Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Technical Review of MHRA Analytical Quality by Design Project.

Published: June 2019

Produced by Medicines and Healthcare products Regulatory Agency

10 South Colonnade,
Canary Wharf,
London E14 4PU

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. As a concept, it aims to assure the quality of medicines by using enhanced approaches to design, development and manufacture of medicinal products. The application of QbD principles to analytical methods is being explored by industry, regulators and academia.

Pharmacopoeial standards are a key component of a regulatory framework. For medicinal products in the UK they are published in the British Pharmacopoeia (BP), a publication of the MHRA. Pharmacopoeial standards evolve with advances in the manufacture of medicinal products.

The MHRA has explored how Analytical Quality by Design (AQbD) may apply to pharmacopoeial standards in collaboration with industry experts. This case study focussed on the practical application of AQbD principles to the development of an analytical procedure for the Assay of Atorvastatin in Atorvastatin Tablets.

Adopting a structured risk-based approach to pharmacopoeial method development utilising AQbD principles has demonstrated clear added benefits. This paper provides a critical review of the project, while introducing initial key outcomes and conclusions. The outcomes of this case study do not represent recommendations or guidance on best practice but represents the cumulative experiences and learnings to date. This report supports a public consultation that seeks to fully understand the implications of adopting AQbD principles in pharmacopoeial standards.

Contents

1. Introduction

The principles of Quality by Design (QbD) aim to assure the quality of medicines by using enhanced approaches to the design, development and manufacture of medicinal products. The benefits of integrated approaches focused on understanding, controlling and mitigating sources of variability have been widely recognised by industry and regulatory authorities as pivotal to manufacturing process robustness and enhanced product quality; these principles are illustrated in ICH guidelines Q8, Q9, Q10 and Q11, which are widely applied as a framework to the application of QbD to drug substance manufacture, finished product formulation and process development

Application of QbD to analytical methods (AQbD) has been explored by industry, academia and Pharmacopoeias[1, 2, 3, 4]. This includes defining the method performance requirements via an Analytical Target Profile (ATP) and the use of structured, risk-based approaches to method development and evaluation (e.g. FMEA and DoE). Attempts have been made to more fully define the ATP concept, which, for example, can be considered the maximum permitted measurement uncertainty associated with the reportable value, based on the accuracy and precision performance requirements of the analytical method. However, a lack of an agreed definition has led to a variety of approaches being proposed[3,5].

Pharmacopoeial standards enable users to make an objective assessment in relation to the quality of a material by the provision of analytical procedures and acceptance criteria. Pharmacopoeial quality standards are one of the foundations of ensuring acceptable quality, along with GXP and regulatory assessment

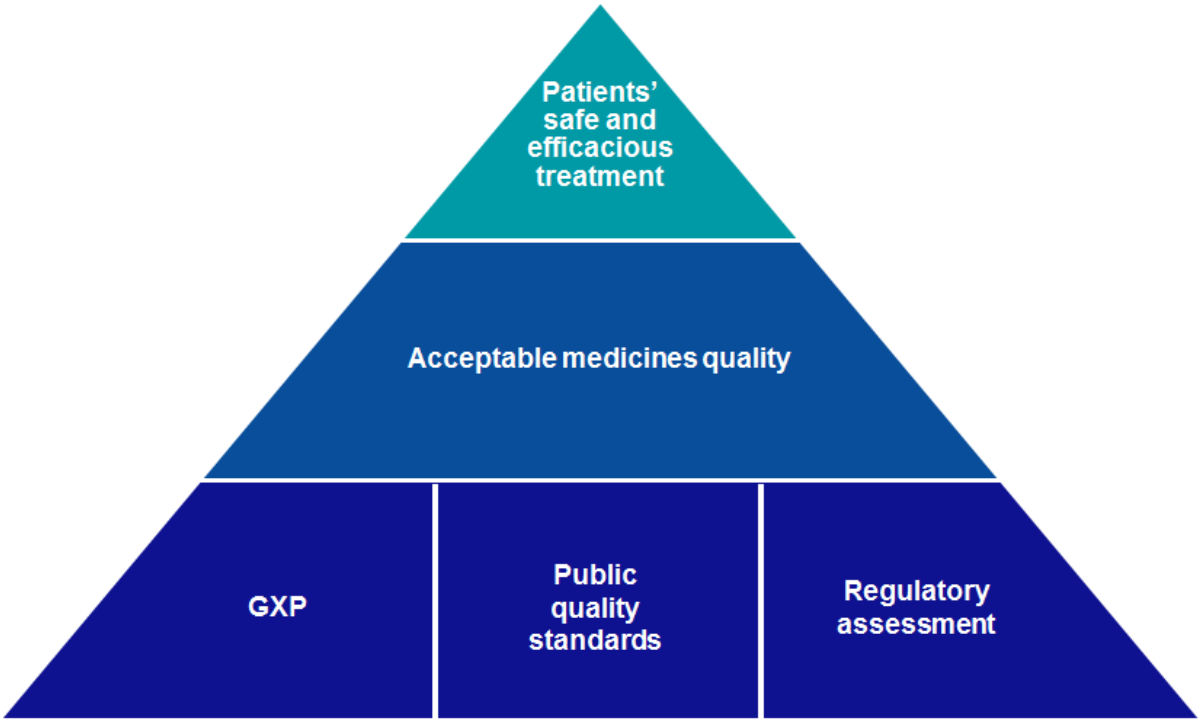

Figure 1 - GXP – This refers to good practice quality guidelines and regulations. For medicines manufacture this refers to good manufacturing, distribution (GDP), clinical (GCP), laboratory (GLP) and pharmacovigilance (GPvP) practice.
Regulatory assessment – The independent review by a national competent authority of pharmaceutical, non-clinical and clinical data to demonstrate the quality, safety and efficacy of a medicinal product in order to evaluate its suitability for commercial supply.

British Pharmacopoeia (BP) scientists, together with MHRA Licensing and GMDP Inspectorate colleagues have undertaken a unique collaborative project to investigate the application of AQbD principles to compendial analytical methods. The project also aimed at ensuring alignment across regulatory and standard setting functions of MHRA, as well as maximising learnings across the Agency.

Engagement with stakeholders has been critical to the success of the project and therefore an official working party of the BP was convened to provide oversight; the working party comprised expertise from our peers in the Therapeutic Goods Administration of Australia (TGA), multinational biopharmaceutical manufacturers, the generics manufacturing industry and from the field of metrology.

The project investigated:

- The application of different approaches to defining/using the ATP to better understand the use and value of the ATP concept and explore its relevance and applicability to compendial methods.
- The application of AQbD enhanced approaches to pharmacopoeial method development and verification, to improve robustness and understanding of the analytical procedure.

The investigations, outcomes and critical appraisal of the project are described in this paper. The outcomes of this case study do not represent recommendations or guidance on best practice but represents the cumulative experiences and learnings to date.

2. Strategic case for AQbD

At a national level, there are a number of Government initiatives designed to support growth and enable innovation in the healthcare sector. This includes the Accelerated Access Collaborative[6] and more recently the life sciences industrial strategy and associated sector deals[7].

Within the MHRA, the Agency's Corporate Plan 2018-23[8] identifies technological and scientific changes along with new areas of regulation as key strategic challenges to be addressed. Key objectives include:

- *We will ensure the safe production and supply of medicines and healthcare products through enhanced systems and strong international partnerships*
- *We will support and enhance innovation and accelerate routes to market to benefit public health and be a magnet for life sciences*

There is a compelling case for the pharmacopoeia, working with the wider Agency, to consider how it can further support these important strategic objectives.

The publication in November 2018 of the concept paper; ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical validation included using AQbD concepts as a potential approach to both Analytical Development and Validation.

Pharmacopoeial standards have and should continue to evolve and adapt to meet public health needs and expectations arising from novel technology and new medicines. However, the current conventional design and model for monographs and their component analytical procedures have not changed substantially since the initial elaboration of the modern BP monograph.

Whilst the outcome of the consultation on the Agency strategy for pharmacopoeial pharmacopoeial standards for biological medicines was published in late 2017[9] and forms an important component of the pharmacopoeias future work, this AQbD project has been undertaken to consider the future approach for existing and future pharmacopoeial standards and medicines.

The case study sought to address two key challenges which were strongly aligned to the Agency's strategic objectives:

- Ensuring pharmacopoeial standards and their component analytical procedures, are robust and fit-for-purpose in a more complex medicines landscape
- Ensuring that pharmacopoeial standards act as enablers and are supportive of innovation.

3. MHRA AQbD case study

3.1 Selection of Atorvastatin Tablets

The elaboration of a validated assay procedure by HPLC for a new BP monograph for Atorvastatin Tablets was chosen as the project case study, for the following reasons:

- Medicinal Product
  Atorvastatin Tablets, indicated for the management of hypercholesterolaemia and prevention of cardiovascular disease, are widely prescribed for long term, repeat use. Due to the diverse supply chain and the large generic market for Atorvastatin Tablets in the UK, there is a significant drive for the BP to publish a product specific monograph to further ensure high standard in product quality across the large number of manufacturers of Atorvastatin Tablets.

  Furthermore, these products have a relatively high percentage content of active substance and standard tabletting processes, making it a good candidate for this case study.

- Monograph Test: Assay
  Tablet content assay was the preferred focus for the project, with limits of 95-105% labelled strength. Ensuring the correct content of active substance in a medicinal product is one of the fundamentals of a product's control strategy. For Quality Control (QC), a fully quantitative, validated assay procedure is required for most medicinal products. If appropriate, the learnings from initially investigating the Assay procedure could then be applied to other tests (eg: dissolution, related substances) with additional and more complicated variables.

  The aim of the project was for the BP to apply and evaluate several AQbD concepts to understand how they could support the development of a pharmacopoeial assay method that was fit for purpose, robust and capable of providing adequate control of the quality attributes of the reportable value for content of active substance.

- Method procedure
  For approved atorvastatin tablets, typical methods of analysis were isocratic reverse-phase HPLC, a technique ubiquitous in QC testing of medicinal products.

An initial evaluation compared two different, validated reversed-phase HPLC methods, one isocratic provided by the innovator and the other a gradient elution method from the EP atorvastatin calcium trihydrate drug substance monograph used for the assay and related substances tests.

The isocratic procedure was chosen for ease of use for the analyst, without loss of functionality or selectivity.

3.2 Experimental

The chosen method was subject to a series of investigations designed to explore different AQbD tools and concepts (as listed below) for their suitability in the assessment of Atorvastatin Tablet products authorised for the UK market:

- Establishment of an ATP
- Detailed risk assessment techniques
- Review and effect of formulation study
- Design of Experiments (sample preparation, chromatographic parameters, solution stability)
- Further Design of Experiments (mobile phase organic content)

Each experiment is detailed below.

3.2.1 Method Risk Assessment

A structured risk assessment was undertaken to fully understand the significant sources of potential variability and inform the subsequent experimental designs.

Prior to identifying any factors, a 'method walkthrough'[10] was conducted by representatives from industry, the BP laboratory and the MHRA, to ensure effective knowledge transfer of the method development history. This allowed a detailed process map to be developed for the procedure with an extensive list of variables assigned to each step.

A number of tools were then used to facilitate the risk assessment. A fishbone diagram was used to brainstorm all the potential factors that could affect the variability of the analytical procedure. Factors were then categorised as either 'C' ('controlled' - factor intended to be fixed and controlled), 'N' ('noise' - factor not controlled), 'X' (experimental factor - intended to explore experimentally to establish values/ranges)[11]. Quantitative risk assessments (e.g. use of failure mode effect analysis (FMEA)) were used to assess the 'N' and 'X' factors which could affect the performance (e.g. variability, accuracy, sensitivity) of the analytical procedure. Factors relating to the sample preparation, chromatography and solution stability were identified as having the greatest impact.

3.2.2 Review and Effect of Formulation study

A short study to determine the impact of different formulations on the extraction of Atorvastatin from the finished product was performed. The range of the products were selected to represent a "worst case" scenario for pharmacopoeial methods. The involvement of MHRA Licensing colleagues ensured that there was a full and comprehensive review of over 100 different products authorised in the UK.

This review revealed a diversity of formulations, with a wide range of excipients with different properties and functionality, containing different active substance polymorphic forms and produced using different manufacturing processes e.g. wet granulation or direct

compression. Five products, including the innovator product, were selected to be test materials for the AQbD case study. These five products were chosen to cover the wide range of authorised products and challenge the analytical method in terms of potential matrix effect.

The results of this study demonstrated that there was no significant impact observed on the Assay of Atorvastatin across the 5 products due to sample extraction, recovery and chromatographic interference.

3.2.3 Design of Experiments (DoE)

Based on the outcomes from the *Method Risk Assessment* (3.2.1) and the *Review and Effect of Formulation study* (3.2.2) three DoE studies were performed to investigate the following:

1. Sample preparation
2. Chromatographic parameters
3. Effect of storage and environmental conditions

The DoEs were designed to meet the purpose of each study. Each study focused on different method performance requirements. For example, since the sample preparation factors impacted the extraction of Atorvastatin, the content value and repeatability were selected as responses. The chromatographic parameters relating to the mobile phase however impacted specificity, so this was chosen as the main response for DoE 2. The Analytical Target Profile (ATP) has been explored separately (section 3.3) however in practice, the ATP could be used as responses in such DoEs.

DoE 1 - Sample Preparation

During method development, sample preparation is key to assuring that the full content of the compound of interest is extracted from the matrix. For a pharmacopoeial method, this carries additional importance as the preparation must be robust not only to differences to individual analysts, but also differences in formulation and manufacturing process. The sample preparation procedure must ensure full extraction of Atorvastatin from the range of different products chosen and may require minor modifications to account for the specific formulation. Therefore, the sample preparation DoE consisted of 4 experimental factors.:

1. Shaking time (include ranges)
2. Buffer pH
3. Extraction solvent composition
4. Filter type

The assay and sample repeatability were chosen as the reporting attributes for this investigation.

An orthogonal Resolution IV 2^{4-1} Fractional Factorial design with four centre-runs was chosen for the experimental plan. Main effects are estimated clear of two-way interactions in this design, and the centre runs provide an estimate of run-to-run variability (repeatability).

The data generated led to conclusions that the method sample preparations were appropriate, with no significant effects observed from the changes made to the extraction parameters. Content values ranged from 96.9% label claim to 98.1% label claim across the twelve experimental runs, with a repeatability estimate (standard deviation of samples) of 0.4% label claim.

DoE 2 – Chromatographic Parameters
The factors for this investigation were chosen based on the method risk assessment, which highlighted that changes to the composition of the mobile phase could significantly affect the performance of the method for use in a pharmacopoeial monograph, these factors were:

1. Proportion of tetrahydrofuran
2. Proportion of acetonitrile
3. Proportion of the buffer solution
4. pH of the mobile phase

The orthogonal Resolution IV 2^{4-1} Fractional Factorial experimental design varied the factors above in line with the maximum allowable changes within Appendix III D – Chromatographic Separation Techniques, of the British Pharmacopoeia (Ph. Eur. method 2.2.46). The reported attributes of the investigation were chosen as: main peak retention time, total run time, resolution between Atorvastatin and its related compound F, peak efficiency, and peak symmetry.

The investigations concluded that changes around the composition of the organic components of the mobile phase impacted significantly on the chromatography. If the changes were at the limits of the allowable changes within the pharmacopoeia, the method would not meet system suitability criteria for peak resolution.

DoE 3 – Effect of Storage and Environmental Conditions
This investigation involved studying the stability of the sample solutions. Samples and standards were subjected to simple changes of environmental conditions such as exposure to light/darkness and temperature. The design was based on stability and method validation data shared by the collaborating manufacturer. Assay and repeatability were selected as the relevant method attributes that would indicate any impact from the solution stability.

A three-factor full factorial design was chosen to examine the extremes of storage and environmental conditions on solution stability. Replicate samples at the end of the storage time provide a measure of degradation compared to fresh solutions.

It was concluded that there were no significant effects to sample or standard solution stability due to storage or changes in environmental conditions.

3.2.4 Further investigations and modelling of method robustness

It was observed during the investigations on the chromatographic parameters that the maximum allowable changes to the organic content of the mobile phase allowed by BP Appendix III D. Chromatographic Separation Techniques (Ph. Eur. method 2.2.46), resulted in extended run times and failure of system suitability (SST) requirements.

The effect of alterations in the composition of the organic components of the mobile phase was further investigated augmenting DoE 2 to a central composite design. Eight additional runs to fully understand the effect of organic composition were executed and the results of the twenty total runs assessed. The attributes assessed were the retention time of the Atorvastatin peak and resolution between Atorvastatin and related impurity F.

The investigations carried out by the laboratory were used to model the effect on retention time of Atorvastatin with regard to the % organic components of the mobile phase. It was found that changes of the content of the mobile phase bound by the central composite design did not excessively affect the retention time of Atorvastatin or related compound F.

Figure 2 was modelled on the laboratory data to show the relationship.

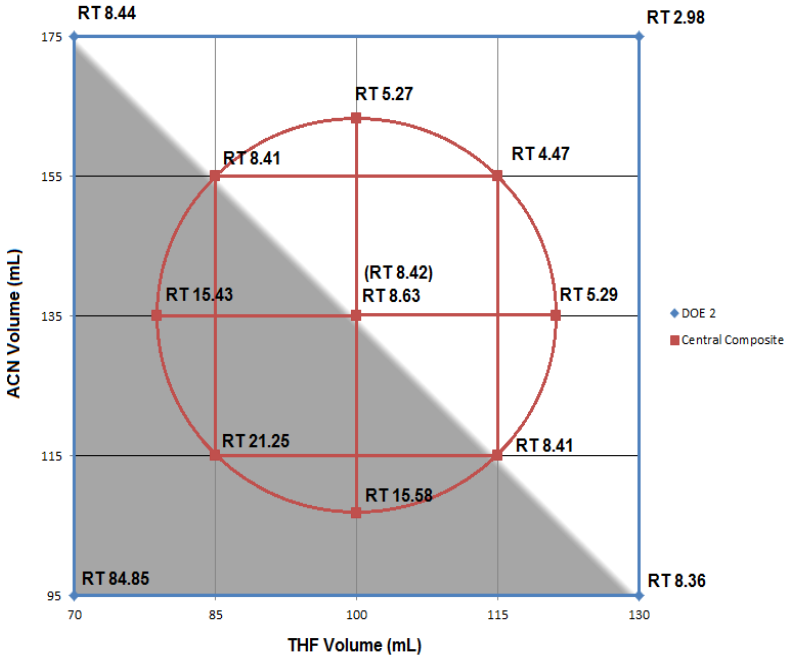

Figure 2 - Retention time (mins) of Atorvastatin from DoE2 and central composite design study (RT ≤ 10 mins preferred).

The region of stability for the method with respect to the organic:aqueous ratio of the mobile phase was modelled in figure 3 as a desirability plot that models the ability of the method to pass system suitability criteria (desirability criteria based on optimising retention time, resolution, efficiency and peak asymmetry).

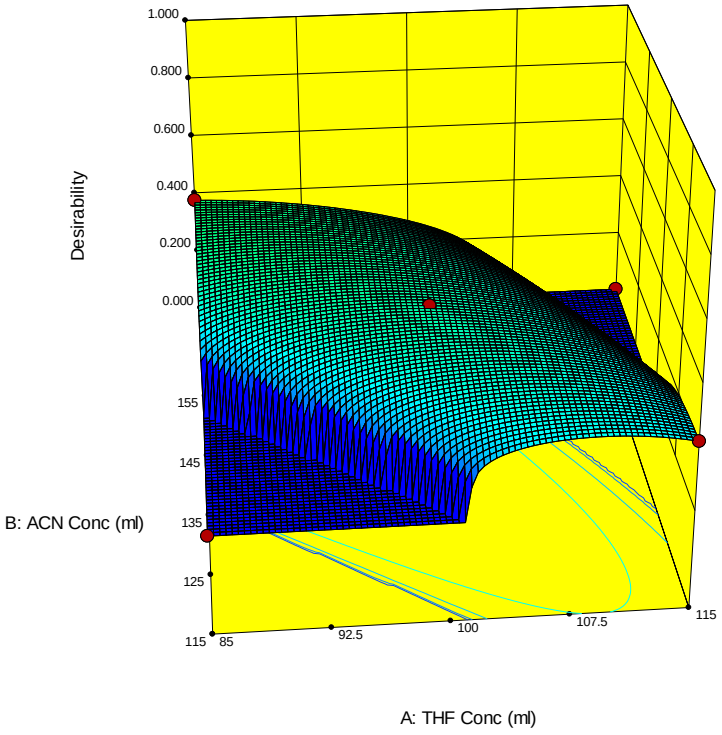

Figure 3– observed chromatographic robustness modelled by the Design Expert™ software

Figure 3 shows that at the normal operating conditions the method (central red spot) was robust with respect to minor variation in the chromatographic conditions.

3.2.5 Summary Conclusions

In summary, the draft Assay method for Atorvastatin Tablets has been demonstrated to be suitable for its intended purpose and is robust to minor changes in sample preparation and chromatographic parameters to ensure adherence to system suitability requirements. Conclusions and lessons learned are discussed in more detail in section 4.1.

3.3 Application of the Analytical Target Profile

Analytical methods for the assessment of the properties of pharmaceutical finished products require a certain level of assurance in the quality of the data being produced to ensure the method is suitable for its intended purpose. Typically, this assurance comes from method validation, technology (or method) transfer or comparative testing. An understanding of the quality of the data being produced (e.g. uncertainty) can assist both the manufacturer when developing the methods and the regulator during review.

The use of the ATP has been explored for its ability to provide this assurance to analytical methods, however, several approaches to its design and application have been seen in the literature and there is no industry wide consensus currently of how ATPs should be defined or applied. The application of the ATP to pharmacopoeial methods has also not previously been explored.

It was important to the case study that the current understanding of the ATP was known, the text below details the current views held by industry and the pharmacopoeia.

Industry view

Published literature[1, 12, 13] liken the ATP as analogous to the well-established Quality Target Product Profile (QTPP) which is a summary of the required quality characteristic of a drug product. For example, it has been proposed as 'The combination of all performance criteria required to ensure the measurement of a critical quality attribute (CQA) is fit for purpose.' The papers discuss the ability of the ATP to enhance and support:

- the development of fit-for-purpose methods;
- method validation and transfer between laboratories;
- innovation over the analytical lifecycle.

The Pharmaceutical industry has explored using the ATP to predefine requirements for the data produced by an analytical method in order to reliably control product quality, in conjunction with sound manufacturing processes.

The ATP is being suggested as a tool which can both be a driver for method development, as well as a mechanism to assess whether the quality of the data produced is fit-for-purpose.

Pharmacopoeial view

A method published in the BP is expected to be implemented unless the user ensures that any alteration made produces data of "equivalent accuracy", the following extract is from the BP General Notices II:

"… . The analyst is not precluded from employing alternative methods, including methods of micro-analysis, in any assay or test if it is known that the method used will give a result of equivalent accuracy. …"

An innovative use of the AQbD and ATP concepts for application in the pharmacopoeia could help both the company and the regulator because it would provide an objective basis for evaluation of the suitability of in-house procedures. For example, suitability could be

demonstrated based on meeting the requirements defined in the ATP rather than simply requiring “equivalent accuracy”.

The ATP concept, if correctly applied in a published pharmacopoeial monograph could have the potential to support suitable justification for analytical change management and associated regulatory actions throughout the product lifecycle, while reducing the amount of direct comparative analytical testing.

3.3.1 Defining appropriate ATPs

Traditionally, separate limits for accuracy and precision are used in the pharmaceutical industry. However, a new approach has been explored to develop ATPs by combining the accuracy and precision measurements[1, 13], a process that is also quite well established in the chemical industry[14]. Frequentist statistics are used to analyse validation data as standard practice. However, Bayesian statistics can also be used[15, 16].

A review of the literature suggested that there are two principal approaches to defining an ATP:

Empirical

Using prior knowledge and method performance expectations.

Setting validation criteria based on prior knowledge and performance expectation is the historical norm for pharmaceutical analytical methods for chemicals.

Using the Horwitz function and sample concentration[17, 18].

The Horwitz function is based on the general observation that as analyte concentrations decrease by two orders of magnitude, test method standard deviations increase by a factor of two. EU Directive 519/2014 on the determination of toxins in foodstuffs, specifies performance criteria derived from the Horwitz function.

Rational

Using the test uncertainty ratio (TUR) derived from assay specifications and a simple formula to manage patient and supplier risks [19, 20].

The use of TUR is well-established in the engineering industry. Similarly, and more generally for chemicals, the TUR is derived from assay specifications that act as goal posts, and a simple formula including uncertainty (variability) to manage patient and supplier risks. The TUR uses the knowledge that results must adhere to these predefined goalposts.

Using statistical modelling to determine the operational characteristics (OC) of an analytical test from estimates of manufacturing process variability, sampling errors, and measurement uncertainties.

Statistical modelling could be used to produce the operational characteristic (OC) curves for tests with different measurement uncertainties. Coupled with understanding of inter-batch and intra-batch variability of a standard tablet manufacturing process and sampling errors, and likely attribute specifications, an operational ATP is chosen from the test with an appropriate OC curve.

For the purposes of this case study, three empirical and one rational ATP were considered. The ATP criteria were designed at the intermediate level of precision, other than ATP 3, which also included ATP criteria at the reproducibility level of precision and accuracy.

Precision

The precision of analytical results depends on many factors including test method and conditions, the sample and analyte concentration[21]. Figure 4 shows that as test conditions include more variables, then standard deviation increases[14].

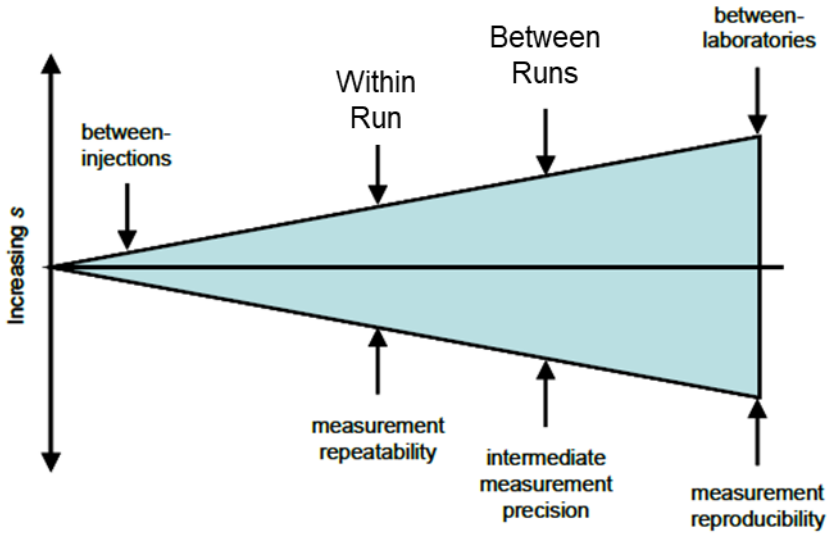

Figure 4 -Diagram illustrating relationship between precision estimates, as standard deviation (s), under different measurements conditions. As conditions include more variables e.g. moving from between injections, to repeatability between samples to intermediate precision between analysts and equipment and days to reproducibility between laboratories.

For ATPs, limits should be set for precision through the measurement of repeatability, intermediate precision or reproducibility (though repeatability is not usually required), as appropriate. The level of precision specified in the ATP should be based on its use, for example, where intermediate precision is the norm for a finished product assay, for most pharmacopoeial applications, a level of reproducibility could be considered during monograph development.

Reproducibility was considered in this project because the assay will be published in the BP monograph and is expected to be adopted and implemented by many different users[22]. The TGA Laboratory agreed to participate to enable reproducibility between laboratories to be evaluated.

Another source of variability for the BP, not normally encountered in pharmaceutical companies, is due to the different sources and formulations of atorvastatin tablets.

Five sources of atorvastatin tablets from the UK market, including the innovator product, were included in the case study. These sources have various distinctive formulations and manufacturing processes and were chosen to be representative of the whole UK market (see section 3.2.2 Effect of Formulation).

Accuracy

Accuracy of finished product assays of unit dose forms, such as tablets, cannot be directly determined because it is not possible to empirically distinguish between the variability in product manufacture and the accuracy uncertainty of the analytical test method.

Instead, according to ICH Q2(R1)[22], accuracy of finished product test methods may be determined by:

- use of synthetic mixtures of product components to which known quantities of the active substance have been added.
- standard addition
- comparison with results obtained from a second, well-characterised independent procedure.
- accuracy inferred once precision, linearity and specificity have been established.

For this project:

The use of synthetic mixtures was not possible given the large diversity of excipients used in authorised products;

Standard addition was rejected because the procedure is another source of variability and concerns that the procedure cannot sufficiently reflect interactions within the product;

A second, well-characterised, independent, reference procedure is not normally required for chemical products, and not possible given the diverse product formulations selected.

The points above echo the difficulties and challenges to determining accuracy for tablets formulations. Therefore, accuracy was inferred with a null variability component surrounding this figure being adopted, based on the following considerations:

- The method was developed with minimal, or practically absent, systemic bias.
- No evidence of bias was observed during method development or the sample preparation DoE.
- No evidence of lack of specificity was observed.

Investigated ATPs

Four ATPs were investigated for this study after considering the factors mentioned above. A 5th ATP based on statistical modelling of standard tableting manufacturing processes, sampling protocols and replicate analysis was considered, but not developed. The method used for this case study was the same method selected for the investigations in section 3.1. As discussed, this method was a fully validated procedure provided by a collaborating manufacturer.

Empirical ATP 1: Independent Accuracy and Precision criteria

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value with an accuracy of 99.0% - 101.0% and a precision coefficient of variation (CV) of not more than 1.5%.

ATP 1 is the norm for pharmaceutical methods and in line with ICH Q2, treating Accuracy and Precision as separate entities.

Empirical ATP 2: Combined* Measurement Uncertainty

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value, with an accuracy and precision (CV) such that results reside within not more than 3.0% of the true value, with 95% probability.

*For this case study, ATP 2 is also an empirically derived ATP, with the intention of calculating a combined measurement uncertainty (CMU) from accuracy and precision variabilities. However, the case study has assumed the accuracy value and its associated variability as previously discussed, meaning that the values obtained are not the true Combined Measurement Uncertainty in the metrological sense. Rather they are a joint

measurement of accuracy and uncertainty. For brevity, this report refers to the intended purpose of the ATP, as combined measurement uncertainty. This is akin to ATP 4 below.

Empirical ATP 3: Horwitz function

This ATP was developed using the protocol in Codex Alimentarius Commission Procedural Manual (2) and a nominal concentration of atorvastatin of 10%w/w in the tablet matrix.

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets to the following requirements:
Range: 70% to 130% of all strengths
Intermediate Precision (CV): < 2%
Accuracy: 98.0% – 102.0%
Predicted Reproducibility Precision (CV): < 3%
Obtained Reproducibility Precision (CV): < 6%
Horwitz Ratio <2 (obtained/predicted reproducibility)

ATP 3 is derived using an empirical perspective based on the relative concentration of Atorvastatin in Atorvastatin Tablets (~10% w/w). This concentration of active led to a Predicted Reproducibility Precision of <3% CV. Using the following formula, the criteria for the Obtained Reproducibility Precision would be <6% CV:

$$\text{Horwitz Ratio } (< 2) = \frac{Obtained\ Reproducibility\ Precision}{Predicted\ reproducibility\ precision}$$

At the intermediate level, the concentration of Atorvastatin in Atorvastatin Tablets led to the acceptance criteria of 99.0 – 101.0% for Accuracy and < 2% CV for precision.

Rational ATP 4: Test Uncertainty Ratio (TUR)

Range: 70% to 130% of all strengths
Combined Measurement Uncertainty (CMU): 1.25%, with 95% probability.

ATP 4 is rationally derived taking into account the ratio of specification of the test measurement in relation to the uncertainty in measurement results. This acceptance criterion is standard in engineering and manufacturing industries when verifying the acceptability of a single instrument against the desired specification for performance. The TUR is calculated through:

$$T.U.R = \frac{USL_i - LSL_i}{2u_i}$$

where,
TUR = Test Uncertainty Ratio
USL = Upper Specification Limit
LSL = Lower Specification Limit
u = expanded uncertainty

In terms of Atorvastatin Tablets, the draft content limits will be 95.0 – 105.0%, which when a 4:1 ratio is applied, gives a requirement for expanded measurement uncertainty of 1.25%. The ATP 4 is similar to ATP 2 since both define criteria upon a joint assessment of accuracy and precision.

3.3.2 Verification of the assay and compliance to ATPs

A verification study was undertaken by the BP and TGA laboratories using five sources of atorvastatin tablets. A fully validated methodology provided by a collaborating manufacturer was used for the study, which helped to inform the study design.

The study design permitted repeatability, intermediate precision and reproducibility to be determined, allowing the verification of the 4 different ATPs.

As discussed in 3.2.2, accuracy was inferred and not directly determined. For statistical analysis, the value given through the innovator's method validation package was used. The range of the method, and other ICH Q2 validation criteria were not evaluated as part of this study as the method used for monograph development was supported by a full validation package. The range of the method was assumed and therefore remains as a feature in the ATPs.

The study design is summarised in Table 1 where the number of preparations for each source and analysis condition is given:

Table 1 - Validation Study Design

	Lab 1				**Lab 2**			
	Analyst 1		**Analyst 2**		**Analyst 3**		**Analyst 4**	
	Day 1/ LC1	**Day 2/ LC2**	**Day 3/ LC1**	**Day 4/ LC2**	**Day 5/ LC3**	**Day 6/ LC4**	**Day 7/ LC3**	**Day 8/ LC4**
Source 1	2	1	1	2	2	1	1	2
Source 2	1	2	2	1	1	2	2	1
Source 3	2	1	1	2	2	1	1	2
Source 4	1	2	2	1	1	2	2	1
Source 5	2	2	2	2	2	2	2	2
Total Preparations	*8*	*8*	*8*	*8*	*8*	*8*	*8*	*8*

3.3.3 Statistical approach to ATP verification

Precision and combined measurement uncertainty were determined using two approaches – one was to use all of data (i.e. across both labs) – by accounting for the variation that is due to differing laboratories (reproducibility) in the total precision model, within laboratory (intermediate) precision can be estimated using combined laboratory data. The other approach was to evaluate the ATP at the intermediate precision level (i.e. whilst all the data was used to construct the statistical model, due to repeatability precision differing between the 2 labs the accuracies and the repeatability component of the precisions were estimated separately for the 2 labs).

It is important to remember that, where appropriate, the accuracy value from the manufacturer’s method validation package was used as the true value.

Note that there were also some differences in statistical analyses performed for the two approaches, for example for intermediate precision for the pooled approach a model term was fitted for the eight combinations of analyst, instrument and day within lab, while

accounting for inter-laboratory differences. For the approach providing separate estimates for each lab, individual random terms for analyst, instrument and day were fitted. This is expected to make little difference to the estimates provided but the difference concerning the modelling of terms for analyst, instrument and day would make a substantial difference to confidence limits for estimates of intermediate precision (the former being narrower). It is important to note that the researcher must decide upon what entity are inferences to be made. Is the experimental question about the assay performance, even across multiple laboratories, or is it to assess individual laboratory conformance?

Note that this analysis considers an ATP applied across multiple sources (products). The analysis assumes that the products included in the study are representative of the intended scope of the method, and sufficiently similar in level and expected recovery to make a combined statistical analysis valid.

3.3.4 Results

Table 2 - Summary of Results

ATP #	ATP Requirements	Results – Pooled Data	Results – Individual labs	Complies with ATP?
ATP 1	**CV** ≤ 1.5% **Accuracy:** 99.0 – 101.0%	**CV:** 0.9885	**CV (int precision):** 1.29 (lab 1), 0.58 (lab 2). **CV (repeatability):** 1.21 (lab 1), 0.36 (lab 2).	Complies for both pooled and individual.
ATP 2	**CMU** ≤ 3.0% with 95% probability.	**CMU:** *see figure 6.*	**CMU (int precision):** 2.74 (lab 1), 1.16 (lab 2). **CMU (repeatability):** 2.59 (lab 1), 0.72 (lab 2).	Complies for both pooled and individual.
ATP 3	**Accuracy(int):** 99.0 – 101.0% **Int Precision**: < 2.0% CV Accuracy (reproducibility): N/A **Horwitz ratio:** <2	**Horwitz Ratio:** 0.17	**For Int Prevision and Accuracy, see ATP 1 results.**	Complies
ATP 4	(Based on TUR of 4:1) **CMU:** <1.25%	**CMU:** *see figure 7.*	**CMU:** *see ATP 2 results*	Does not comply for pooled data. Complies for Laboratory 2.

The results detailed in table 2 show that ATP's 1-3 were satisfied by the data produced, however the method was found unsuitable when assessed against the requirements of ATP 4, both when the data is pooled and for one of the individual laboratories. The individual merits for each ATP have been considered in the section below:

ATP1 - Independent Accuracy and Precision

The results detailed in table 2 show that the precision of the method is suitable to satisfy the pre-defined requirements in ATP1, both for individual laboratories and when the data is pooled. Figure 5 below shows a representation of the results for the pooled within laboratory data precision (cv) and where it fits in terms of the individual requirements for accuracy and precision.

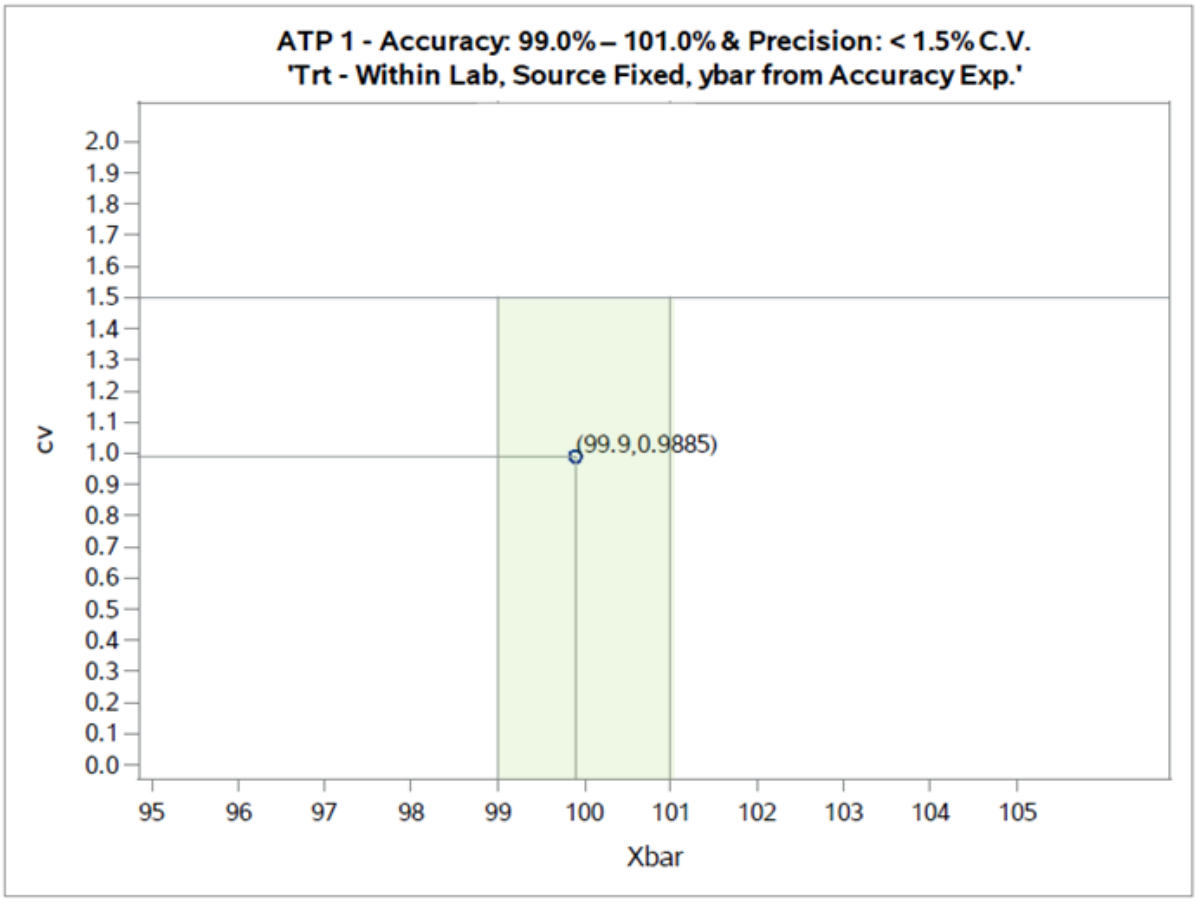

Figure 5 - Pooled data set results against acceptable results. The grey/green rectangle represents the acceptable region, the grey circle represents the experimental value.

As previously discussed, this ATP details currently accepted interpretations of ICH Q2 guidance for method validation criteria for a Solid Oral Dosage Assay procedure. Accuracy and Precision are treated independently of each other, which gives rise to the rectangular acceptance region.

ATP 2 - Combined Measurement Uncertainty

The results in Table 2 show that the ATP is satisfied when treating the laboratories individually and when the data is pooled. Figure 6 below shows the results from the pooled within laboratory data, indicating the results and 95% confidence surrounding these results, sit well inside the required region for CMU. Both approaches to assessing the data satisfy the pre-defined requirements of ATP2.

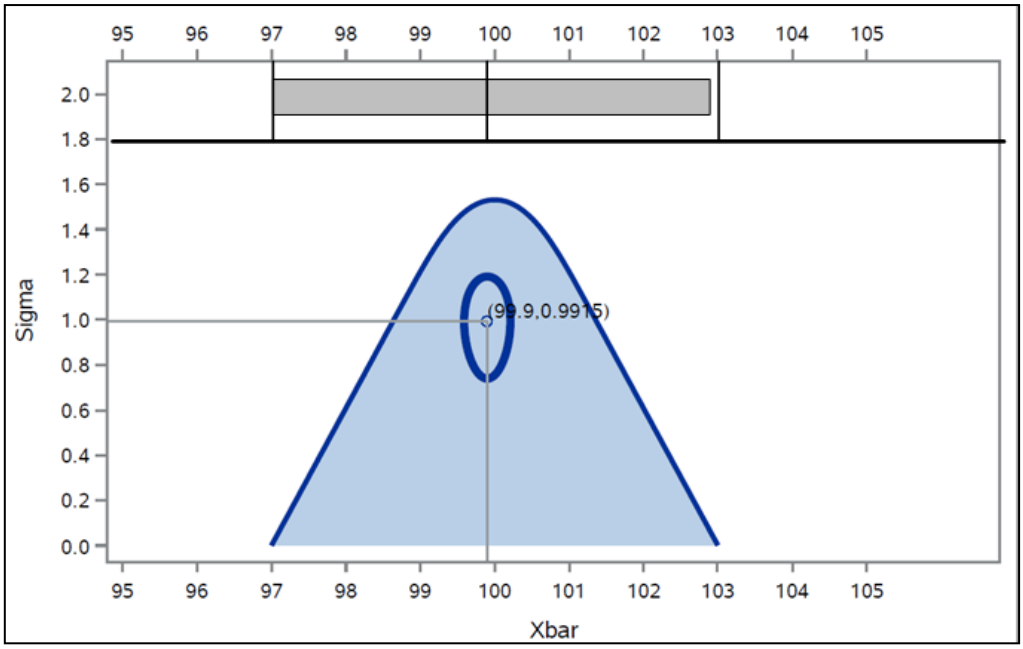

Figure 6 - Pooled data set results against acceptable results. The blue cone represents the acceptable region, the grey circle represents the experimental value and blue oval is the confidence region for the estimated mean and standard deviation.

There are several statistical analyses that can establish conformance to ATP 2 of a specific data set, each with their own merits for the study design. Two of these are displayed in Figure 6; tolerance interval (bar above graph) and joint confidence interval for accuracy and precision (ellipse within the parabolic acceptance region). The point estimate of the probability of satisfying the requirements of the ATP for both the pooled and individual laboratory analysis can also be calculated using the following model:

$$100 * (1 - \phi(-(3 - abs(bias))/SD - \phi(-(3 + abs(bias))/SD)$$

Where ϕ represents the cumulative standard normal distribution function.

The combined nature of the accuracy and precision criteria leads to the parabolic (cone shaped) acceptance region in figure 6 and 7, showing the trade-off between the independent criteria of accuracy and precision separately. This model also allows a confidence region (e.g., joint confidence interval or tolerance interval) to be visualised, based on the data set obtained from the study, knowledge of the position of this region of confidence with respect to the general acceptance region is a key attribute of this ATP and a good indicator of the quality attributes of the method.

ATP 3 - Horwitz Function

The rationally derived acceptance criteria for ATP 3 has split accuracy and precision into separate entities. At the intermediate level, the acceptance criteria for the precision is wider than that for ATP 1, while the criteria are the same for accuracy across both ATPs, as such, this section of the ATP requirements are satisfied. The Horwitz ratio has been calculated at 0.17, which is well under the limit of 2. This reflects that the obtained precision at the reproducibility level (CV=1.0074% which is only slightly larger than the intermediate precision) is significantly under the requirement of 6.0%. It is however noted that there are only 2 labs associated with the study, therefore the uncertainty associated with this value is large.

The ease to which this ATP has been satisfied suggests that the precision and/or Horwitz ratio of 2 requirements may not be appropriate for a HPLC Assay procedure to determine the content of active in a Solid Oral Dosage form across 2 laboratories. However, a different approach to the Horwitz ratio could be suitable for use as an ATP, based on the number of laboratories involved in the study.

ATP 4 - Test Uncertainty Ratio

Figure 7 shows that the method results did not satisfy the requirements for ATP 4, when combining the results of both laboratories at the intermediate precision level. However, the ATP is satisfied through one laboratory, but not the other, as seen in table 2. The ability of this ATP to distinguish between a set of results that were more variable than another set using the same method could have added benefit when troubleshooting potential process capability differences between different sites or different contract manufacturing organisations. These results also show that the ATP could have potential benefits to monitor a laboratories performance during method transfer.

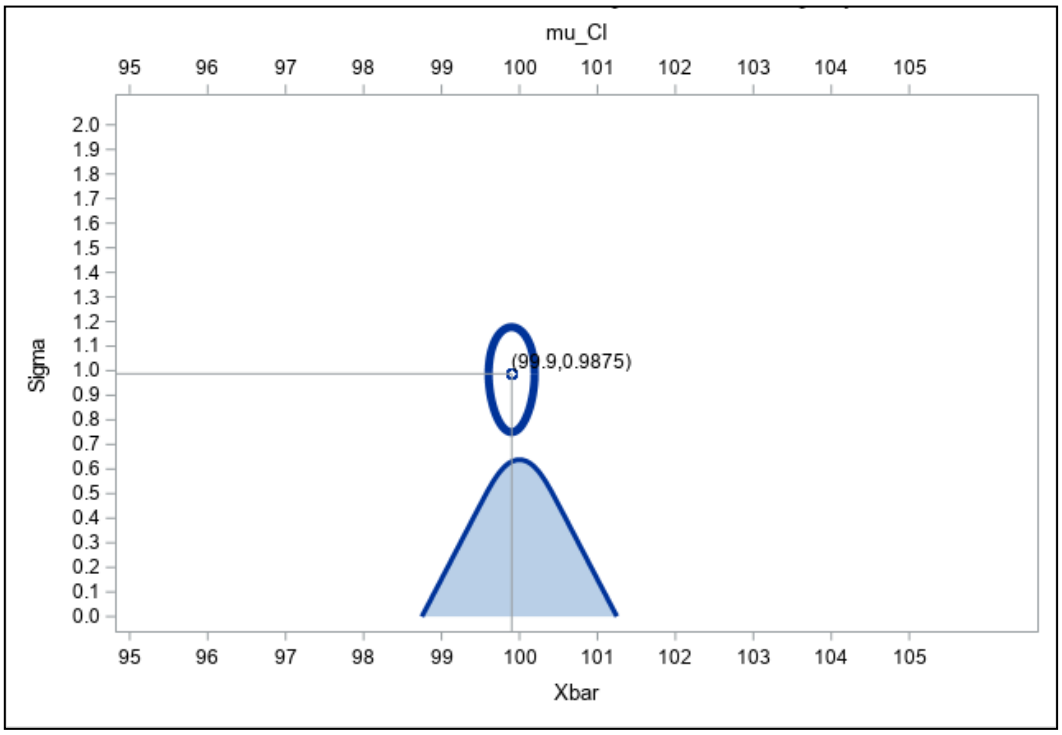

Figure 7 - Pooled data set results against acceptable results. The blue cone represents the acceptable region, the grey circle represents the experimental value and blue oval is the confidence limits

It has been discussed that the use of a TUR of 4:1 has previously been limited to the calibration of specific instrumentation, particularly in the engineering sector (where repeat testing can often be performed on the same item). The application to the determination of an Assay value by HPLC is different as it involves multiple instruments and subsequent processes to gather the final reportable result and is performed on different samples with potential variability from sample to sample; this could indicate that the ratio of 4:1 could be too tight for this methodology.

Utilising the Test Uncertainty Ratio as a rational approach to the ATP should consider the methodology and the specification of the reportable result to make an informed decision on the ratio to adopt.

4. Discussion

The draft Assay method for Atorvastatin Tablets was shown to be robust to minor changes in sample preparation, chromatographic parameters and system suitability. It is considered fit for purpose.

Some key findings are given below.

4.1 AQbD can add value to pharmacopoeial method development

The structured approach to pharmacopoeial method development utilising AQbD processes can have clear added benefits. The key benefit identified is the enhanced understanding of both method performance and robustness, gained from the following:

- *Knowledge Transfer from Industry*
  The advantages of effective knowledge transfer were evident throughout the project.

  Prior knowledge is a key theme in the ICH Q8 guideline for pharmaceutical development. There is a large amount of such knowledge produced during the development and validation of an analytical method.

  Effective prior knowledge transfer was achieved through access to the manufacturer's method and validation reports and the method walkthrough by scientists from the manufacturer and the Agency's laboratory.

- *Structured risk assessment approach*
  The use of structured risk assessments led to an improved understanding of the severity and likelihood of risks associated with sources of variability in the procedure and allowed the experimental design to focus on those variables most likely to have a significant impact on the procedure performance.

  A current review of the monograph development process will consider further embedding this concept into the BP current work practice.

- *Multiple formulations*
  Monograph development needs to efficiently account for the diverse range of formulations in authorised products.

  A review of product formulations prior to laboratory analysis allowed the case study to select a limited number of approved products, covering the spectrum of excipients used and methods of manufacture, representative of most products on the market.

  This systematic review of marketed product formulations has been adopted into the BP current work practice.

- *Design of experiments (DoE)*
  Valuable practical experience in the application of a DoE approach to the monograph development has been gained by the Agency in the project.

  This has enabled the laboratory to identify and focus on key factors relating to the method's performance, aided decision making and helped the efficient use of resources.

  Assurance that procedures are robust, situated in a region of stability, provides confidence in the continued satisfactory performance of methods.

In addition, method development knowledge should help BP scientists and users of the BP to better troubleshoot and resolve method related problems.

4.2 The ATP drives method selection and development and provides a means of assessment of fitness-for-purpose

In this case study the ATP concept was applied to a specific analytical method measuring a specific analyte. The ATPs were not used to drive method selection and two of the example ATPs were based empirically on typical requirements of HPLC assay methods. In the industry view outlined in section 3.3, the ATP can predefine method requirements by describing the quality attributes required of the reportable value independent of the method. In that case, the ATP can aid method selection. The following points are focussed on knowledge gained through this case study:

- The requirements of each ATP were similar – but this may be expected for a standard HPLC method, when applied to a product manufactured using well-established tabletting procedures, with a high active substance content and a relatively non-interfering matrix.

  On further review, we can say each approach can have a different but complementary focus:

  (i) the analytical method, including sample preparation and chromatographic conditions (empirical ATP),

  (ii) the sample concentration and matrix (Horwitz ATP)

  (iii) the product specification or required range of operation for measurements (rational ATP).

  All these elements (analyte, sample and its matrix, specification) should be considered in turn when developing the ATP and choosing the analytical method for a specific reportable value.

  The requirements for repeatability given in the BP Appendix III Chromatographic Separation Techniques (Ph. Eur. method 2.2.46) change depending upon specification limits and number of injections. This acknowledges that a method's fitness for purpose and assessment of that, depends on many factors.

- Developing an ATP by statistical modelling of standard tableting manufacturing process, sampling protocols and replicate analysis was not undertaken for this project. However, further work on this would develop our understanding and provide important insights into how the ATP criteria fits into the overall process variability with respect to a stated specification range.

- When minor changes occur in the analytical method (within the ranges studied during method development), sample or specification, applying the ATP could help to improve regulatory communication between industry and regulators and facilitate sound scientific and risk-based approval as well as improve post-approval change management of analytical procedures.

- To aid setting ATP limits for more than one measurement condition, their empirically observed relationships with standard pharmaceutical analysis should be investigated to see if similar "rules-of-thumb" can be developed.
- The rationale for the statistical analysis of data should also be clearly justified as this would have a significant impact on the interpretation of the analytical method's conformity to the pre-defined criteria of the ATP. Approaches such as an *a priori* experimental design and analysis plan could assist in providing suitable rationale.
- ATPs provide suitable criteria for demonstrating a method's fitness for purpose. In addition, they would potentially enable a user of a pharmacopoeia to efficiently compare their own procedure for equivalence to that of the monograph. This would be a more robust, and clear framework than that which currently exists in the BP.

5. Conclusion

As set out in the introduction to this paper, there is a compelling justification for a review of the pharmacopoeial *status quo* and consideration of how pharmacopoeial standards can continue to evolve to meet the needs of users and protect public health.

This pivotal and unique case study has enabled the Agency to conclude the following:

- An enhanced risk-based approach to the development and evaluation of analytical procedures for use in the pharmacopoeia has clear benefits, which include enhanced method understanding and further confidence that a given procedure will be fit for its intended purpose across multiple users. In addition, this approach offers efficiency benefits to the pharmacopoeia by focussing resources to identify and manage the greatest risks. It will be important to understand what guidance on these concepts (appendices, supplementary chapter and training) would be of value to users and how best this could be accommodated in a pharmacopoeial standard, including an individual product monograph.

- The ATP provides a pre-defined set of requirements that can be used to demonstrate whether a procedure is fit for its intended purpose. The ATP may also provide a robust framework or tool to enable a user to clearly assess the suitability of an alternate method to that included in the public standard (monograph). However, in the current regulatory framework, the ATP alone does not enable fundamental change in the analytical technology without regulatory scrutiny.

- Taken together, the enhanced risk-based approaches and the ATP concept provide a potential platform for ensuring that the pharmacopoeial standard (monograph) can continue to evolve throughout its lifecycle.

- The pharmacopoeia must manage the significant complexity of providing a meaningful pharmacopoeial standard for all relevant marketed products; this represents an additional challenge to the application of AQbD concepts currently undertaken in industry.

The case study has demonstrated that the draft procedure for the Assay of Atorvastatin Tablets satisfies criteria defined from a range of approaches to developing an ATP and can be elaborated to show assurance of ongoing method performance and give confidence in the reportable result.

Further work is required to understand how the ATP could support the evolution of pharmacopoeial procedures and lay a framework for the innovation of analytical methods in line with technological advancements. A key component to the future evolution of the pharmacopoeia is ensuring that the needs of users are fully considered in the development of future policy.

The MHRA will therefore be undertaking a formal public consultation to seek views on how these concepts could be implemented in the pharmacopoeia, as well as the guidance that would be needed to ensure successful implementation of any policy change.

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