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Analytical Validation Within the Pharmaceutical Lifecycle

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1.1 Development of Process and Analytical Validation Concepts

The concept of validation in the pharmaceutical industry was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid-1970s in order to improve the quality of pharmaceutical products [1]. Validation of processes is now a regulatory requirement and is described in general and specific terms in the FDA's Code of Federal Regulations – CFR21 parts 210 and 211 as well as in the European Medicines Agency (EMA) GMP Guide Annex 15. The 1987 FDA guide to process validation [2] defined validation as "Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." While the first validation activities were focused on the processes involved in making pharmaceutical products, the concept of validation quickly spread to associated processes including the analytical methods used to test the products.

Regulatory guidance on how analytical methods should be validated has also existed for some time [3]; however, it wasn't until the establishment of the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) in 1990 that there was a forum for dialogue between regulatory authorities and industry and one of the first topics within the quality section was analytical procedure validation. The ICH was very helpful in harmonizing terms and definitions [4a] as well as determining the basic requirements [4b]. Of course, due to the nature of the harmonization process, there were some compromises, inconsistencies, and deficiencies, such as the focus on chromatographic methods and chemical actives. Indeed, despite the existence of ICH Q2, a number of regulatory authorities developed their own additional guidance [5, 6].

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The recognition that the current Pharmaceutical Industry's manufacturing performance was not as state of the art as other industries [7–9] has resulted in unprecedented efforts over the last 20 years to modernize pharmaceutical development and manufacturing. In August 2002, the FDA announced a significant new initiative to enhance and modernize the regulation of pharmaceutical manufacturing and product quality which resulted in the issue of a report in September 2004 entitled "Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach" [10]. The aims of the initiative included encouraging industry to adopt modern quality management techniques and to implement risk-based approaches that focused both industry and regulatory attention on critical areas. The need to modernize the approach to quality management was also recognized by ICH and resulted in a series of new ICH guidelines being produced. In November 2005, ICH Q8 [11] and Q9 [12] were issued to provide guidance on best practice in pharmaceutical development and risk management. These guidances were followed by ICH Q10 [13] in June 2008, which described the key aspects of a modern pharmaceutical quality system, and by ICH Q11 [14] in May 2012, which gave guidance on the development and manufacture of drug substances. In November 2008, an updated version of ICH Q8 was issued [15], which included an annex that described the concept of Quality by Design (QbD), which was defined as "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."

In November 2007, Borman *et al*. published a paper that recognized that the concepts of QbD, which had been developed with an aim of enhancing the robustness of manufacturing processes, could also have applicability to analytical procedures [16]. The authors noted that the existing guidance on method validation as described by ICH Q2(R1) would need to be substantially rewritten to take account of the QbD risk-based approaches.

FDA had also recognized that existing guidance on manufacturing process validation would need to be revised to better align with modern quality assurance concepts and the report on "Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach" included recommendations that the 1987 industry guideline on process validation be revised to include 21st century concepts, including risk management and adoption of a lifecycle approach. In January 2011, FDA issued a new guidance for industry document entitled "Process Validation: General Principles and Practices" [17]. This guidance aligns process validation activities with a product lifecycle concept and with the ICH Q8, 9, and 10 guidances. The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. The FDA guidance revised the definition of process validation to "the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product" and recognized that process validation

involves a series of activities taking place over the lifecycle of the product and process. The guidance describes process validation activities in three stages:

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

The guideline emphasized that understanding and controlling variation was key to ensuring a process delivered a fit for purpose product. It suggested that manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes

Control the variation in a manner commensurate with the risk it represents to the process and product and recognized that focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variation may not lead to adequate assurance of quality. It also acknowledged that after establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.

1.2 Alignments Between Process and Analytics: Three-Stage Approach

In 2010, Nethercote *et al*. [18] suggested that just as process validation can benefit from a product lifecycle approach so can analytical method validation. They also suggested that there were a number of key factors that are important in a QbD/lifecycle approach. These include:

- The importance of having predefined objectives
- The need to understand the method, or being able to explain the method performance as a function of the method input variables
- The need to ensure that controls on method inputs are designed such that the method will deliver quality data consistently in all the intended environments in which it is used
- The need to evaluate method performance from the method design stage throughout its lifecycle of use.

They proposed that method validation be defined as "The collection and evaluation of data and knowledge from the method design stage throughout its lifecycle

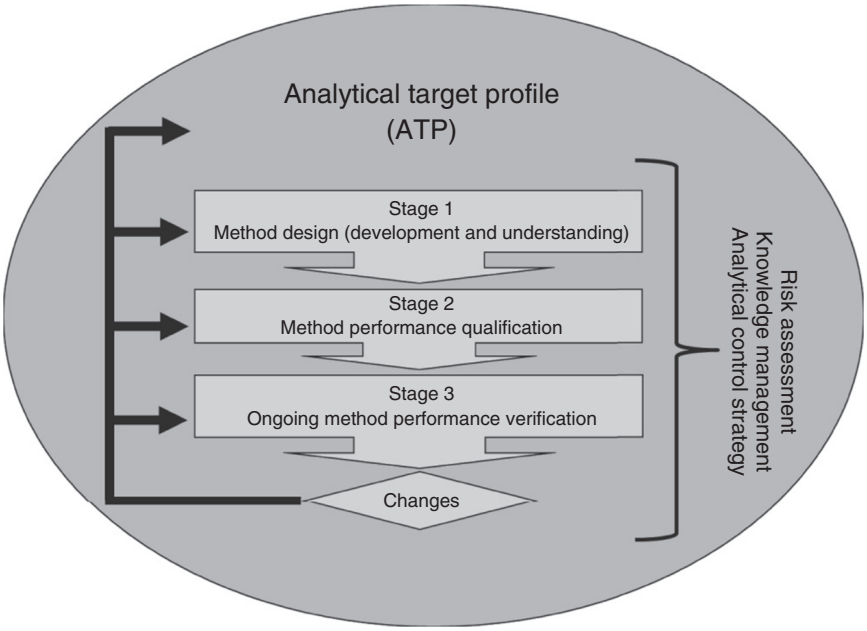

Figure 1.1 Three-stage approach to analytical lifecycle validation.

of use which establishes scientific evidence that a method is capable of consistently delivering quality data," i.e. that, like FDA's definition of process validation it should apply to all activities performed throughout the methods lifecycle of use – not just the qualification step that was traditionally associated the concept of method validation. The only difference being that the output from the method validation activity is the data, whereas from the manufacturing process it is the product. It was also suggested that the three-stage approach defined by FDA could be applied directly to the validation of analytical methods, as illustrated in Figure 1.1. These concepts were further developed in a paper by Nethercote and Ermer in 2012 [19] and by the United States Pharmacopeia (USP) Expert Panel on Validation and Verification [20]. In these papers, the importance of having a well-defined target for the method was emphasized – the concept of having an *Analytical Target Profile* (ATP) – as well as a recognition that the "Stage 3" activities involved both routine performance monitoring and effective assessment of change.

Following on from the recognition in 2007 that the adoption of a QbD/lifecycle approach to analytical method validation has numerous advantages in ensuring the suitability of the analytical procedure [16] work began to ensure regulatory guidance's facilitation of such an approach. Cooperation between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) resulted in the publication of a white paper in 2010 [21] which highlighted these advantages and what actions needed to be taken to enable such an approach. In 2012, a conference was held in Liverpool, UK, which brought together representatives from industry, the FDA, the UK's Medicines and Healthcare Products Regulatory Agency

(MHRA), and the major pharmacopeias, the USP, the European Pharmacopoeia (Ph.Eur.), and the British Pharmacopoeia (BP), to further develop the concepts and identify what actions each group could take to move the ideas forward [22]. The workshop agreed on a number of key actions including pursuing revision of the ICH guidelines, ensuring alignment of pharmacopoeial/regulatory texts on the topic, agreeing terminology, and developing case studies that would illustrate the concepts in practice. In support of these objectives, USP formed a validation and verification expert panel, which produced a number of stimuli articles on the subject [20, 23–25], culminating in the introduction of the new General Information Chapter <1220> "The Analytical Procedure Lifecycle" [26], and the BP\MHRA formed an Analytical QbD (AQbD) working party, which issued a case study on the application of QbD principles to atorvastatin tablets [27].

One additional potential advantage of adopting an AQbD approach was the opportunity to facilitate continuous improvement and innovation of analytical methodology. In the EFPIA/PhRMA paper of 2010 [21], it was highlighted that the introduction of the ATP concept maybe one way in which innovation might be made easier. Subsequent discussions led to a recognition that ICH Q12 [28] should include some guidance relating specifically to analytical methods, for example, performance-based Established Conditions (EC), which correspond to a technique-specific ATP. This was further enhanced with the publication of ICH Q14 in 2023 [29]. This evolution process as well as the links to compendial and ISO approaches is well summarized in two papers by Guiraldelli and Weitzel [30].

It is our intention to guide the reader with the book chapters through all stages of the analytical lifecycle and describe both fundamentals and application to facilitate the utilization of these advantages. We are convinced that a comprehensive utilization of the proposed QbD/lifecycle from the start will provide the most benefit. However, aspects such as the ATP or gaining a more thorough understanding on the sources of analytical variation and its monitoring can be applied to analytical procedures already in routine use, in order to improve their control and reliability. In fact, most of the concepts and tools are not new, but their systematic integration will help to modernize pharmaceutical analytics to better align with future challenges.

1.3 Predefined Objectives: ATP

Obviously, the "predefined objectives" [11] for an analytical procedure will determine its suitability, and the concept of an ATP was proposed in 2010 by a joint EFPIA/PhRMa working group [21]. It parallels the concept of a Quality Target Product Profile described and defined in ICH Q8, as illustrated in Figure 1.2.

Note: in order to facilitate the readability, in particular of the proposed terms for the validation stages, "method" is used in the whole book synonymously for "analytical procedure," i.e. all steps are included such as sample preparation, analytical methodology, calibration, definition of the reportable result, as well as specification limits.

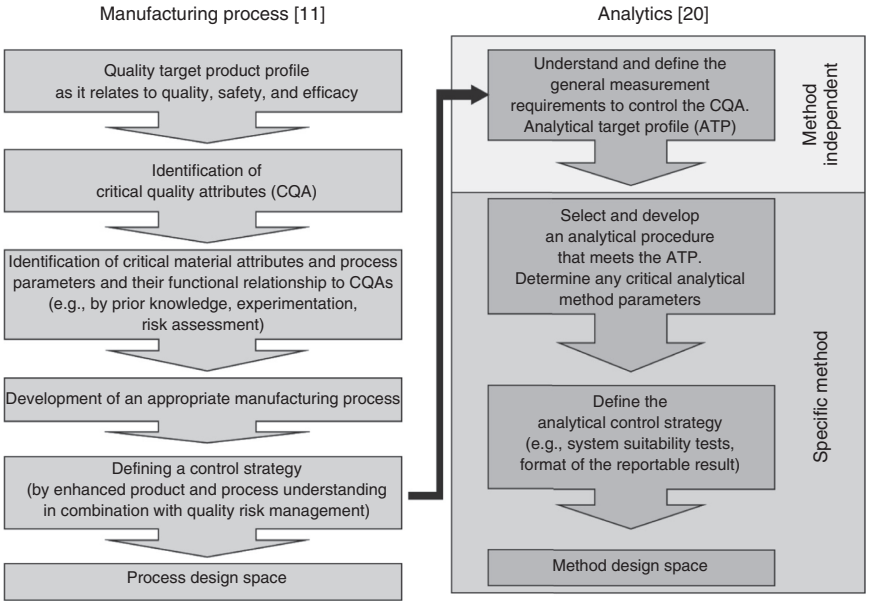

Figure 1.2 Alignment of QbD principles for pharmaceutical product/manufacturing and for the corresponding analytical measurements.

The ATP defines the performance requirements for the measurement of a given Quality Attribute, or more exactly, for the "product" of the test procedure, which is the reportable result, i.e. the final result, which is to be compared to the acceptance limits of the specification [31] (see Chapter 5). The ATP is extensively discussed in ICH Q14 [29] and can be regarded as the very "heart" of the whole lifecycle approach (see Figure 1.1). As the measurement requirements will stay valid as long as the given Quality Attribute needs to be controlled, the ATP acts as the focal point for all stages of the analytical lifecycle. Consequently, the ATP concept facilitates the integration of the various activities dealing with analytical performance, which were in the past often isolated, such as method development (now Stage 1), initial validation (now Stage 2), change control and associated activities, e.g., re-qualification, control charts, etc. (now Stage 3). The ATP describes the maximum acceptable uncertainty in the reportable result and is the target that must be achieved by the analytical procedure. Note that the ATP is focused on defining the acceptable quality of the reportable result and is (as far as possible) independent of a specific analytical procedure. Therefore, precision (see Section 7.1) and accuracy (see Section 7.2) over the required range of the given Quality Attribute are the relevant or *primary performance characteristics* to be defined in the ATP. The other performance characteristics defined in the ICH Guideline [32], i.e. specificity (see Section 7.3), calibration model (see Section 7.4), lower range limit (detection and quantitation limit, see Section 7.5) are method-specific and are eventually consolidated in accuracy and precision, or uncertainty. Depending on the criticality and the level of risk control desired for the given Quality Attribute, the ATP requirements can be based on simple *decision rules*

or incorporate numerical risk control (see Chapter 6). For example, in case of an assay, the ATP may look like:

- The procedure must be able to quantify (analyte) in (presence of X, Y, Z) over a range of A%–B% of the nominal concentration with a precision of less than C% RSD and an accuracy of less than D% bias.

or

- The procedure must be able to quantify (analyte) in (presence of X, Y, Z) over a range of A%–B% of the nominal concentration with an accuracy and uncertainty so that the reportable result falls within ±C% of the true value with at least a 90% probability determined with 95% confidence [26].

The application of the ATP concept is also feasible and recommended *retrospectively* for marketed products. Here past and current process and product information and knowledge can be summarized in order to establish explicitly the requirements to define an ATP, which can then be used as focal point during the further analytical lifecycle. Chapter 6 describes an approach to developing an ATP that draws on concepts of "measurement uncertainty" and "*decision rules*" described in consensus standards documents such as American Society for Testing and Materials (ASTM), Eurachem guidance, American Society of Mechanical Engineers (ASME), etc. This approach is based on a recognition that in many situations analytical data are generated in order to make a decision on whether a material is or is not of acceptable quality (making the decision is the "purpose" in fit for purpose). In principle, such decisions should be made taking into account the uncertainty in the data. By understanding what decisions will be made with the data generated by a method and what level of risk of making the wrong decision is acceptable, it is possible to define a maximum measurement uncertainty that the method can have in order that there is adequate confidence in the decisions being made. Such approaches, while not yet common within the pharmaceutical industry, provide a rationale link between the use of data and the validation requirements for the method generating that data.

1.4 Analytical Lifecycle

As robust processes for ensuring data integrity and the use of *qualified equipment* are essential prerequisites for any analytical measurement, the book begins with these topics (see Chapters 2 and 3), applying lifecycle management to analytical instrument qualification and computerized system validation.

The topic of ongoing assurance of instrument performance, i.e. the counterpart to Stage 3 of the analytical procedure lifecycle, is covered in Chapter 4.

While the ICH guidelines were intended to be regarded as the basis and philosophical background for analytical validation, and not simply used as a checklist – "It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for their product" [4], re-emphasized in Revision 2 [32] – in practice both industry and regulatory authorities often resort to adopting a checklist

approach. As what is required to gain a high degree of assurance that a specific method will consistently produce fit for purpose data obviously varies, at least with the type of procedure, it must be reflected in the analytical validation activities and acceptance criteria. This includes the identification of the performance parameters relevant for the given procedure, the definition of suitable acceptance criteria, and the appropriate design of the validation studies. In order to achieve this, the analyst must be aware of the fundamental meaning of these performance parameters, as well as the calculations and tests and their relationship to the specific application. A lack of knowledge or (perhaps) a wrong understanding of "efficiency" will lead to validation results that address the real performance of the analytical procedure only partly or insufficiently. This is, at the very least a waste of work, because the results are meaningless. In Chapter 7, *procedure performance characteristics* are discussed, along with appropriate performance parameters, calculations, and tests. They can be categorized into the "universal" or "primary" characteristics of precision and accuracy, which are directly related to the ATP, and method-specific or "secondary" characteristics, such as specificity, calibration model, detection, and quantitation limit, which are dependent on the respective method and included in accuracy and precision. An appropriate performance is also key to avoid variability-caused results outside specification limits (OOS), i.e. to ensure compatibility between analytical performance and the specification criteria.

The following chapters focus on various specific aspects of the lifecycle of the analytical procedure, i.e.

- **Stage 1**: Method Design and Understanding (Chapters 8–12)
- **Stage 2**: Method Performance Qualification (Chapters 13–19)
- **Stage 3**: Ongoing Method Performance Verification (Chapters 20 and 21)

Chapter 8 starts with an overview of the new ICH Guideline on Analytical Procedure Development. Chapter 9 describes the selection of an appropriate method according to the requirements defined in the ATP, the use of QbD tools in method development, and the establishment of the analytical procedure control strategy.

The focus of Chapter 10 is the development of multivariate analytical procedures, a topic that has been added to ICH Q2(R2) to broaden the scope of the guideline.

An important part of analytical procedure development is the systematic investigation of robustness (Chapter 11) and the closely linked topics of risk assessment and analytical procedure control strategy (Chapter 12).

Having determined a set of operational method controls during the design phase, the next step is to qualify that the method will operate in its routine environment as intended, i.e. as defined in the ATP. This includes submission validation, as covered by ICH Q2. Revision 2 of the ICH validation guideline addressed (some of) the gaps and deficiencies and is critically summarized in Chapter 13.

Case studies to illustrate specific validation strategies are provided in Chapters 14–16. Other examples of qualification activities are described in Chapter 17, implementation of compendial procedures, and Chapter 18, transfer of analytical procedures. Closely linked to Stage 3, a lifecycle approach to analytical transfer is discussed in Chapter 19.

The goal of Ongoing Method Performance Verification is to continually assure that the procedure remains in a state of control during routine use. This includes both routine monitoring of the performance of the procedure (Chapter 21) and ensuring appropriate actions are taken when issues are identified with the performance or the procedure is modified or changed as part of continual improvement (Chapter 20).

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