



Applying Quality by Design Principles to Analytical Methods Associated with OINDPs

Andy Rignall (AstraZeneca) on behalf of IPAC-RS Analytical Methods Working Group



Content

- Background and points to consider
 - The evolving medicines development landscape
 - Analytical QbD - timeline, activities & outcomes so far
- Applying QbD concepts to a specific OINDP method
 - Role of analytical methods in the OINDP development lifecycle
 - Defining the Analytical Target Profile (ATP)
 - Using the ATP to design the analytical method
 - Understanding the impact of method parameters on performance – defining critical parameters
 - Developing a method control strategy, monitoring & continual improvement
- Summary & Future Opportunities



The Evolving Medicines Development Landscape

- Increasing focus on improving both capability and robustness of manufacturing processes by
 - Extensive deployment of lean and six sigma methodologies
 - Increasing adoption of Quality by Design approaches to process and product development (focus on science and risk based strategies)
- Increased pressure to exploit technical innovation to reduce costs to society

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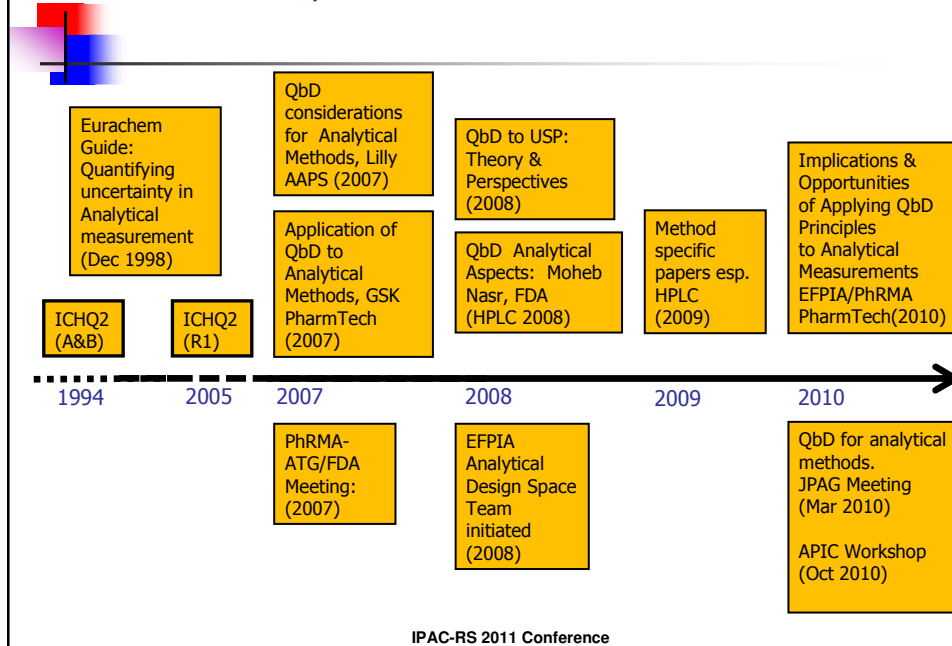
What does this mean for the Analytical Scientist?

- A significantly increased focus on understanding the contribution of the analytical measurement system to the overall process capability.
- A greater recognition of the need to better understand the measurement uncertainty if we are to truly understand our processes.
- Increased pressure to ensure all analytical methods work right first time – every time.
- An increasing need to be able to innovate and continually improve our analytical methods

Can Quality by Design principles be applied to analytical methods?

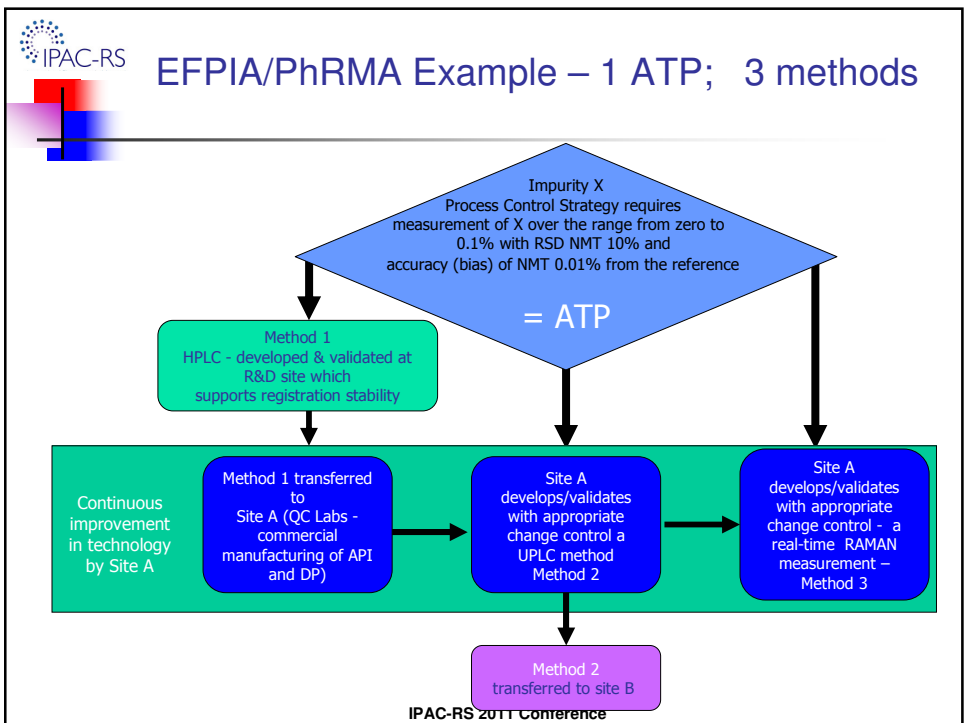
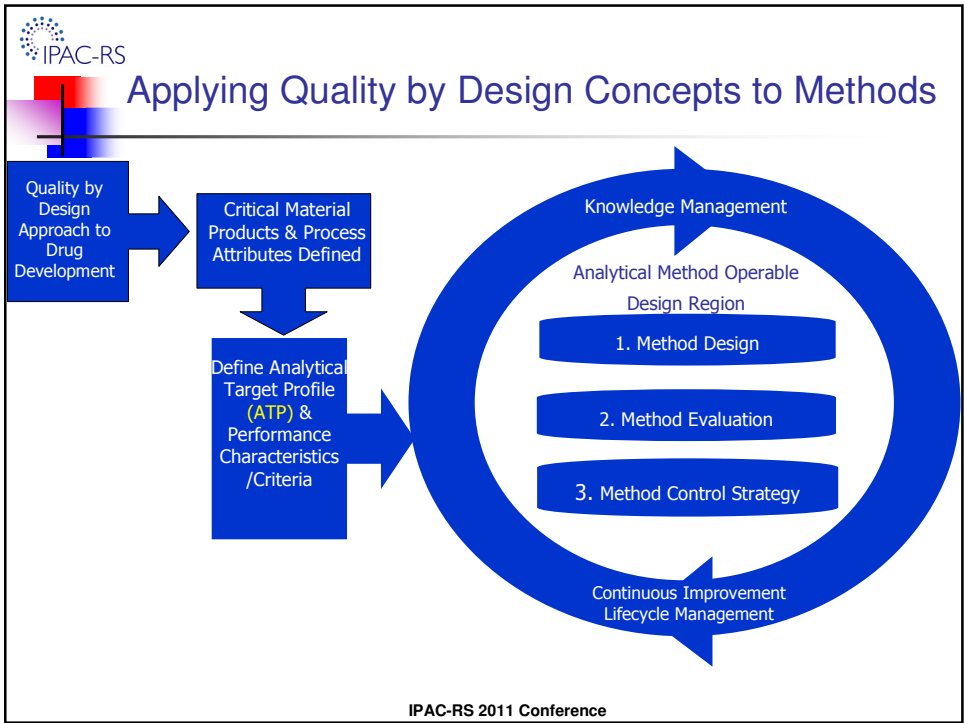
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Timeline, activities and outcomes so far



EFPIA/PhRMA Joint White Paper (PharmTech Feb 2010)

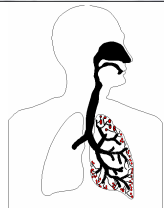
- Describes ideas on how the QbD concepts and tools applied to manufacturing process can be applied to analytical methods, intended as stimulus for further discussion and engagement
- Highlights drivers for change - the evolving regulatory landscape and issues observed with current state
 - Some challenges during validation, transfer and routine operation
 - Challenges for industry in implementing improved methods
- Introduces the concept of the **analytical target profile (ATP)**
- Highlights potential opportunities presented by using the ATP
- Includes a hypothetical case study to illustrate the concepts, provides a glossary to terms & definitions, proposes next steps



EMA Interaction

- EFPIA group developed examples using the proposed concepts
 - Assay (titrimetric), Identification (spectroscopic), Quantification of soluble aggregates.
- A copy of the white paper was submitted, with examples and cover letter, to European Medicines Agency Quality Working Party (QWP) in Nov 2009, feedback received July 2010
- Comments from Quality Working Party were not supportive
- However, the response also recognised that the development of the concepts are still at an early stage and needed further discussion
- Face to face dialogue has been requested and the EFPIA group are scoping further input to facilitate the discussions and reach a common understanding of the issues

Orally Inhaled & Nasal Drug Products

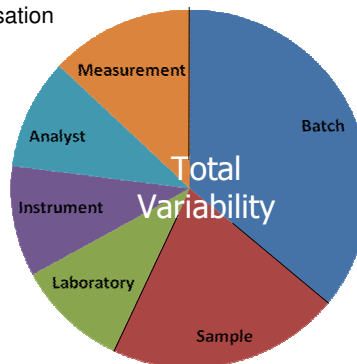
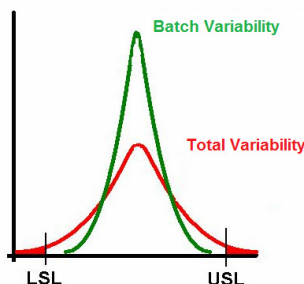


- IPAC-RS Analytical methods group convened in 2007.
- Group exploring how Quality by Design principles can be applied to analytical methods intended for use with orally inhaled and nasal drug products
- Group developing a case study to exemplify some of the approaches further and provide an example for inhalation products

The Role of Analytical Methods in OINDP Development

Analytical Methods support;

- Product and process selection and optimisation
- Input raw material and component quality
- In-process monitoring and control
- Continued product quality & suitability
- Monitoring for trends
- Development of design space



$$\sigma^2_{total} = \sigma^2_{batch} + \sigma^2_{sample} + \sigma^2_{method}$$

Applying Quality by Design Concepts to Methods

Define desired method performance upfront

Understand the method requirements and develop an Analytical Target Profile (ATP)

Design method to meet target criteria

Select, develop and validate an analytical method that meets the ATP

Understand impact of method parameters on performance

Determine any critical analytical method parameters

Identify and control sources of variability

Understand how these critical parameters will effect the result and develop a strategy to control them

Monitor performance to ensure consistent output

Monitor method performance and continually improve

Defining an Analytical Target Profile

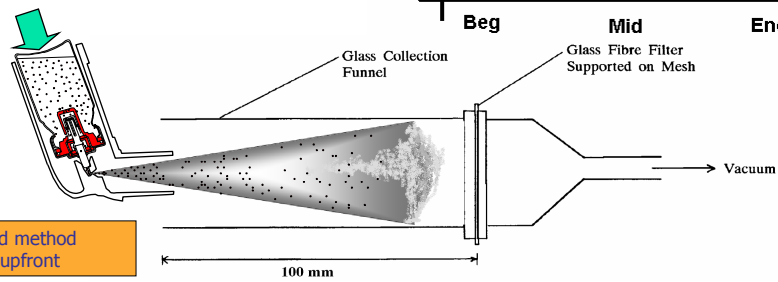
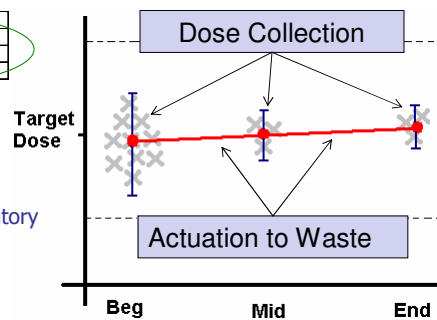
- Start with the Patient (product safety, efficacy & quality)
- Use prior knowledge, regulatory guidance, compendial considerations, voluntary consensus standards
 - Understand what needs to be measured (i.e. which product, material and component properties are critical to process and/or product performance – Critical Quality Attributes)
 - The level of precision and accuracy required to demonstrate that product safety and efficacy requirements are routinely met
 - The discriminating power required to detect any changes that would impact safety and efficacy
- Understand the operating environment for the method, throughout its lifecycle
- Develop an **Analytical Target Profile (ATP)**.

Define desired method performance upfront

Delivered Dose Uniformity

Can Number	Beginning	Middle	End
1	✓	✓	✓
2	✓	✓	✓
3	✓	✓	✓
4	✓	✓	✓
5	✓	✓	✓
6	✓	✓	✓
7	✓	✓	✓
8	✓	✓	✓
9	✓	✓	✓
10	✓	✓	✓

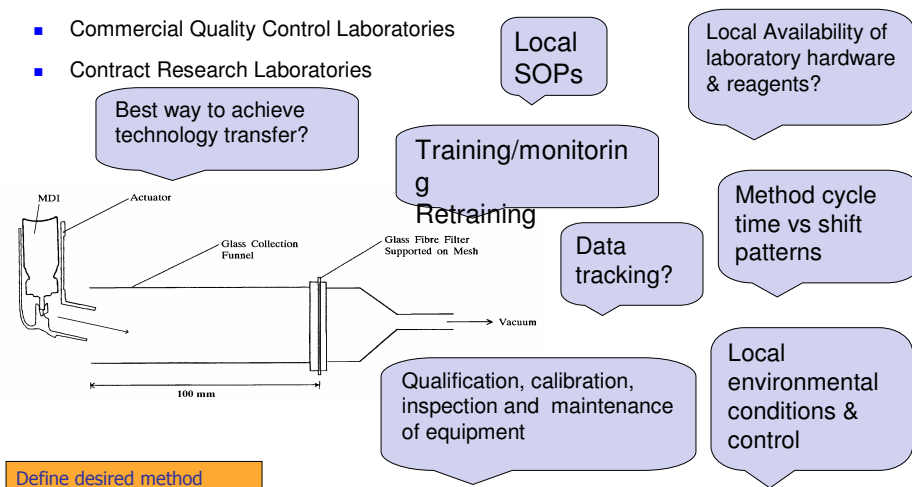
DDU is referenced in Pharmacopoeias & Regulatory Guidance



Define desired method performance upfront

Consideration of Method Operating Environments

- Development Laboratories
- Commercial Quality Control Laboratories
- Contract Research Laboratories



Define desired method performance upfront

Consideration of Human Factors

- An analysis of human error in the analytical measurement task in chemistry, Heller, Edgeworthy & Lee, *Int. J. Cognitive Ergonomics*, 5 (4) p445
- Analytical task demands range from accuracy in manual skill-based activities to complex knowledge-based activities.
- They are multistage tasks that are manually and cognitively demanding, and are highly repetitive and can be prone to human error
- A typical analytical method was selected and a hierarchical task flow was developed via observation followed up with interviews
- Errors associated specific sub-tasks were identified
- General ergonomic recommendations were made including seating/standing, control of extraneous noise, written checklists/method proformas, equipment storage and glassware colour coding
- Specific recommendations for each sub-task also made.

A QbD approach to methods should incorporate 'Error

Analytical Target Profile

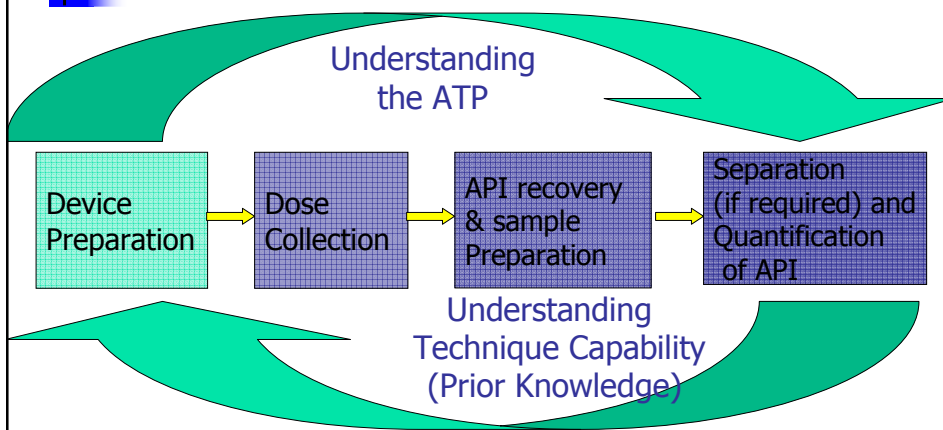
"Measure the within canister and though-life delivered dose from a pMDI with a precision of x% RSD and an accuracy of not more than y% bias, over a range A to B mcg per actuation"

Analytical Target Profile	Criteria
Precision	± X% label claim
Accuracy	± Y% label claim
Range	A-B microgrammes/actuation
Additional assurance that the required ATP criteria can be routinely met:	
Calibration model (for example linearity)	Meets calibration criteria (for example is linear over specified range)
Specificity	Specific for active ingredient in presence of excipients/impurities
Robustness assessment under typical operating conditions	Impact of small perturbations in critical method factors understood & controlled
Ruggedness assessment under typical operating conditions	Impact of random day to day method factor variation understood & controlled

Define desired method performance upfront

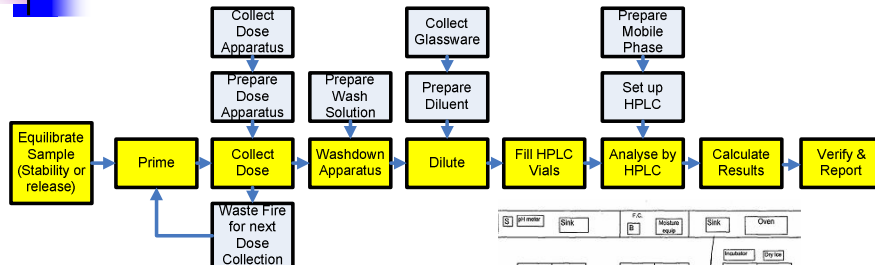
Now need to select, develop and validate an analytical method that meets the ATP

Designing the Analytical Method



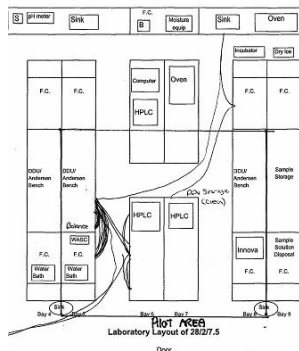
Design method to meet target criteria

Method Design – Process Flow

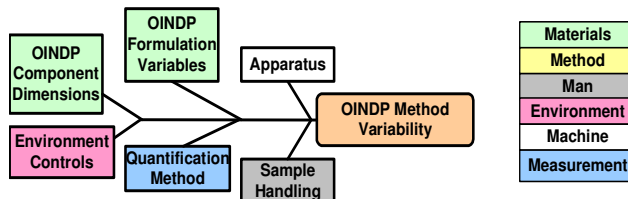


- Applying additional lean tools to analytical methods can increase the efficiency of the testing process (reduced cycle times, minimisation of raw material usage and optimised use of resources)

Design method to meet target criteria

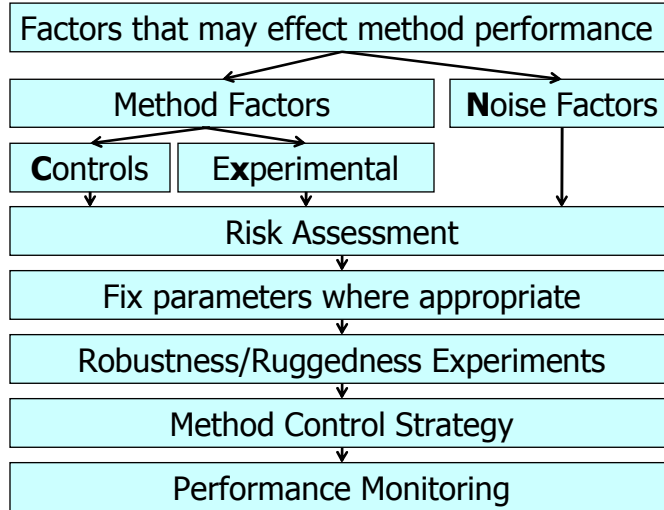


Determination of Critical Method Factors



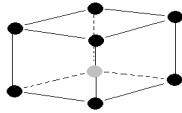
- Cause and effect analysis is instructive in identifying the factors that might influence method performance
- The factors can be grouped according to their influence on the method and the CNX system is a useful classification tool
 - C Analytical Method Factors which form part of the method definition and which can be specified at **C**ontrollable unique levels (SOPs)
 - N Analytical Method **N**oise Factors, unintentional variations that if identified as potentially critical may require **ruggedness** testing to assess impact
 - X Analytical Method Factors which form part of the method definition and which can be varied continuously and if potentially critical may require robustness **eX**perimentation to define the method operable design region

Assessing the Factors that may Influence Performance

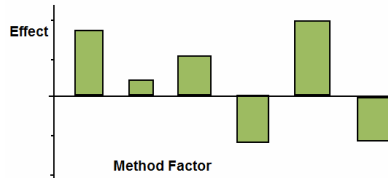
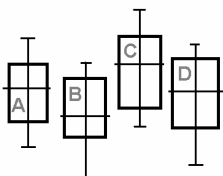


Understand impact of method parameters on performance

Design of Experiments for Experimental Factors



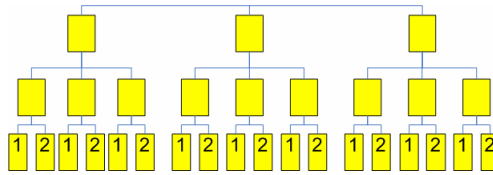
- Assess impact of defined 'internal' control & experimental factors
- Design of Experiments and multivariate analysis used to define the **method operable design region (MODR)**
- DoE approach important to identify any interactions between experimental factors
- Develop **control strategy** and set out in our method



Understand impact of method parameters on performance

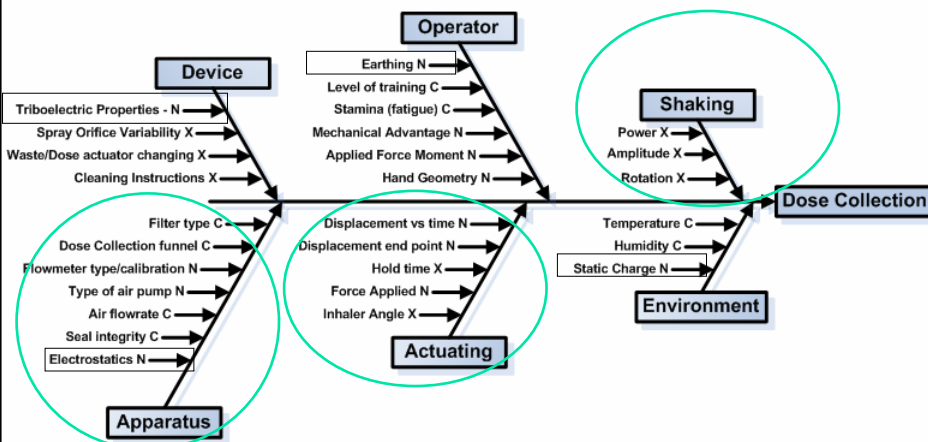
Measurement Systems Analysis of Noise Factors

- 'External' Noise factors that influence the ruggedness of the method can be assessed using measurement systems analysis (e.g gauge R&R)
 - For example, explore analyst, reagent grade, instrument, apparatus
- Study complexity dependant on no of factors/levels studied
- Nested/Crossed designs can be useful
- Perform ANOVA on the output
- Gain knowledge on source & extent of random variability



Understand impact of method parameters on performance

Dose Collection



Understand impact of method parameters on performance

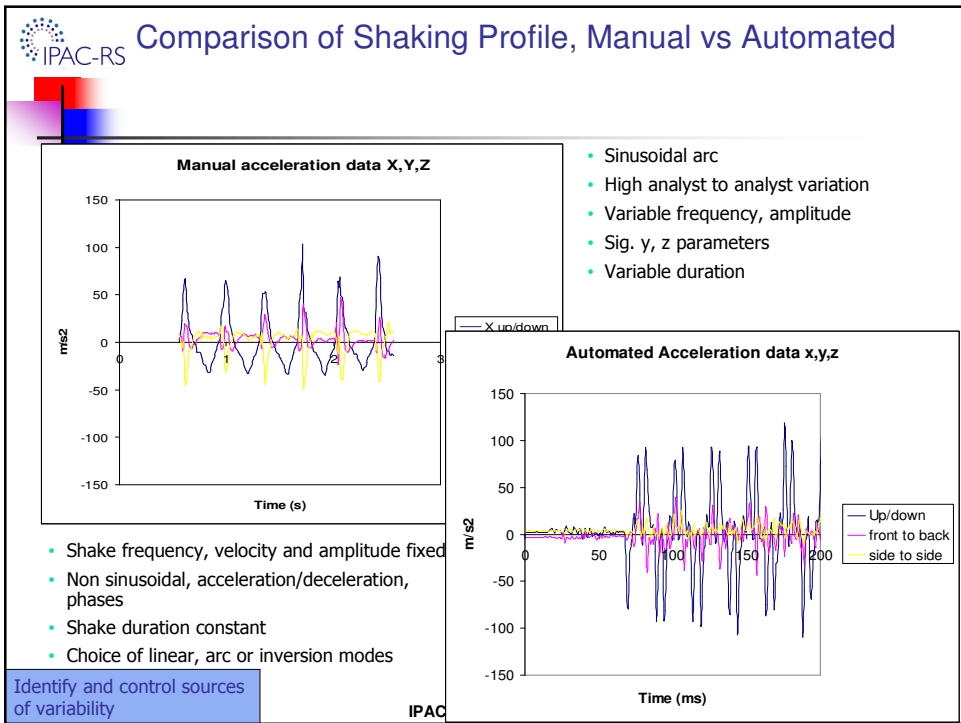
IPAC-RS **Prioritisation Matrix for Dose Collection X Factors**

Prioritisation Matrix							
Weighting	7	10	9	8	1	1	
	Accuracy	Repeatability	Intermediate precision	Reproducibility	Specificity	Linearity	Risk Score
Shaking to collect	9	9	9	9	0	0	306
Shaking to waste	9	9	9	9	0	0	306
Firing to collect	9	9	9	9	0	0	306
Firing to waste	9	9	9	9	0	0	306
Shaking to firing interface	9	9	9	9	0	0	306
Shaking Technique	9	3	9	9	0	0	246
Dose-Collector (Material & Dimensions)	3	1	3	9	1	0	131
Mixing time and process (Sample Prep)	3	3	3	3	0	1	103
Diluent composition (Sample Prep)	1	1	1	1	0	1	35
Volume of diluent (Sample Prep)	1	1	1	1	0	1	35

Understand impact of method parameters on performance

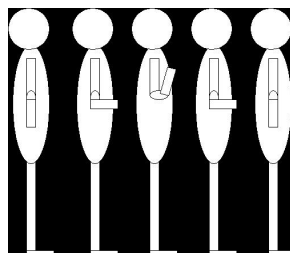
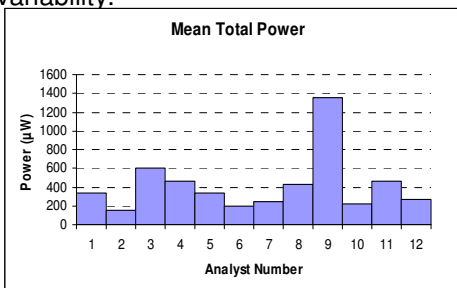
9= High
3= Medium
1= Low
0= none

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Standardised Manual Shaking Profile

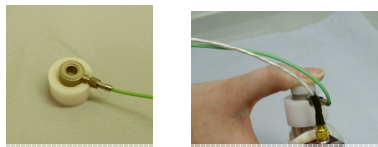
- Observations of manual shaking technique showed wide variation in technique and total power imparted to the device
- A standardised shaking profile introduced
 - Slow frequency, device moved through 180°
 - Short training video made & used extensively
 - Metronomes used as frequency guides
- In conjunction with training rig, helped to minimise analyst to analyst variability.



Comparison of Actuation Mechanism

Automated

- Fixed Down stroke/ hold/ release times
- Constant velocity
- Controlled, distance driven actuation between fixed points



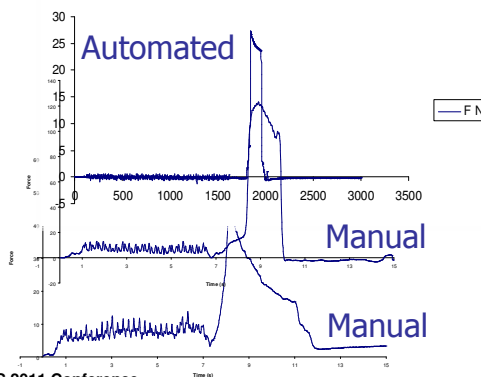
F N

Manual

- Variable force
- Lateral twist movements
- Variable timings

Improved actuation instructions were defined in the method

Identify and control sources of variability

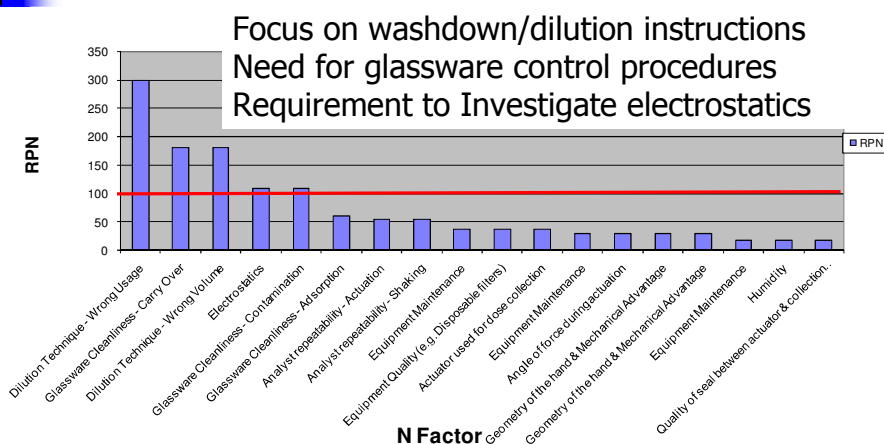


Dose Collection Noise Factors FMEA (Excerpt)

Category	Specific Factor	Potential Failure Mode	Potential Failure Effects	SEV	Potential Causes	OCC	Current Controls	DET	RPN
What is the factor category concerned?	What is the specific potential cause?	In what ways does the specific factor go wrong?	What is the impact on the Key Output Variables (ATP)	How Severe is the effect on the ATP?	What causes the Specific Factor to go wrong?	How often does cause of FM occur?	What are the existing controls and procedures that prevent either the cause or the Failure Mode?	How well can you detect cause of FM?	Risk Priority Number
Man	Dilution Technique	Incorrect use of volumetric glassware	Would impact both accuracy & precision	10	Analyst Error	3	Training	10	300
Man	Glassware Cleanliness	Unclean glassware	"Carryover" from previous analysis - impacts accuracy & precision	10	Ineffective Cleaning	3	Analyst pre-wash and/or machine wash process	6	180
Man	Dilution Technique	Use of wrong volume	Would result in an incorrect result but it would be precise	10	Analyst Error	3	Training, labelling & organisation of the lab.	6	180
Environment	Electrostatics	Changeable electrostatic effects	Could impact accuracy & precision	6	Lack of control	3	Understanding how electrostatics affect the result & then implementation of necessary controls	6	108
Man	Glassware Cleanliness	Unclean glassware	Interference - impacts accuracy, precision & specificity	6	Ineffective Cleaning	3	Analyst wash and/or machine wash process	6	108

Risk = Severity x Occurrence x Detection

Dose Collection Noise Factors - Prioritisation



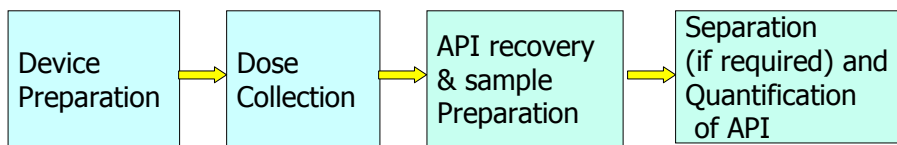
Identify and control sources of variability

Develop the Method Control Strategy

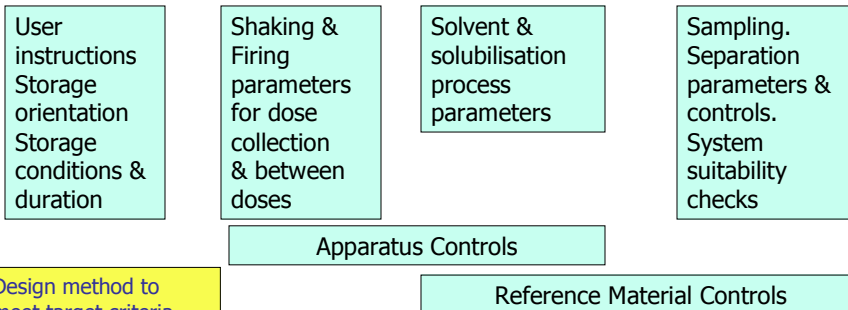
- Ensure the method requirements are consistently met via control of the identified critical analytical method factors.
- System suitability checks, instrument performance checks and run qualification procedures may all be used.
- For the manual Delivered Dose Uniformity method, continued training and monitoring is also important
- Automated Delivered Dose Uniformity method offers controls of specific critical parameters

Identify and control sources of variability

Analytical Method Controls

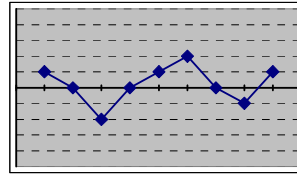


Example Control Strategies



Monitor Method Performance and Continually Improve

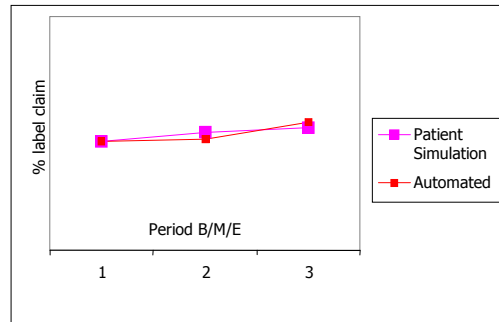
- Confirm continued method performance using control charts
- Assessment of analytical method capability expressed as a precision to tolerance ratio, may be instructive.
- Use accumulated knowledge base to assess the impact of any planned or proposed changes including method improvements and technological advances.
- Use the quality management system (see ICH Q10) to manage changes



$$\frac{6\sigma_{method}}{USL - LSL}$$

Monitor performance to ensure consistent output

Finalised Methods



- A comprehensive work programme resulted in an automated delivered dose uniformity method that produces dose profiles that are comparable with those obtained collecting doses as instructed by the patient user instructions.
- Knowledge gained allowed further optimisation of the manual method to also deliver comparable profiles

Summary

- Applying QbD Principles to Analytical Methods should result in;
 - Incorporation of the best scientific practice by linking prior knowledge of techniques and methods to an ATP
 - A mechanistic understanding, based on chemical & physical knowledge, of the factors that influence method performance
 - An investigation of multivariate relationships across method factors
 - An understanding how variation in these method factors affect the analytical result
 - This knowledge will provide
 - An insight on contribution method variability has on the overall product and process variability
 - More focussed method control strategy
 - A thorough understanding of the impact of any planned method changes
- Resulting in better methods in both their operation and outcome

Future Opportunities

- Does the Analytical Target Profile provide a means of proposing more advanced regulatory approaches to method submission and review for orally inhaled and nasal drug products?
- If we fully understand the sources of variability in each of the method 'modules' and take steps to control them we can;
 - Use risk based approaches to focus method design and control efforts in the most important areas
 - Propose greater flexibility for the modules that present the least risk or impact on the method outcome
 - This may facilitate continual improvement by making it easier to exploit advances in analytical technology

Acknowledgements

■ Working group members;

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