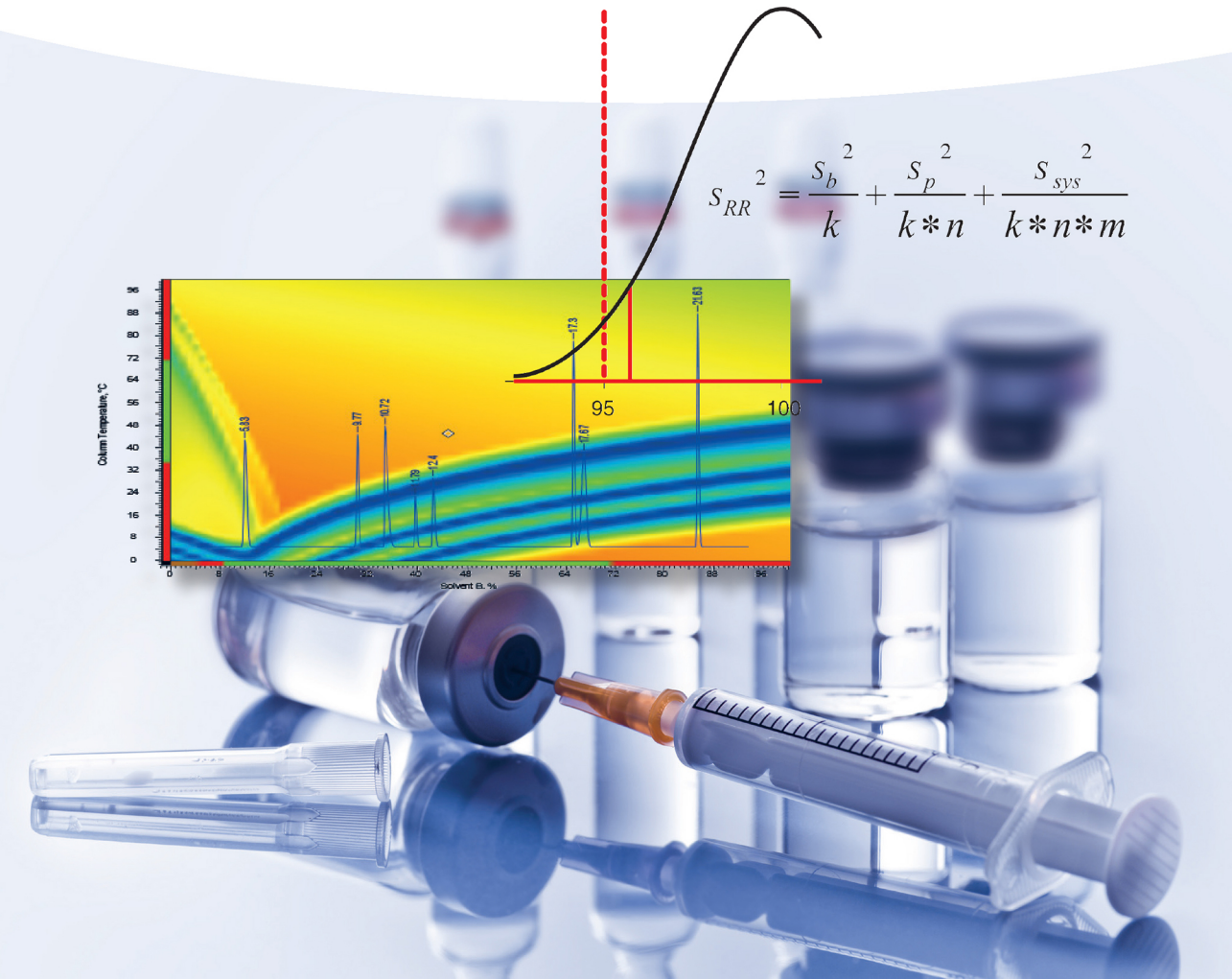
WILEY-VCH

Edited by
Joachim Ermer and Phil Nethercote

Method Validation in Pharmaceutical Analysis

A Guide to Best Practice

Second, Completely Revised and Updated Edition



Edited by
Joachim Ermer and Phil Nethercote

Method Validation in Pharmaceutical Analysis

Related Titles

Bhattacharyya, L., Rohrer, J.S. (eds.)

Applications of Ion Chromatography for Pharmaceutical and Biological Products

2012
Print ISBN: 978-0-470-46709-1,
also available in digital formats

Mascher, H.

HPLC Methods for Clinical Pharmaceutical Analysis

A User's Guide

2012
Print ISBN: 978-3-527-33129-1

Hansen, S., Rasmussen, K., Pedersen-Bjergaard, S.

Introduction to Pharmaceutical Chemical Analysis

2012
Print ISBN: 978-0-470-66122-2,
also available in digital formats

Xu, Q., Madden, T.L.

Analytical Methods for Therapeutic Drug Monitoring and Toxicology

2011
Print ISBN: 978-0-470-45561-6,
also available in digital formats

Storey, R.R. (ed.)

Solid State Characterization of Pharmaceuticals

2011
Print ISBN: 978-1-405-13494-1,
also available in digital formats

Edited by Joachim Ermer and Phil Nethercote

Method Validation in Pharmaceutical Analysis

A Guide to Best Practice

Second, Completely Revised and Updated Edition

WILEY-VCH
Verlag GmbH & Co. KGaA

Editors

Dr. Joachim Ermer
Sanofi-Aventis Deutschl. GmbH
Industriepark Höchst D710
Quality Control Service / R.202
65926 Frankfurt
Germany

Dr. Phil Nethercote
GSK - GlaxoSmithKline
Shewalton Road
GMS Quality
KA11 5AP Irvine, Ayrshire
United Kingdom

Cover
Background Photo.
Source Fotolia © Alexander Raths

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-33563-3
ePDF ISBN: 978-3-527-67219-6
ePub ISBN: 978-3-527-67218-9
Mobi ISBN: 978-3-527-67217-2
oBook ISBN: 978-3-527-67220-2

Cover Design Bluesea Design, McLeese Lake, Canada
Typesetting Laserwords Private Limited, Chennai, India
Printing and Binding Markono Print Media Pte Ltd., Singapore

Printed on acid-free paper

Contents

Foreword

In 2002, FDA began an initiative entitled "Pharmaceutical Quality for the 21st Century." This initiative identified a number of problems in the pharmaceutical industry: pharmaceutical manufacturing processes often had low efficiencies in comparison to other industry sectors with significant levels of waste and rework, reasons for manufacturing failures were not always understood, the uptake of new technologies was slower than in other sectors, and manufacturing cycle times and costs were high. In September 2004, the FDA published a report "Pharmaceutical cGMPS for the 21st century – A risk based approach" which made a series of recommendations aimed at encouraging the early adoption of new technological advances, facilitating application of modern quality management techniques, encouraging adoption of risk-based approaches, and ensuring that regulatory review and inspection polices were consistent, coordinated, and based on state-of-the art pharmaceutical science. In October 2005, Janet Woodcock of the FDA described the desired state of the pharmaceutical industry as a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. Between 2005 and 2012, the International Conference for Harmonisation (ICH) developed a series of guidances (ICH Q8,9,10 and 11) that were intended to modernize the pharmaceutical industries approach to Quality Management and embed more scientific and risk-based approaches to pharmaceutical development and manufacturing. This new paradigm was based on a philosophy of "Quality by Design" (QbD). ICHQ8,9,10, and 11 described how systematic approaches to process understanding and control of risk coupled with implementation of effective quality management systems could deliver more robust manufacturing processes.

A critical enabler to ensuring manufacturing processes consistently produce products that are fit for patients and consumers is the analytical data that allows an understanding of the process and confirms the quality of the product produced. Many of the problems and issues with pharmaceutical manufacturing processes uncovered via the FDAs "Pharmaceutical Quality for the 21st Century" initiative were also true for analytical methods used by the industry. Uptake of new analytical technologies was slow, repeat occurrences of out-of-specification results due to lab errors were common, and levels of waste and rework were high. Clearly,

analytical testing is simply a "process" in the same way that manufacturing is a process – the difference being that the output of a manufacturing process is a product, while the output from an analytical measurement is data. It follows therefore that it should be possible to apply the QbD principles described in the ICH Q8–Q11 guidances to enhance the understanding, control, and performance of analytical methods.

In the second edition of Method Validation in Pharmaceutical Analysis, the editors have included chapters written by subject matter experts, which illustrate how the QbD principles can be applied to analytical methods. These include the following: how an analytical target profile (ATP) can be established to predefined the objectives for the quality of the data that the method is required to produce (which parallels the concept of a QTPP used to define the quality of product a manufacturing process needs to produce), how the lifecycle approach to process validation developed for manufacturing processes can also be applied to analytical methods, and how the need for effective change and knowledge management process throughout the lifecycle are as equally important for analytical methods as they are for manufacturing processes.

The concepts described in this book reflect modern quality management practices and include approaches used widely in other industries (e.g., measurement uncertainty). The establishment of "fit-for-purpose" criteria in an ATP will facilitate a more scientific and risk-based approach to method validation activities ensuring efficient use of resources that are focused on the areas of highest risk and will bring the pharmaceutical industry in line with other science-based industries. Ultimately, this will help promote regulatory as well as business excellence and public health through the better understanding and control of the measurement of quality of pharmaceutical products.

Moheb Nasr, Ph.D.
VP, CMC Regulatory Strategy, GSK

List of Contributors

Christophe Agut
Biostatistics and Programming
Sanofi R&D, 195
Route d'Espagne
Toulouse Cedex 1 31036
France

Christopher Burgess
Burgess Analytical Consultancy Limited
The Lendings
Startforth
Barnard Castle DL12 9AB
UK

Todd L. Cecil
USP
12601 Twinbrook Parkway
Rockville MD 20852
USA

Joachim Ermer
Sanofi-Aventis Deutschland GmbH
Industrial Quality and Compliance, Frankfurt Chemistry
Room 605/Building D711
Industriepark Höchst
Frankfurt 65926
Germany

Melissa Hanna-Brown
Pfizer Global R&D
Analytical Research and Development
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

Brent Harrington
Pfizer Global R&D
Analytical Research and Development
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

Mary Lee Jane Weitzel
Consultant
15 Park Royal Bay
Winnipeg
Manitoba R3P1P2
Canada

Gerd Kleinschmidt
Sanofi-Aventis Deutschland GmbH
R&D LGCR Analytical Sciences
Building H823/Room 206
Industriepark Höchst Frankfurt am Main 65926
Germany

Rosario LoBrutto
TEVA Pharmaceuticals
Pharmaceutical Development
(Steriles)
223 Quaker Road
Pomona NY 10970
USA

R. D. McDowall
McDowall Consulting
73 Murray Avenue
Bromley
Kent BR1 3DJ
UK

Pauline McGregor
PMcG Consulting
Analytical Services
221 Ross Lane
Oakville ON L6H 5K6
Canada

Phil Nethercote
GSK – GlaxoSmithKline
GMS Quality
Shewalton Road
Irvine
Ayrshire KA11 5AP
UK

Andy Rignall
AstraZeneca R&D
Pharmaceutical Development
Charter Way
Hurdsfield Industrial Estate
Macclesfield SK10 2NA
UK

Roman Szucs
Pfizer Global R&D
Analytical Research and
Development
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

Hermann Wätzig
Technical University
Braunschweig
Institute of Medicinal and
Pharmaceutical Chemistry
Beethovenstrasse 55
Braunschweig D-38106
Germany

1
Analytical Validation within the Pharmaceutical Lifecycle

Phil Nethercote and Joachim Ermer

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 EMA's Good Manufacturing Practices (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 was not 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 and inconsistencies.

Table 1.1 shows the ICH view on the required validation characteristics for the various types of analytical procedures.

The recognition that the current pharmaceutical industry's manufacturing performance was not as state of the art as other industries [5–7] has resulted in unprecedented efforts over the last 15 years to modernize pharmaceutical development and manufacturing. In August 2002, the FDA announced a significant new

Method Validation in Pharmaceutical Analysis: A Guide to Best Practice, Second Edition.
Edited by Joachim Ermer and Phil Nethercote.

Table 1.1 Validation characteristics normally evaluated for the different types of test procedures [4a] and the minimum number of determinations recommended [4b].

Validation characteristic	Minimum Number	Analytical procedure			
		Identity	Impurities		Assay[a)]
			Quantitative	Limit	
Specificity[b)]	Not applicable	Yes	Yes	Yes	Yes
Linearity	5	No	Yes	No	Yes
Range	Not applicable	No	Yes	No	Yes
Accuracy	9 (e.g., 3 × 3)	No	Yes	No	Yes
Precision					
Repeatability	6 or 9 (e.g., 3 × 3)	No	Yes	No	Yes
Intermediate precision/ reproducibility[c)]	(2 series)[d)]	No	Yes	No	Yes
Detection limit	Approach dependent	No	No[e)]	Yes	No
Quantitation limit		No	Yes	No	No

Yes/no, normally evaluated/not evaluated.

a) Including dissolution, content/potency.

b) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

c) Reproducibility not needed for submission.

d) No number given in [1], logical conclusion.

e) May be needed in some cases.

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* [8]. 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 the ICH and resulted in a series of new ICH guidelines being produced. In November 2005, ICH Q8 [9] and Q9 [10] were issued to provide guidance on best practice in pharmaceutical development and risk management. These guidelines were followed by ICH Q10 [11] in June 2008, which described the key aspects of a modern pharmaceutical quality system and by ICH Q11 [12] 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 [13], 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.* [14] published a paper that recognized that the concepts of QbD that had been developed with an aim of enhancing the robustness of manufacturing processes could also have applicability to analytical procedures. 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.

The 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 *Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach* included recommendations that the 1987 industry guideline on process validation be revised to include twenty-first century concepts, including risk management and adoption of a life-cycle approach. In January 2011, the FDA issued a new guidance for industry document entitled *Process Validation: General Principles and Practices* [15]. This guidance aligns process validation activities with a product life-cycle concept and with the ICH Q8, 9, and 10 guidelines. The life-cycle 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 life cycle 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 on the basis of 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 that 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 Alignment between Process and Analytics: Three-Stage Approach

In 2010, Nethercote *et al.* [16] suggested that, just as process validation can benefit from a product life-cycle approach so also can analytical method validation. They suggested that there were a number of key factors that are important in a QbD/life-cycle approach. These include

- the importance of having predefined objectives;
- the need to understand the method, i.e. 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 life cycle 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 life cycle of use which establishes scientific evidence that a method is capable of consistently delivering quality data,* that is, that, similar to the FDA's definition of process validation, it should apply to all activities performed throughout the method's life cycle of use – not just the qualification step that was traditionally associated with the concept of method validation. The only difference is 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 [17] and by the USP (United States Pharmacopoeia) Validation and Verification Expert Panel [18]. 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.

Adoption of a QbD/life-cycle approach to analytical method validation will have numerous advantages in ensuring the suitability of the analytical procedure whenever it is applied. It is our intention with this book to guide the reader through all stages of the analytical life cycle, and describe both fundamentals and application to facilitate the utilization of these advantages. We are convinced that a comprehensive utilization of the proposed QbD/life cycle from the start will provide the

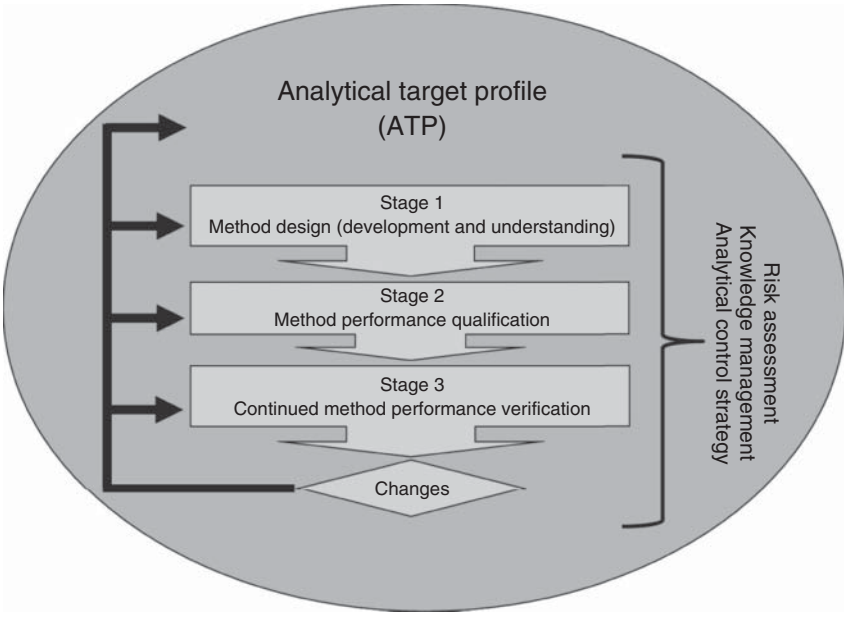


Figure 1.1 Three-stage approach to analytical life-cycle validation.

maximum 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: Analytical Target Profile

Obviously, the *predefined objectives* [9] 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 [19]. 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,* that is, all steps are included such as sample preparation, analytical methodology, calibration, definition of the reportable result, as well as specification limits.

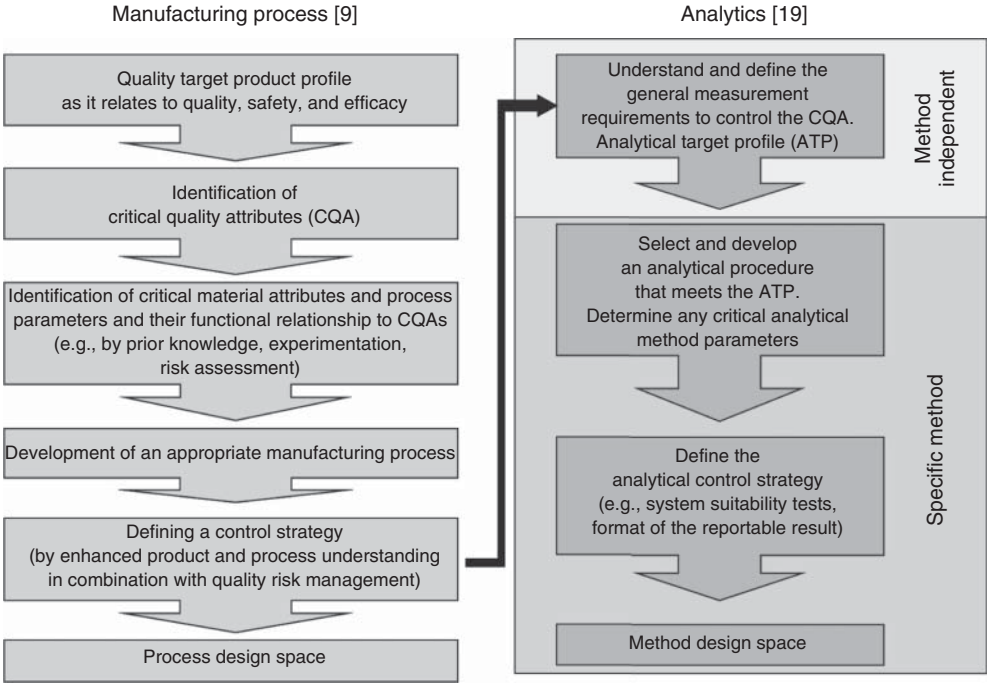


Figure 1.2 Alignment of QbD principles for pharmaceutical product/manufacturing and for the corresponding analytical measurements.

The ATP defines the performance requirements for the measurement of a given quality attribute, or more exactly, for the "product" of the test procedure that is the reportable result, that is, the final result that is to be compared to the acceptance limits of the specification [20]. The ATP can be regarded as the very "heart" of the whole life-cycle 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 life cycle. Consequently, the ATP concept facilitates the integration of the various activities dealing with analytical performance that were often performed and considered isolated in the past, such as method development (now Stage 1), initial validation (now Stage 2), change control, and the associated re-qualification, control charts, and so on (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 *independent of a specific analytical procedure*. Therefore, precision (see Section 5.2) and accuracy (see Section 5.3) 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 [4], that is, specificity (see Section 5.4), linearity (see Section 5.5), detection and quantitation limit (see Section 5.6) 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 3). For example, in case of an assay, the ATP may look as the following examples:

- The procedure must be able to quantify [analyte] in [presence of X, Y, Z] over a range of A% to B% of the nominal concentration with a precision of less than C% RSD (relative standard deviation) and an accuracy of less than D% bias.
- The procedure must be able to quantify [analyte] in [presence of X, Y, Z] over a range of A% to 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 [18].

The paradigm change in establishing the requirements of "what" needs to be measured, instead of the "how" guarantees a close link between the suitability of the eventually applied analytical procedure and the manufacturing process and product requirements. It is proposed that eventually, the ATP is submitted to and approved by regulatory authorities and not an individual analytical procedure, that is, any analytical procedure conforming to the defined ATP would be regarded as acceptable. The current analytical procedure for each critical quality attribute would be included in the dossier as an example or reference procedure in order to allow official control laboratories to implement the testing. As such, an example procedure may include much more operational method and handling details, without facing the risk of regulatory constraints; this approach would also facilitate the work of official control laboratories. It would also *facilitate continuous improvements,* ranging from changes of method parameters such as mobile phase composition or gradient in LC up to application of a different analysis technique. Of course, any change must be strictly handled according to the internal change control management of the company (see Section 8.4).

The application of the ATP concept is also feasible *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 life cycle. Chapter 3 describes an approach to developing an ATP that draws on concepts of "measurement uncertainty" and *decision rules* described in consensus standards documents such as ASTM, Eurachem guidance, ASME, and so on. This approach is based on the recognition that in many situations, analytical data is 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 rational link

between the use of data and the validation requirements for the method generating that data.

Similar approaches described or intended in the USP such as the performance-based concept in the USP's medicines compendia are discussed in Chapter 4.

By focusing on the required performance of the reportable result, greater consideration will be given to the performance of the routine application of the analytical procedure, which is sometimes neglected during validation.

1.4 Analytical Life Cycle

As *qualified equipment* is one of the essential prerequisites for any analytical measurement, the book begins with this topic (see Section 2.1), including the concept of *continuous performance qualification* (see Section 2.2) as an efficient way to collect equipment performance results.

While the ICH guidelines were intended to be regarded as the basis and philosophical background to analytical validation and not to be 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] – in practice, both industry and regulatory authorities often resort to adopting a checklist approach. As what is required to gain 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 5, *method performance characteristics* are discussed, along with appropriate performance parameters, calculations, and tests. They can be categorized as the "universal" or "primary" characteristics precision and accuracy, which are directly related to the ATP, and method-specific or "secondary" characteristics, such as specificity, linearity, detection and quantitation limit, which are dependent on the respective method and included in accuracy and precision.

The following chapters reflect the life cycle of the analytical procedure, that is,

- *Stage 1*: Method Design and Understanding (Chapter 6)
- *Stage 2*: Method Performance Qualification (Chapter 7)
- *Stage 3*: Continued Method Performance Verification (Chapter 8).

Chapter 6 starts with a discussion of 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 control strategy (see Section 6.1), followed by two examples of robustness investigations (see Sections 6.2 and 6.3) and a discussion on system suitability tests as part of the method control strategy (see Section 6.4).

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. Method qualification involves demonstrating that the defined method will, under routine operating conditions, produce data that meet the precision and accuracy requirements defined in the ATP (Section 7.1); this is illustrated by a case study (Section 7.2). As a specific example, the development of a delivered dose uniformity procedure for a pressurized metered dose inhaler is presented in Section 7.3. Other examples of qualification activities are described in Section 7.4, implementation of compendial procedures and Section 7.5, transfer of analytical procedures.

The goal of continued 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 (Section 8.2) as well as ensuring appropriate actions are taken when issues are identified with the performance or when the procedure is modified or changed as part of continual improvement (Section 8.4). Of course, closely linked to the evaluation of normal behavior of method performance is the topic of aberrant or atypical results (Section 8.3), including treatment and investigation of out-of specification (OOS) results.

References

1. Agalloco, J. (1995) Validation: an unconventional review and reinvention. *PDA J. Pharm. Sci. Technol.*, **49** (4), 175–179.
2. FDA and CDRH/CDER (1987) Guideline on General Principles of Process Validation, May 1987.
3. US Food and Drug Administration, Centre for Drugs and Biologics, and Department of Health and Human Services (1987) Guidelines for Submitting Samples and Analytical Data for Methods Validation.
4. (a) ICH CPMP/ICH/381/95 (Q2A): Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (Step 5 – adopted November 94), *http://www.ich.org/* (accessed 11 March 2014); (b) ICH CPMP/ICH/281/95 (Q2B): Note for Guidance on Validation of Analytical Procedures: Methodology (Step 4 - adopted December 96), *http://www.ich.org/* (accessed 11 March 2014).
5. Staff Reporter (2002) Pharmaceuticals Trouble in the Making: Sloppy Manufacturing Comes Under Fire, but Inefficiency is the Real Problem. The Economist (Aug. 29).
6. Abboud, L. and Henslye, S. (2003) New prescription for drug makers: update the plant. *Wall Street J.*, (Sep. 3).
7. Carey, J. and Arndt, M. (2004) Making Pills the Smart Way: Drug Makers are Revamping Factories to Save Money and Avoid Production Mishaps. Business Week Online (May 3), *http://www.businessweek.com:/print/magazine/content/04_18/b3881602.htm?mz* (accessed 11 March 2014).

8. US Food and Drug Administration and Department of Health and Human Services U.S. Food and Drug Administration (2004) Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach, September 2004.
9. ICH (2005) Guidance for Industry, "Q8 Pharmaceutical Development", November 2005, *http://www.ich.org/* (accessed 11 March 2014).
10. ICH (2006) Guidance for Industry, "Q9 Quality Risk Management", June 2006, *http://www.ich.org/* (accessed 11 March 2014).
11. ICH (2009) Guidance for Industry, "Pharmaceutical Quality Systems", April 2009, *http://www.ich.org/* (accessed 11 March 2014).
12. ICH (2012) Guidance for Industry, "Development and Manufacture of Drug Substances", May 2012, *http://www.ich.org/* (accessed 11 March 2014).
13. ICH (2009) Guidance for Industry, "Q8 R2 Pharmaceutical Development", August 2009, *http://www.ich.org/*(accessed 11 March 2014).
14. Borman, P., Nethercote, P., Chatfield, M., Thompson, D., and Truman, K. (2007) The application of quality by design to analytical methods. *Pharm. Technol.*, **31** (10), 142–152.
15. FDA (2011) Guidance for Industry, Process Validation: General Principles and Practices, Revision 1, January 2011.
16. Nethercote, P. *et al.* (2010) PharmaManufacturing 2010, *http://www.pharmamanufacturing.com/articles/2010/060.html* (accessed 11 March 2014).
17. Nethercote, P. and Ermer, J. (2012) Quality by design for analytical methods: implications for method validation and transfer. *Pharm. Technol.*, **36** (10), 74–79.
18. Martin, G.P., Barnett, K.L., Burgess, C., Curry, P.D., Ermer, J., Gratzl, G.S., Hammond, J.P., Herrmann, J., Kovacs, E., LeBlond, D.J., LoBrutto, R., McCasland-Keller, A.K., McGregor, P.L., Nethercote, P., Templeton, A.C., Thomas, D.P., and Weitzel, J. (2013) Stimuli to the revision process: lifecycle management of analytical procedures: method development, procedure performance qualification, and procedure performance verification. *Pharmacopeial Forum* **39**(5) *http://www.usp.org/usp-nf/notices/stimuli-article-lifecycle-management-analytical-procedures-posted-comment* (accessed 11 March 2014).
19. Pharmaceutical Research and Manufacturers of America Analytical Technical Group and European Federation of Pharmaceutical Industries and Associations (EFPIA) Analytical Design Space Topic Team (2010) Implications and opportunities of applying QbD principles to analytical measurements. *Pharm. Technol.*, **34** (2), 52–59.
20. USP General Chapter <1010> "Interpretation and Treatment of Analytical Data", *http://www.uspnf.com/uspnf/login* (accessed 28 May 2014).

2
Analytical Instrument Qualification

2.1
Analytical Instrument and System Qualification

Christopher Burgess and R. D. McDowall

2.1.1
Data Quality and Integrity in a GMP Environment

Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. A high degree of confidence is needed that the analytical procedure will generate reportable results that meet requirements under all conditions of use as the procedure progresses through the life cycle. Application of quality risk management (QRM) concepts and tools (International Conference on the Harmonisation, ICH, Q9) can be useful in providing a mechanism for achieving this. The analytical laboratory may be seen as a manufacturing process converting samples into information. This conversion process may be illustrated as data to information transformation shown in Figure 2.1. Assuming, sample relevance, the conversion foundation relies upon data integrity. Data integrity is predicated upon the assurance that instruments and systems employed as part of the analytical procedure are in a state of control. A state of control is established for instruments by calibration and qualification activities and for software applications, by validation.

The analytical laboratory manufacturing process, developed by us, is illustrated in Figure 2.2.

2.1.1.1 Criteria for Quality Data

To assure laboratory data integrity, qualified instruments, validated systems, and procedures are critical factors to control. The purpose of this chapter is to consider requirements and approaches to achieve a state of control for instruments and systems to underpin validated analytical procedures, which is the topic of this book.

The foundation for any analytical procedure is that its development and use are underpinned by four main factors:

Method Validation in Pharmaceutical Analysis: A Guide to Best Practice, Second Edition.
Edited by Joachim Ermer and Phil Nethercote.

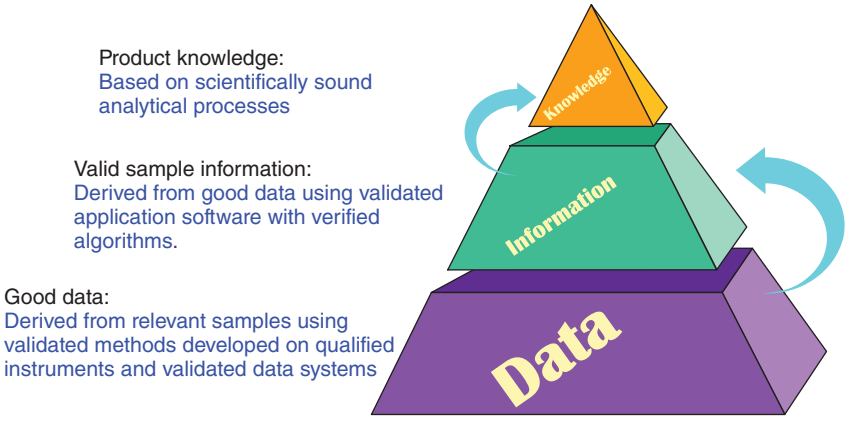


Figure 2.1 Data to knowledge transformation.

1) The apparatus, instruments, and systems are calibrated/qualified according to their purpose
2) The reference materials are traceable
3) The reagents used are of a specified quality
4) The analysts are qualified and competent.

2.1.1.2 Regulatory Rationale for Qualified Analytical Instruments

It is essential to ensure that qualified instruments and validated systems are employed in the regulated environment. The GMPs (good manufacturing practices) both in the United States and the European Union require demonstrable control of instruments and systems.

For example, in the United States, 21 Code of Federal Regulations (CFR)§ 211.160, the general requirements are

> Laboratory controls shall include:
> (b) (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met.
> Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

2.1.2 USP General Chapter <1058>

United States Pharmacopeia (USP) General Chapter <1058> on Analytical Instrument Qualification (AIQ) became effective in August 2008 [1]. The general chapter started life as an AAPS meeting output on the qualification (originally