Medicines & Healthcare products
Regulatory Agency

Consultation

Application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines

Consultation period: 3 June to 31 August 2019

CPRD NIBSC MHRA

Application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines

Summary

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasises 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 manufacturing science and technology. Therefore, the MHRA has explored how Analytical Quality by Design (AQbD) principles may be applied to pharmacopoeial standards in collaboration with industry experts.

This consultation is to understand the views of Agency stakeholders on the application of AQbD principles to pharmacopoeial standards and includes a series of examples to illustrate the potential models for inclusion in the pharmacopoeia. The consultation is supported by a technical report which provides a critical review of the project, while introducing initial key outcomes and conclusions.

You can respond to this consultation by using the form at the end of this document, or by downloading a Microsoft Word version. Responses should be sent to AQbDStds@mhra.gov.uk by **31 August 2019**.

When the consultation is closed, we will use the responses to construct a final report which will be published towards the end of 2019.

In this document there is:

- an introduction
- an overview of an Agency case study
- examples of potential approaches to describe an Assay test in a monograph
- a response form

Confidentiality of information

Information we receive, including personal information, may be published or disclosed in accordance with the access to information regimes (primarily the Freedom of Information Act 2000 (FOIA), the Data Protection Act 1998 (DPA) and the Environmental Information Regulations 2004).

Please let us know if you would like any information you provide to be treated in confidence, and please indicate any commercial sensitivities. We will maintain that confidence and resist disclosure under the access to information regimes where possible and in compliance with our legal obligations. We will also consult you and seek your views before any information you provided is disclosed.

Introduction

The Agency is committed to ensuring the quality of medicines through its activities in the development of public quality standards. Quality helps ensure medicines work and are acceptably safe. This is aligned to two of the key priorities in the Agency corporate plan[1]. To ensure the safe production of medicines through enhanced systems and to support and enhance innovation.

Within the Agency, the British Pharmacopoeia[2] (BP) is responsible for the delivery of public quality standards for medicines as pharmacopoeial standards. These standards enable users to make an objective assessment in relation to the quality of a material. Quality is critical to ensuring the safety and efficacy of medicines taken by patients every day. Pharmacopoeial quality standards are one of the foundations of ensuring acceptable quality.

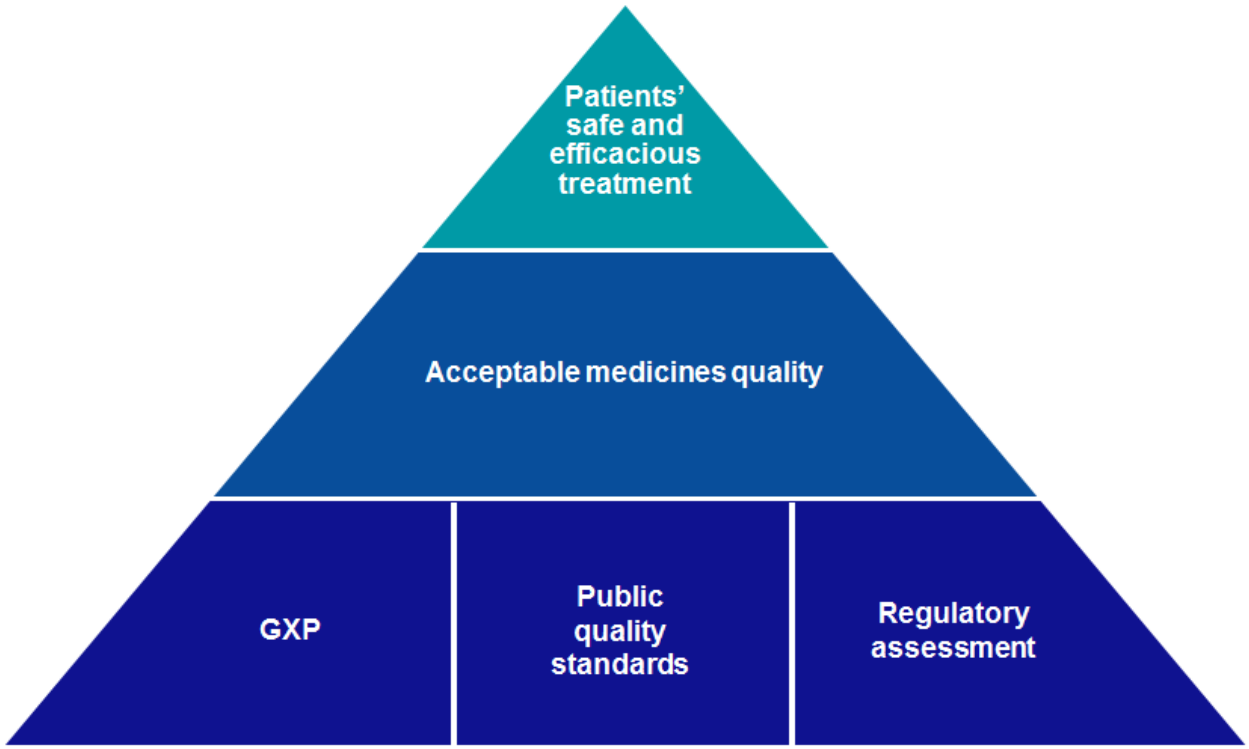

Figure 1 – Product Quality Assurance
GXP – This refers to good practice quality guidelines and regulations. For medicines manufacture this refers to good manufacturing (GMP), distribution (GDP), clinical (GCP), laboratory (GLP) and pharmacovigilance (GPvP) practice.
Regulatory assessment – The independent 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.

The contribution that these three activities make to the assurance of product quality is interlinked. The successful implementation of each activity is reliant on the contribution of the others to ensure quality of medicines.

Within the above framework, pharmacopoeial standards provide:

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[1] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/702075/Corporate_Plan.pdf

[2] www.pharmacopoeia.com

1. General monographs
    - A description of the minimum quality attributes required for all medicines
    - The specific quality attributes required to ensure dosage-form product quality

2. Monographs
    - A description and statement of quality characteristics for a medicine (for example identity, potency, purity)
    - A publicly available description of the analytical methods used to demonstrate compliance with these characteristics
    - A publicly available description of the performance characteristics (e.g. System Suitability requirements) of those methods
    - A description of the reference materials to be used in a monograph including the performance of analytical methods
    - Support for independent drug analysis, including in the evaluation of adverse reactions or product defects

3. Appendices
    - Standardised descriptions of analytical technologies that support the specific monograph
    - Consistency to standards for analytical technologies to the wider environment
    - Standardised test methods that support the specific monograph

4. Supplementary Chapters
    - Best practice guidance for new and emerging technologies, processes and products, often non-mandatory in nature

Agency case study

The Agency case study was led by representatives from the Pharmacopoeia, Licensing Division and GMDP Inspectorate in collaboration with industry experts. It sought to learn about AQbD concepts through a laboratory-based investigation of:

- the application of AQbD approaches to pharmacopoeial method development and verification, with a view to improving the robustness and understanding of the analytical procedure.
- different approaches to define method performance requirements using the concept of an Analytical Target Profile (ATP), to better understand their use and value as well as to explore their relevance and applicability to compendial methods.

The development of a pharmacopoeial Assay procedure for Atorvastatin tablets, a highly prescribed product, was selected for this practical investigation. A working draft of an ATP had been defined to set out the desired method performance characteristics before undertaking the risk assessment and experimental studies. Risks associated with the Assay procedure, which had been donated by a manufacturer, were explored in discussions between their analysts and the Agency laboratory using tools such as Ishikawa fishbone diagrams and Failure Mode and Effects Analysis. Variables in the procedure which were considered to have the greatest risk (e.g. in chromatographic conditions) were practically assessed using statistical design of experiments approaches in order to more fully understand their impact on the procedures output.

This led to an understanding of the effect of variability in the method parameters and the range of conditions in which the Assay operated satisfactorily. This process provided additional assurance that the method would be robust and rugged throughout its lifecycle.

The working draft ATP was based on "combined measurement uncertainty" derived from method accuracy and precision. In addition, several other models for ATPs were considered where the required performance was defined using independent accuracy and precision criteria, the Horwitz function, or test uncertainty ratios. Assessment of the ability of the Assay procedure to meet these ATPs showed that a variety of statistical approaches could be used.

This work also demonstrated how ATPs could be a valuable tool to demonstrate a method's fitness-for-purpose as well as providing analysts a way of demonstrating and further justifying that their own alternative procedures comply with the pharmacopoeia. Since the statistical approach applied can influence the conclusion about the conformance of a procedure with an ATP, clear guidance for their interpretation would be required in a compendial setting.

The full technical report[3] of this case study describes the investigative approach undertaken by the team in more detail and includes interim findings regarding the application of AQbD principles to pharmacopoeial standards.

Enhanced approaches to describe Assay

The AQbD approach has the potential to enable the BP to publish additional information about an analytical procedure to help users ensure the procedure described in the monograph performs robustly in their laboratory or to describe the performance requirements that the monograph procedure has been designed to meet, potentially enabling users to justify the adoption of alternative methods that have been shown to meet the performance requirements in the ATP.

1. **Enhanced method development knowledge**
   Providing users with the additional knowledge gained through an AQbD approach on the critical elements of an analytical procedure could allow users the means to troubleshoot procedures more effectively and potentially provide assurance of the methods suitability for a formulation. Work is needed to understand how this can be provided, ranging from simply incorporating the tabulated ranges for key variables in a monograph, to a more complex set of information covering data for the variables identified and the perceived risks associated with these.

2. **Method Performance Requirements**
   Providing users with the performance requirements for a procedure may facilitate and support the demonstration that an alternative procedure is fit for purpose. For the purpose of this consultation, ATPs have been considered a tool to provide these requirements in terms of Accuracy and Precision. Different definitions and approaches for ATPs exist and a standardised structure would need to be developed for use in a pharmacopoeial context. If included in a pharmacopoeial procedure, further guidance would need to be developed to explain their use and statistical interpretation.

The following illustrative examples 2-5 are designed to stimulate consideration and discussion of some potential approaches to inclusion of an ATP and/or operable ranges in a pharmacopoeial

[3] Link to case study report on GOV.UK

Assay procedure. Example 1 is provided for comparison, representing the current style for the description of an Assay procedure without an ATP or operable ranges.

Example 1 – Description of procedure (no ATP or operable ranges)
Example 2 – Description of procedure with operable ranges
Example 3 – Description of procedure with ATP
Example 4 – Description of procedure with ATP and operable ranges
Example 5 – An ATP only

Example 1 – Description of procedure

[ACTIVE] Tablets

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of [ACTIVE], add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(2) 0.005% w/v of *[ACTIVE] BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *[ACTIVE] for system suitability EPCRS* (containing impurity X) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucelosil-100 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 225 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of valsartan.

MOBILE PHASE

1 volume of *glacial acetic acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to [ACTIVE] (retention time, about 5 minutes) is: impurity X, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity X and [ACTIVE] is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of [ACTIVE] in the tablets using the declared content of [ACTIVE] in *[ACTIVE] BPCRS*.

Example 2 – Description of procedure with operable ranges

[ACTIVE] Tablets

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of [ACTIVE], add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

Parameter	Target value	Lower range	Upper range
Solvent composition	50 volumes acetonitrile	45	55
	50 volumes water	45	55
Mixing time (ultrasound)	20 minutes	15 minutes	25 minutes

(2) 0.005% w/v of *[ACTIVE] BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *[ACTIVE] for system suitability EPCRS* (containing impurity X) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Parameter	Target value	Lower range	Upper range
Column	Use a stainless steel column (10 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.7 µm)	-	-
Flow rate	1 mL per minute	0.5	1.5
Column Temperature	20°C	18	22
Injection Volume	10 µL	-	-
Mobile phase composition	1 volume glacial acetic acid	0.5	1.5
	500 volumes	450	550

	acetonitrile		
	500 volumes water	450	550
Mobile phase pH	7.2	7.0	7.4
Detection wavelength	225 nm	-	-

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to [ACTIVE] (retention time, about 5 minutes) is: impurity X, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity X and [ACTIVE] is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of [ACTIVE] in the tablets using the declared content of [ACTIVE] in *[ACTIVE] BPCRS*.

Example 3 – Description of procedure with an ATP

[ACTIVE] Tablets

ASSAY

The analytical method is capable of quantifying [ACTIVE] in [ACTIVE] Tablets from 70% to 130% of the true value with accuracy and precision such that results reside within not more than 3.0%, with 95% probability.

This Analytical Target Profile (ATP) for the content of Atorvastatin is included in this monograph for the convenience of users for which the following procedure conforms. Alternative procedures should be demonstrated to conform with these requirements.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of [ACTIVE], add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(2) 0.005% w/v of *[ACTIVE] BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *[ACTIVE] for system suitability EPCRS* (containing impurity X) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucelosil-100 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 225 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of valsartan.

MOBILE PHASE

1 volume of *glacial acetic acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to [ACTIVE] (retention time, about 5 minutes) is: impurity X, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity X and [ACTIVE] is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of [ACTIVE] in the tablets using the declared content of [ACTIVE] in *[ACTIVE] BPCRS*.

Example 4 – Description of procedure with an ATP and operable ranges

[ACTIVE] Tablets

ASSAY

The analytical method is capable of quantifying [ACTIVE] in [ACTIVE] Tablets from 70% to 130% of the true value with accuracy and precision such that results reside within not more than 3.0%, with 95% probability.

This Analytical Target Profile (ATP) for the content of Atorvastatin is included in this monograph for the convenience of users for which the following procedure conforms. Alternative procedures should be demonstrated to conform with these requirements.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of [ACTIVE], add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

Parameter	Target value	Lower range	Upper range
Solvent composition	50 volumes acetonitrile	45	55
	50 volumes water	45	55
Mixing time (ultrasound)	20 minutes	15 minutes	25 minutes

(2) 0.005% w/v of *[ACTIVE] BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *[ACTIVE] for system suitability EPCRS* (containing impurity X) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Parameter	Target value	Lower range	Upper range
Column	Use a stainless steel column (10 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.7 µm)	-	-
Flow rate	1 mL per minute	0.5	1.5
Column Temperature	20°C	18	22

Injection Volume	10 µL	-	-
Mobile phase composition	1 volume glacial acetic acid	0.5	1.5
	500 volumes acetonitrile	450	550
	500 volumes water	450	550
Mobile phase pH	7.2	7.0	7.4
Detection wavelength	225 nm	-	-

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to [ACTIVE] (retention time, about 5 minutes) is: impurity X, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity X and [ACTIVE] is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of [ACTIVE] in the tablets using the declared content of [ACTIVE] in *[ACTIVE] BPCRS*.

Example 5 – ATP only

[ACTIVE] Tablets

ASSAY

The analytical method is capable of quantifying [ACTIVE] in [ACTIVE] Tablets from 70% to 130% of the true value with accuracy and precision such that results reside within not more than 3.0%, with 95% probability.

This Analytical Target Profile (ATP) for the content of Atorvastatin is included in this monograph for the convenience of users. Assay procedures should be demonstrated to conform with these requirements.

Response document for MHRA consultation on the application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines

About You
Name:

Position:

Organisation:

Email:

Familiarity with AQbD concepts:

None □ Awareness□ Understanding□ Knowledge□ Expertise□

Please indicate if you are responding to this consultation as an individual or on behalf of an organisation

Individual □ Organisation □

About your Organisation
Type:

□ **Generics** – *a pharmaceuticals manufacturer of any size with most of its sales from generic drug products*
□ **Large Pharma** – *a pharmaceuticals firm with annual sales of more than $2bn, and which develops and manufactures patented drug products as its primary activity*
□ **Small/ Medium Pharma** – *a pharmaceuticals firm with less than $2bn in sales, and which develops and manufactures patented drug products as its primary activity*
□ **Supplier** – *a supplier of services, materials or equipment to the pharmaceutical industry (includes testing companies, consultancies, raw materials suppliers)*
Government –
□*OMCL* □*Regulator* □*Other*
□ **Public Health** – *hospitals and medical clinics*
□ **Academia** – *universities and colleges*
□ **Other (Please state)** –

Focus: *Please indicate your organisations focus on small and large molecules using the scale below. 3 indicates an equal focus on small and large molecules.*

Small 1□ 2□ 3□ 4□ 5□ **Large**

Location (country):

Head office: Your site:

Organisation Size:

1-5 □ 6-50 □ 51-250 □ 250-1000□ 1001-9999□ 10,000+ □

1. What do you see as the greatest opportunities and challenges affecting the quality of medicines in the next 5 years?

2. How can AQbD concepts ensure methods are fit for purpose and how can they enable innovation? How are AQbD concepts utilised within your organisation?

3. Please rank examples 1 – 5 in order of preference for presentation in the pharmacopoeia (1 is best). What advantages and disadvantages do you see in presenting AQbD information in the different examples?

Rank 1 – Example
Rank 2 – Example
Rank 3 – Example
Rank 4 – Example
Rank 5 – Example

4. What other options for the application of AQbD concepts to pharmacopoeial standards and presentation of the resulting information in the pharmacopoeia should we consider?

5. How can we work with you and your organisation to further develop our thinking on the application of AQbD concepts to pharmacopoeial standards?

6. Do you have any other comments regarding the application of AQbD concepts to pharmacopoeial standards?

7. Would you be happy for the MHRA to contact you in order to discuss your responses in further detail?

Yes □ No □

8. The MHRA may publish consultation responses. Do you want your response to remain confidential?

Yes □ Partially* □ No □

*If partially, please indicate which parts you wish to remain confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete.

Responses can be continued onto a separate page if required. This form should be returned by email (AQbDStds@mhra.gov.uk) to arrive by **31 August 2019.** Contributions received after that date cannot be included in the exercise.