality	Glassware quality	Glassware quality	Glassware quality

Testing/Firing		Recovery	
Manual	Automated	Manual	Automated
Dose sampling system	Dose sampling system	Water quality	Water quality
		Solvent	Solvent
		Glassware quality	Glassware quality

Measurement

(Difficult to distinguish between Man and Machine)

Preparation testing system		Preparation of the device	
Manual	Automated	Manual	Automated
Testing/Firing	Testing/Firing	Recovery	Recovery
Opening of capsule or blister	Opening of capsule or blister	Diluent composition	Diluent composition
Orientation of device	Orientation of device	Volume of diluent	Volume of diluent
Pump flow	Pump flow	Recovery time and physical effort	Recovery time and physical effort
Actuation time	Actuation time		
Proper seal on device and dose collector	Proper seal on device and dose collector		

Method

Preparation of testing system		Preparation of the device	
Manual	Automated	Manual	Automated
Testing/Firing	Testing/Firing	Recovery	Recovery
Suitable waste shot / priming	Suitable waste shot / priming	Complete recovery	Complete recovery
Repeatability of actuation	Repeatability of actuation	Stability of drug	Stability of drug
Drug loss through filter	Drug loss through filter	Final concentration within HPLC linearity range	Final concentration within HPLC linearity range

Environment

Preparation of testing system		Preparation of the device	
Manual	Automated	Manual	Automated
Testing/Firing	Testing/Firing	Recovery	Recovery
Maintenance	Maintenance	Maintenance	Maintenance
Qualification process	Qualification process	Qualification process	Qualification process
Electrical supply	Electrical supply	Temperature	Temperature
		Humidity	Humidity
		Electrical supply	Electrical supply

CONCLUSIONS

Traditionally it has been acceptable to make changes to method parameters that lie within the validated range for that particular parameter. There are further benefits to taking a Quality by Design approach for analytical methods.

Showing how the critical analytical method parameters have been identified, and demonstrating how they are controlled, will form part of a productive science based regulatory interaction.

Establishing a design space for analytical methods will allow the impact of any changes occurring during the lifecycle of the particular method to be scientifically assessed.

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