Application of Analytical Quality by Design to Pharmacopoeial Methods

Stakeholders are invited to comment on the draft supplementary chapter for the application of analytical quality by design to pharmacopoeial methods.

This chapter is not designed to be mandatory and is to be provided as selective guidance for the application of Analytical Quality by Design principles to pharmacopoeial procedures and across the entire Analytical Method Lifecycle. It is intended that the British Pharmacopoeia, together with its expert working party, will add to and revise this guidance as internal and external knowledge grows and further international standards are developed.

Details for the public consultation of this monograph are as follows:

WP - AQbD	**Working Party - Analytical Quality by Design**
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Deadline for Comment	30th April 2021
Target Publication (subject to change)	BP 2022
Notes:	**NEW SUPPLEMENTARY CHAPTER**

In addition to seeking comments on the document itself, stakeholders are invited to consider the following specific questions in responses to the consultation.

1. Do you/your company have a working knowledge of Quality by Design concepts and their application to analytical methods

2. Do you/your company work with pharmacopoeial methods regularly? In what capacity

3. Does this Supplementary Chapter help to inform you or your analysts on the value of applying AQbD to pharmacopoeial methods? Why? Why not?

4. Please suggest additional content, revisions and improvements that would enhance the value of this supplementary chapter.

5. What additional information, guidance and training would be useful in enabling understanding and adoption of analytical quality by design by users of the pharmacopoeia?

Application of Analytical Quality by Design to Pharmacopoeial Methods

1. Background

The development and control of an analytical method across the product lifecycle is a key element of the overall product control strategy. This control is built around a number of key concepts that have been described as 'Analytical Quality by Design (AQbD)[1]. The MHRA and British Pharmacopoeia have explored the practical application of these concepts to a pharmacopoeial assay procedure and are applying the learnings from this study(footnote) to individual finished product monographs, on a scientific and risk basis. This Supplementary Chapter describes the principles and introduces some practical guidance for the application of Analytical Quality by Design (AQbD) principles to pharmacopoeial procedures. The chapter covers:

- A discussion of Quality Risk Management (QRM)
    - Risk identification tools: Ishikawa/Fishbone
    - Risk analysis tools: FMEA
    - Risk evaluation and control
- Establishment of method understanding
    - Systematic method development and evaluation
    - Experimental design
    - Statistical approaches to support experimental design
- Analytical control strategy and ongoing trending of analytical methods

Supplementary Chapter SC I 'Basis of pharmacopoeial requirements' details the high-level use, application and need for pharmacopoeial procedures. The methods described in the Pharmacopoeia must be robust because they are intended to be used by analysts in a wide range of laboratories, sometimes on an infrequent basis. The General Notices of the British Pharmacopoeia make allowance for the use of alternative methods if it is known that the method used will give a result of equivalent accuracy. For example, where a manufacturer may wish to use their own optimised method. However, in the event of doubt or dispute, the methods of analysis of the pharmacopoeia are alone authoritative. Application of any of the concepts described in this supplementary chapter can support both the development of robust pharmacopoeial methods and alternative methods used by a manufacturer, and also the use of these methods during the product lifecycle to assure the quality of a particular drug substance or its pharmaceutical preparation.

Analytical Quality by Design is an evolving area of analytical science and this supplemental guidance chapter will be updated in future editions of the BP, with additional guidance on the application of the concepts to pharmacopoeial methods and their role within the Analytical method lifecycle.

2. Application to the British Pharmacopoeia

In general, analytical method performance, and therefore the results generated by an analytical method, are subject to variability during routine use. Therefore it is important to

1 https://www.researchgate.net/profile/Joachim_Ermer/publication/282481497_Implications_and_opportunities_of_applying_QbD_principles_to_analytical_measurements/links/5799e3ed08ae29e4fe3947c4/Implications-and-opportunities-of-applying-QbD-principles-to-analytical-measurements.pdf

understand the influence of variability on method parameters (e.g., temperature, solvent composition, etc. for an HPLC method) on the results generated by the method, as well as the effect of typical changes in method conditions that can occur over time and across laboratories (i.e., instrument type/design, reagent quality, sample shakers, analyst training, etc.)

Pharmacopoeial methods are intended to be applicable to a wide range of available formulations and this often requires review of data and laboratory evaluation of submitted, registered methods to ensure the methods are suitable for pharmacopoeial use. This process includes application of quality risk management principles and tools to focus the investigation of the most critical aspects of the method and maximise the knowledge gained from laboratory work.

The case study performed by the MHRA and the BP applied the following principles in a step-wise process in order to learn their how they can be applied effectively to pharmacopoeial procedures. The aim of this work was to demonstrate that AQbD can be used to ensure robust and fit-for-purpose methods being produced in the BP. The case study showed the value of their application to an Assay procedure and the BP is continuing to apply and further investigate the learnt principles to a range of pharmacopoeial procedures.

3. Quality Risk Management for Analytical Procedures

The process of building method understanding begins during method development and continues through the formal validation (in-line with conventional ICH Q2: Method Validation), verification and method transfer exercises and routine use, including with pharmacopoeial methods. Historically, the BP has utilised risk management principles to inform the laboratory evaluation of analytical methods. The outcomes of the AQbD case study have been used to enhance this process.

Users of the pharmacopoeia may not have prior knowledge of a given method, above and beyond what is detailed in the pharmacopoeia. This section summarises the application of quality risk management tools, including risk assessments, to analytical methods in the pharmacopoeia.

Prior knowledge, such as information contained within monographs, supplementary materials in pharmacopoeias, or information in the literature can be leveraged if available. Quality risk management (QRM) tools (See ICH Q9[2]) provide a framework for identifying, studying and understanding the risks to method performance and the results generated by the method. The QRM tools are most effective when initiated during method development or evaluation and applied iteratively. This allows inclusion of the most recent knowledge and reassessment of risks based on any new understanding.

Method development should involve a systematic screening of method conditions, including sample preparation, to identify a set of conditions as a starting point for further evaluation via risk assessments and the QRM process. In the case of a compendial method where formal method development may have been performed by the collaborating manufacturer or by an external laboratory, initial screening of method conditions (for example, screening DoE's –

[2] https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

see section 4) can aid in identification conditions to which the method is sensitive and inform the subsequent risk assessment process.

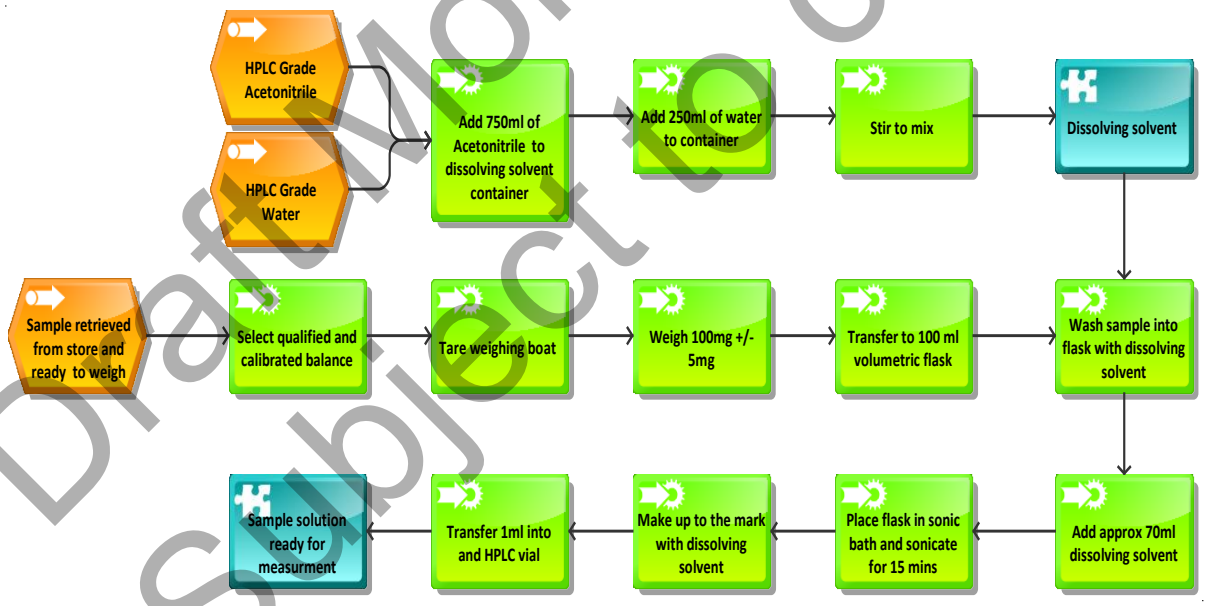
3.1. Quality Risk Management

Prior to 2006 risk management principles were not as extensively used in the pharmaceutical industry as they were in other areas of business. This changed with the publication of ICH Q9 which led to the industry adopting risk assessment processes in support of manufacturing, development and distribution of pharmaceutical products throughout the product lifecycle. One specific area where risk management approaches are being used extensively is in the development of robust control strategies for manufacturing processes. Risk management principles can also be used to develop control strategies for analytical methods. Adopting a risk-based approach ensures that controls applied to analytical methods are focussed on those parameters that are most likely to impact the reliability of the analytical result.

3.2. Risk Identification

The risk process begins by systematically identifying the potential variables associated with the analytical procedure. It is useful to perform a “walkthrough” of the procedure and identify and record all the steps involved. Process mapping and flow charts tools can be used to provide a pictorial presentation of all of the steps involved (fig 1).

Figure 1 – Example of process map for an HPLC analysis

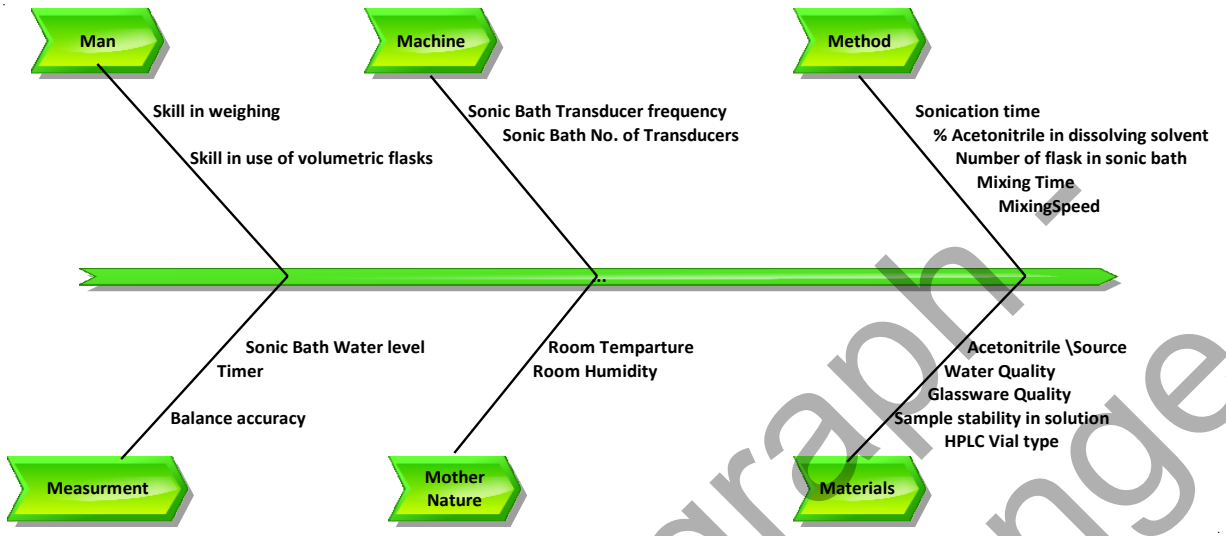


For complicated procedures it can be useful to break the steps down into different “unit operations” eg sampling, measurement, reporting etc.

Based on the process map, each of the steps in the procedure is reviewed and parameters that could potentially vary are identified. Tools such as an Ishikawa\Fish Bone diagram can be used to facilitate the brainstorming session. (Fig 2). A platform

approach could also be adopted with the use of templates for different types of analytical methods.

Figure 2 – Example of Ishikawa\Fish Bone diagram for sample preparation for HPLC Analysis



3.3. Risk Analysis

Risk Analysis involves estimating the risk associated with each of the variables identified in the previous step. It considers both the likelihood that the input may vary (probability) and the impact any variation is likely to have on the reportable result (severity). Numerous tools and approaches can be used to facilitate the risk analysis step (see ICH Q9 appendices for a range of examples).

A commonly used tool for performing a quantitative analysis is Failure Mode Effect Analysis (FMEA) – an extract from an example of which is shown in Fig 4.

Variable	Severity (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in dissolving solvent	3	4	12
Sonication Time (mins)	4	3	12
% Acetonitrile in the mobile phase	3	4	12
Wavelength	4	2	8
Humidity %	1	5	5
Equilibration time	1	2	2

Table 1 – example FMEA extract

With FMEA estimates are made for each input variable with respect to the probability of variation and the impact of any variation (severity) would have on the reportable result. As with identifying potential variables the effectiveness of the risk assessment step is heavily dependent on the knowledge available to support the estimates made. Where the knowledge of the impact a variable may have on the accuracy and\or precision of the reportable result is limited, experimental studies should be performed to provide this understanding. Design of Experiments (DoE) is an approach that can be used to identify effects of variables (separately and in combination) and minimise the experimental work involved in obtaining the necessary knowledge. When using an

FMEA approach it is useful to treat it as an iterative process and update the assessment as more knowledge and understanding becomes available.

3.4. Risk Evaluation and control

Once the risk associated with each input variable is understood an evaluation of the required controls is performed. These controls should focus on the variables which are most likely to impact the reportable result and ideally should eliminate the probability of variation. This is the first step in building an analytical control strategy for a method (see section 5.1). When using an FMEA approach this means identifying steps that will reduce the probability score so that the overall risk is reduced. Once such steps have been identified the risk score should be reassessed with the controls in place.

Where the probability of variation cannot be reduced significantly, consideration should be given to whether there are opportunities to detect the variation before the reportable result is generated. An example of this is where it is believed that batch to batch variation in chromatographic packing material cannot be eliminated, a resolution check may be introduced to detect any potential impact on the accuracy of a result (see section 5.2 for trending concepts). Indeed ideally “system suitability” tests should always be included to mitigate known risks rather than to satisfy a standard method template.

4. Establishing method understanding

The effectiveness of a risk assessment, and ultimately the analytical control strategy for a given method, is related to the level of understanding of the relationship between method parameters and the method output ie the result. Section 4 sets out approaches to ensuring method understanding that can be adopted throughout the product lifecycle?

The MHRA and British Pharmacopoeia case study on Atorvastatin Tablets has been used to illustrate how the Pharmacopoeia may apply AQbD concepts when assessing a methods suitability for compendial use. It is not expected that all of the concepts are used for assessment of the suitability of the method.

4.1 Systematic method development and evaluation

In support of risk assessments, experimental studies are conducted to understand the impact of method parameters and environment on method performance. These experimental studies are usually based around two purposes:

- the influences of deliberate variations in procedure-related method parameters (solvent strength, pH, sample concentration, etc.)
- the influences of ‘noise’ factors (analyst, column batch etc.) which typically cannot be, or are preferred not to be controlled are evaluated.

When investigating deliberate variations in procedure-related method parameters multifactor empirical modelling (e.g., DoE's) is generally preferred compared to One factor at a time (OFAT) experiments, though OFATs may be appropriate in some cases. Mechanistic modelling, or combined mechanistic and empirical modelling, have the potential to reduce the experimental burden and can be employed when demonstrated to be appropriate. The effect of method changes on the results generated by the method can be considered in addition to other key method attributes (for example, resolution, sensitivity, accuracy, etc.) to understand method performance and to optimize method conditions.

'Noise' factors can often be the root cause of issues arising through the routine use of analytical methods. It is possible that not all of these factors can be studied experimentally, however through the systematic investigation of those that can be studied, the risk of method failure may be reduced. Investigations of 'Noise' factors typically require designs applicable to factors with discrete levels and are used to challenge the method and understand their effect on precision in the longer term. Identification of a noise factor having a large effect on the variation of test results may indicate that control of additional method parameters is needed.

The British Pharmacopoeia's case study used several experimental designs, utilising multifactor approaches to determine the effect of several chromatographic, sample preparation and stability factors with minimal injections (see section 4.2). The case study also investigated 'noise' factors though, as that investigated multiple product suppliers which is mainly applicable to pharmacopeial use, a more typical non-pharmacopeial example of the study of 'noise' factors is provided in section 4.2. By necessity the case study explored these concepts extensively and it would not necessarily be appropriate or effective to uniformly apply these concepts for all methods

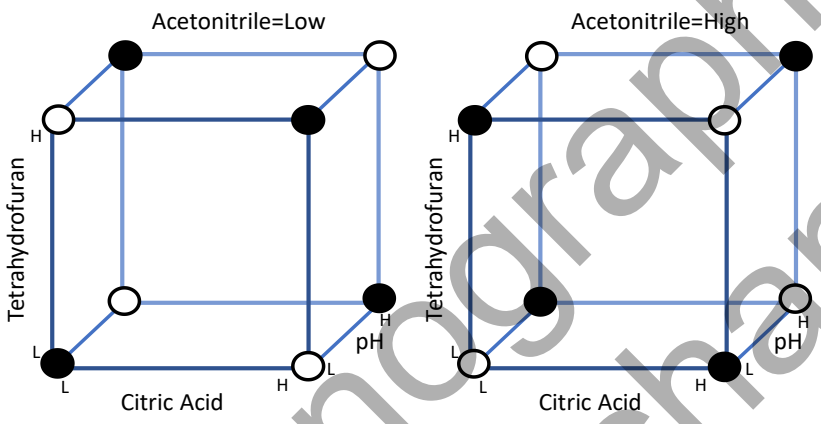
4.2. Utilising method development tools and statistical analysis.

Analytical method parameters are factors related to the operation of the method which can be specified within a continuous range or at controllable, unique levels. Experimentation which uses fractional factorial designs ("DoEs") to develop general purpose (linear) models describing the effect of changes in analytical method parameters is outlined below. These models are used to identify and/or confirm (typically) a setpoint and ranges for analytical method parameters, which in combination assure robustness. It is possible to define a wider operating region throughout which the method may be operated but this is not typically done.

As part of the practical application of AQbD to the pharmacopoeial Assay procedure, DoEs were performed to investigate sample extraction, chromatography and solution stability. The two-level fractional factorial design for the investigation of four mobile phase factors is illustrated in Figure 3. A full two-level factorial design consists of all the combinations of chosen low and high levels of the parameters as represented by the corners of the cubes. A fractional factorial design uses a specific set of points (fraction) - as shown by the solid circles in this example. Here it is a half fraction

because the design uses 8 out of the possible 16 (2^4) combinations of low and high levels for the four factors. In addition, centre points (mid value between low and high and often the planned setpoint for the method) are used to estimate variability at the same conditions and assess whether a linear model in the parameters is adequate. Fractional factorial designs are very effective due to hidden replication (half of the factorial points are performed at a level of a parameter rather than just one for OFAT experiments) and it is not necessary to run all factorial combinations (an adequate model is usually obtained from the effects of single factors or interactions between two).

Figure 3: Fractional factorial design (solid circles) for four factor mobile phase experiment

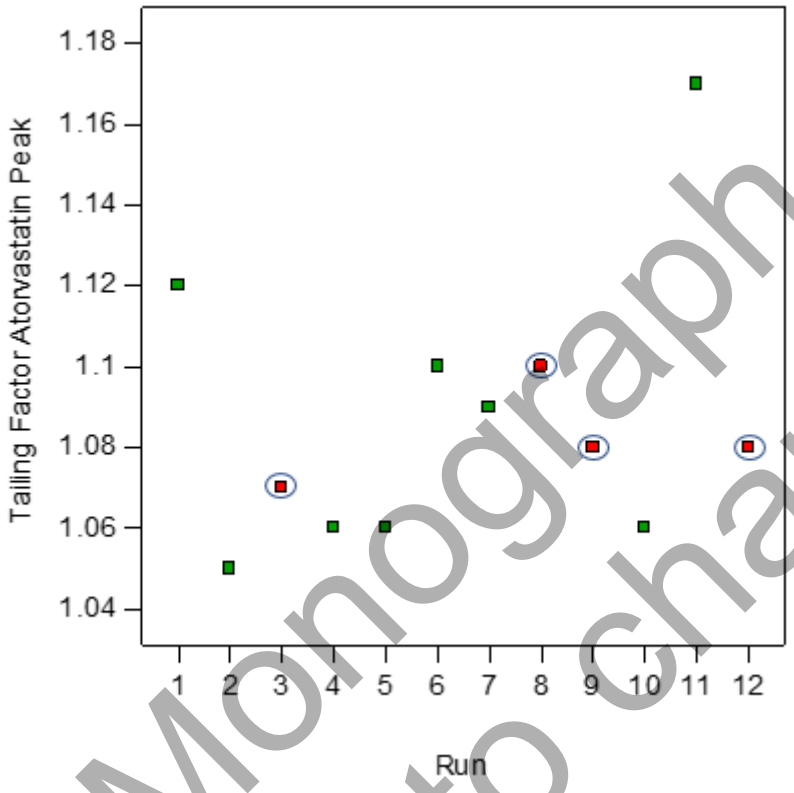


Whilst Figure 3 illustrates the concept, a design listing (see Table 2) is used to describe the design. It is useful for any number of parameters to be investigated and describes the random order in which the design is to be run. The method is operated under the condition for each run in turn and the results recorded. For illustration, the tailing factor response is listed in Table 2 and plotted in Figure 4.

		Factor A	Factor B	Factor C	Factor D	Response 1
Run Order	Space Type	Citric Acid (g)	pH	Tetrahydrofuran (mL)	Acetonitrile (mL)	Tailing Factor Atorvastatin
1	Factorial	8.66	3.8	130	175	1.12
2	Factorial	8.66	3.8	70	95	1.05
3	Centre	9.62	4	100	135	1.07
4	Factorial	10.58	3.8	130	95	1.06
5	Factorial	10.58	4.2	70	95	1.06
6	Factorial	8.66	4.2	130	95	1.1
7	Factorial	8.66	4.2	70	175	1.09
8	Centre	9.62	4	100	135	1.1
9	Centre	9.62	4	100	135	1.08
10	Factorial	10.58	3.8	70	175	1.06
11	Factorial	10.58	4.2	130	175	1.17
12	Centre	9.62	4	100	135	1.08

Table 2: Design Listing for Mobile Phase Composition DoE

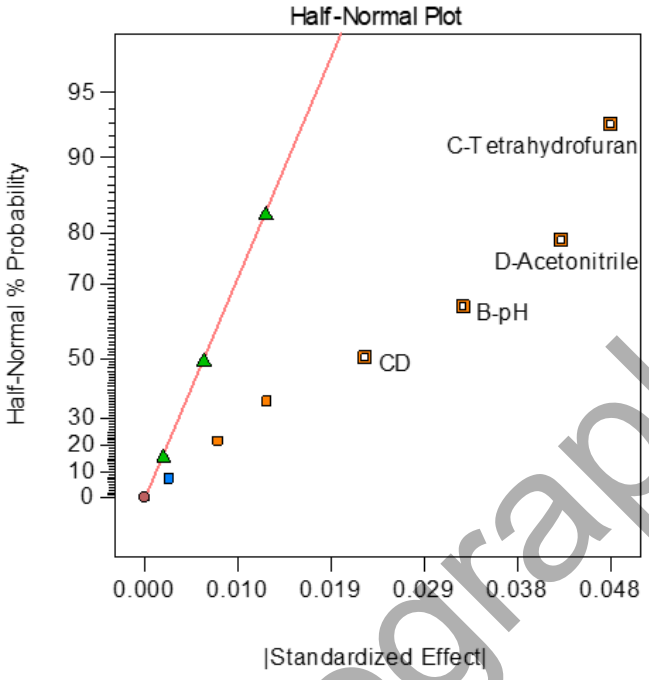
Figure 4: Tailing factor for the Atorvastatin peak plotted against run (centre points are circled)



The acceptance criteria for tailing factor Atorvastatin peak is ≤ 1.2. If all the results from the DoE runs had been far below the acceptance criteria a statistical analysis may not be required, though if there is a wide range between the factorial points it is useful to understand which parameters may cause this. Here it is seen that one run had a value of 1.17. Though this meets the criteria it is possible that a combination of factor settings not explored in the design may exceed 1.2. Also, it is noted that repeating the same conditions will give variable results (see variation in the centre points). Thus, a statistical analysis is desired.

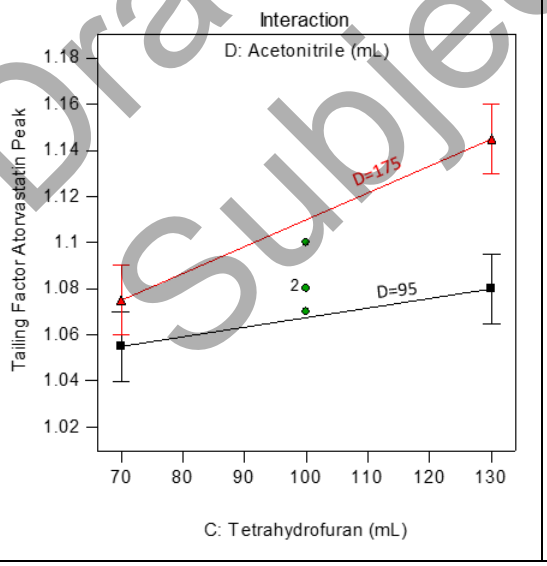
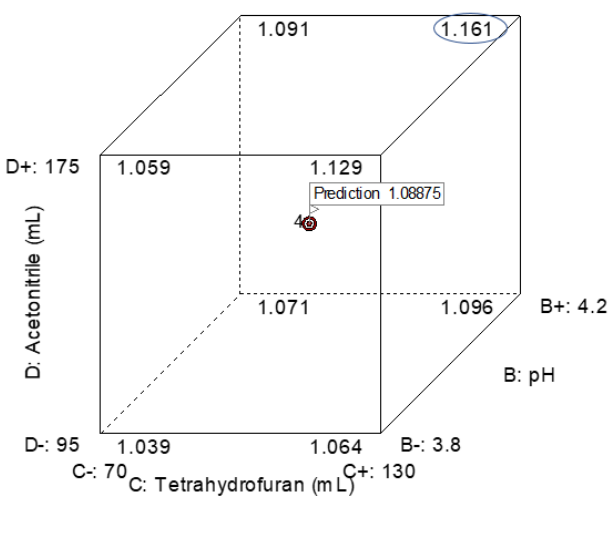
The first step in the statistical analysis is to identify which are the major parameter effects. Figure 5 illustrates one tool – a half-normal plot. Model terms are selected (represented by small squares) which are greater than background noise (to the right of the line through the triangles which represent the background variability estimated from the four centre points). Parameters Tetrahydrofuran (C), Acetonitrile (D) and pH (B) have the largest effects. The fourth term selected is an interaction between two parameters. Statistically it is not possible from the design to know whether this is the interaction between A and B or C and D. Since C and D are the largest effects and this makes analytical sense the CD interaction was also included in the model. The next term was not included in the model. It was not statistically significant, it is small and the design cannot distinguish between the two possible interactions, BC and AD.

Figure 5: Half-normal plot for model terms for Tailing Factor for Atorvastatin peak



A statistical analysis will typically assess statistical significance of terms identified for inclusion in the model and assess assumptions used in the modelling (linear model is adequate, residuals are normally distributed and no outliers are observed). The model is then used to predict the effect of method parameters. Figure 6 shows the effect of Tetrahydrofuran, Acetonitrile and pH on the mean tailing factor.

Figure 6: Effect of Parameters on Tailing Factor.

Effect of Tetrahydrofuran and Acetonitrile at centre conditions of pH (Citric acid not in model, circles are values at centre points)	Combined effect of pH, Tetrahydrofuran and Acetonitrile (worse conditions circled)
	

Various system suitability responses were examined (tailing factors, efficiencies, resolution, retention times). In addition, the effect of method parameters on %assay may be examined. The %RSD of %assay over the combinations investigated may be useful in addition to a similar analysis to that applied to the tailing factor.

If the model only contains linear terms for parameter effects and any interactions then it is sufficient to establish that results are acceptable at the limits of the parameter ranges (in combination). If the model is more complex than linear e.g. curvature in an adverse direction, or a mechanistic model, then evaluation within the parameter ranges may be required. If a model with linear terms is insufficient, response surface designs may be used to include quadratic terms to model curvature. If the results are not acceptable at the limits of the parameter ranges, it may be possible to use the model to predict ranges within those investigated, in which the method could be satisfactorily operated or further experimentation may be required to identify an acceptable region. Where mechanistic models are available (e.g. chromatographic in-silico modelling systems), designs appropriate to the model should be applied (and in some cases little experimentation may be required).

Examples in literature[3] provide a very comprehensive explanation of full and fractional factorial designs and the application of experimental design to analytical methods (focused on chromatography)[4]. The design should be carefully chosen to meet the purpose of the study – is the design intended to identify parameters having an effect or optimise a method over a wide parameter region, or to assess robustness around the setpoint. A limited evaluation of the data could be gained from plotting the data and calculating means at the low and high levels for each factor to establish which has the largest effect. However, to understand interactions between factors, assess statistical significance (i.e. that effects seen are likely not to be due to chance) and produce predictions, software that can fit general purpose models with linear and quadratic terms in the parameters is likely to be required. Software which combines functionality for designing factorial type experimentation with corresponding statistical analysis is particularly helpful. The software may be integrated with a chromatographic system, focused on designed experiments (either entirely or a specific module) or more general statistical software.

4.3 Assessment of variation in method operating conditions

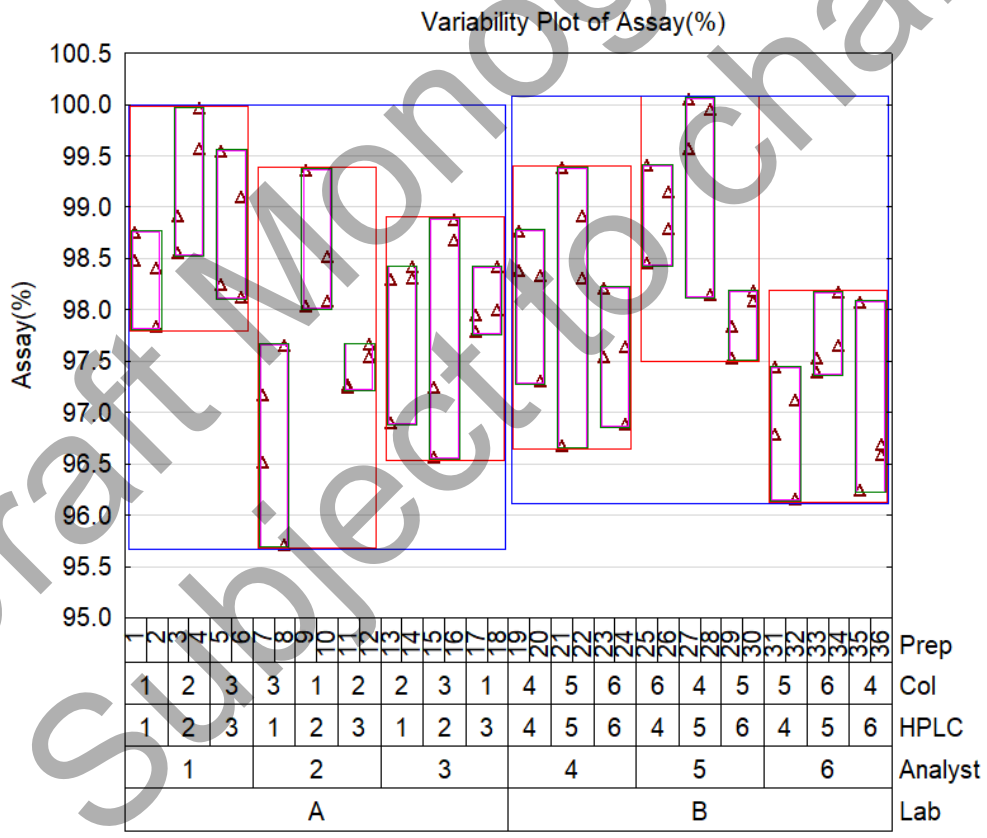
The variation in method operating conditions considered here are typical changes in method conditions that can occur over time and across laboratories, (i.e., instrument type, reagent quality, sample shakers, analyst training, etc.). These are changes which are not specified or controlled as method parameters- “noise factors**”.** Studies are designed with the purpose of challenging the method and to understand their effect on precision in the longer term. Noise factors having a large effect on the precision can be identified and further investigated with the aim of improvement and/or control where possible. In contrast to the designs for assessing the effect of

[3] https://www.springer.com/gp/book/9780387891026 - Mee, Robert. *A comprehensive guide to factorial two-level experimentation*. Springer Science & Business Media, 2009.
[4] https://pubmed.ncbi.nlm.nih.gov/22333438/ - Hibbert, D. Brynn. "Experimental design in chromatography: a tutorial review." *Journal of chromatography B* 910 (2012): 2-13.

analytical method parameters which predominantly evaluate continuous factors, the focus of these studies is on factors with discrete levels, uncontrolled in the method description e.g. analyst. It is often useful to perform such a study as part of a method transfer as the two activities can be combined saving resource and the use of two labs provides more challenge to the method.

Figure 7 shows an example study – the design should be chosen based on the risk assessment and the practicalities which apply. The factors and chosen levels can be seen at the bottom of the plot. Factors may be “crossed” or “nested” in such a design. In the example analyst, HPLC and column (col) are nested within lab, i.e. an analyst only occurs at one site. Prep is nested within each analyst, HPLC and column combination and two injections are performed for each prep. However, analyst, HPLC and column are crossed with each other i.e. an analyst uses more than one HPLC equipment. It is desirable to use a reasonable number of levels for all factors in the design (not just preps and injections) in order to better allow any effects/variation due to the factor to manifest itself during the study (acknowledging that there will be practical constraints).

Figure 7: Plot of assay results from a study of potential noise factors



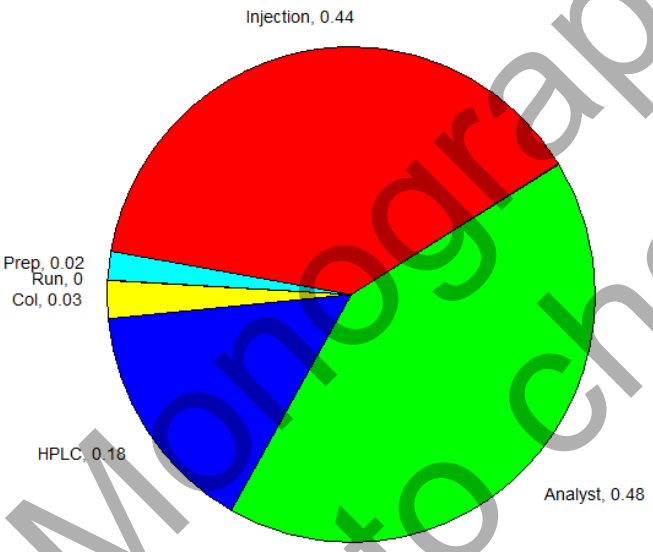
The statistical analysis typically consists of visualising the data and fitting models to estimate the variation due to each noise source or their interactions (variance components). This is usually a variance components or mixed model analysis.

Figure 8 shows the results of a statistical analysis with the estimated variance components shown for the various factors. It is seen that the injection variation and

analyst variation contribute most to the variation. Some variability due to HPLC is also seen but the column and preparation contribute very little variability.

Figures 7 and 8 show the clear benefits of using data visualisation to identfy the cause/s of variation. Figure 5 appears to show variation at all levels other than between laboratories. This indicates a systematic issue with the methodology, which is being replicated from Lab A to Lab B. Digging deeper, figure 6 shows that the main proportion of variance is from injection to injection and analyst to analyst, rather than preparation, column or HPLC instrument. This type of analysis can be key to both identifying issues with procedures during validation as well as during a root cause analysis on existing procedures, where an issue may have occurred.

Figure 8: Variance components from various noise factors



The precision of the analytical measurement can be calculated by summing the variance estimates, taking into account any replication used in providing the reported result. For example, the intermediate precision (variance) for a reported result from the mean of two preparations would be found by summing the variance components for between analytical run sources of variability (Analyst, HPLC, Column, Run) and half of the prep and injection components of variance. Thus:

SD= sqrt(0.48+0.18+0.03+0+0.02/2+0.44/2)=0.96. The overall mean of the results was 98.0 giving a %RSD=100*0.96/98.0 = 0.98%.

Additional literature sources provide further details and examples of such studies[5]. Performing the study and plotting the data can be useful in its own right. However, to perform the statistical analysis to gain most information from the study, software that can fit mixed models is likely to be required (usually Restricted Maximum Likelihood – REML is used).

[5] https://pubmed.ncbi.nlm.nih.gov/21889624/ - Borman, Phil J., Marion J. Chatfield, Ivana Damjanov, and Patrick Jackson. "Method ruggedness studies incorporating a risk-based approach: a tutorial." *Analytica chimica acta* 703, no. 2 (2011): 101-113.

5. The analytical control strategy and its role in ongoing monitoring of method performance.

5.1. Analytical Control Strategy

ICHQ10 defines a control strategy as *a planned set of controls derived from product and process understanding, that assures process performance and product quality*. *The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control*.

Clearly this definition applies to manufacturing processes however the idea of a control strategy for analytical methods mirrors the above if the output of the process is regarded as the reportable result rather than a drug product. The key point is that the control strategy should be comprehensive and consider all of the materials used, operating conditions, system suitability checks, etc that are required to assure the quality of the reportable result.

Sections 3 and 4 detail the concepts one may adopt to produce an analytical control strategy built on deep method and product understanding. The MHRA case study confirmed that a suitable control strategy for the atorvastatin tablets Assay method was to follow system suitability criteria in the form of a minimum resolution between a critical pair (Atorvastatin and close eluting related substance).

For a pharmacopoeial method, the chromatographic conditions and permissible adjustments set out in Appendix III Chromatographic Separation Techniques are complementary to the analytical control strategy developed in line with the processes described in this supplementary chapter.

5.2. Ongoing monitoring of methods

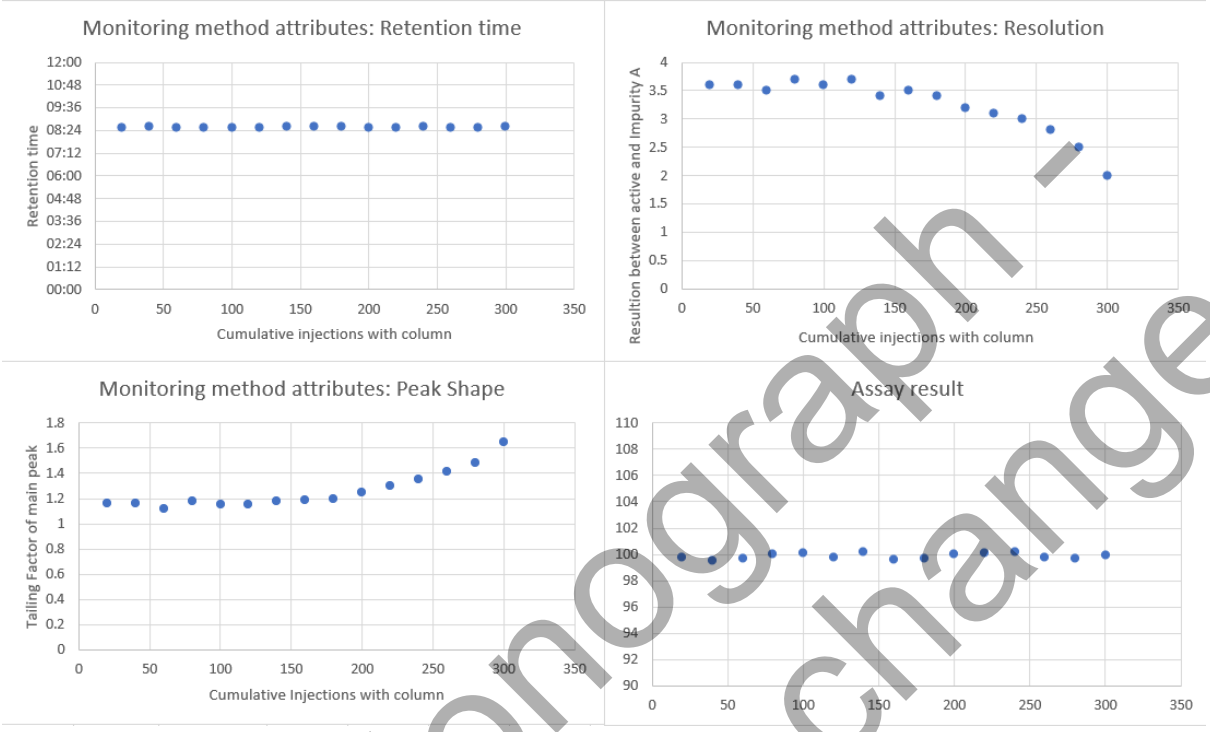
Monitoring of the results of analytical methods helps to build process capability insights. However, additional trending of a range of different method outputs is another strategy used to identify areas of risk and alert users to take action before method failure.

Monitoring an analytical method is helpful since it can alert users to trends. There are different ways to conduct monitoring – trending results, control sample results, performance attributes (e.g. retention time of specific analytes, peak shape of principle peaks and more). Monitoring of measurements for reference or standard material repeatably analysed over time may also be useful.

Figure 9 is a simple model of additional parameters that may require trending through the lifetime of a method (or in this case, an individual column. Here you can see an inverse relationship between the resolution of critical pair and the peak shape of the active. In this instance, an increase in peak tailing is causing a loss in separation between the drug substance and a major impurity. Ultimately, the Assay

value here is unaffected, however the resolution is heading towards a failure of system suitability criteria, as is the peak shape.

Figure 9 – Example of control charts monitoring different aspects of ongoing method performance



It is noted that statistical techniques may also be useful in monitoring the performance of system suitability and/or reference measurements over time.

6. Glossary of Terms

Some of the terms used in this supplementary chapter carry different meanings which depend on their application. For all purposes where the following words are stated in this chapter, the intended meaning is as follows:

Ruggedness – *Effects of 'noise' factors on the performance of the method, ones which may not be specifically controlled in the procedure.*

Robustness – *Effects of changes to the procedure-related method parameters on the performance of the method.*

Variable – *Any aspect of a procedure which may cause variance.*

Parameter – *A Variable specifically related to the analytical method – eg: (HPLC Column temperature, solution concentration etc…)*

Procedure – *Entire process, encompassing the method resulting in a reportable value. This may also detail a study design, a sampling plan, an analytical replication strategy, and calculations.*

Method – *The operational components comprised of instrumentation, reagents, standards, sample preparations, calibrations, controls, and suitability criteria.*

OFAT (one factor at a time) – An experimental design process which adjusts a single parameter in a step-wise fashion to learn the effect that this parameter has on the performance of a method or process.

Reportable Value - The numerical value/s obtained through following set procedures,