



Technical Report No. 57-2

Analytical Method Development and Qualification for Biotechnology Products



PDA Analytical Method Development and Qualification of Biotechnology Products Technical Report Team

Authors

Melissa J. Smith, MJ Quality Solutions, (Chair)

Florence Baudoux, GlaxoSmithKline Biologicals

Marta Germano, Janssen Pharmaceutical Companies of Johnson & Johnson

Joachim Leube, Ph.D., Crucell

Sheila Magil, Ph.D., BioProcess Technology Consultants, Inc.

Carl Gustav-Millinger, Quality & Qualimetrics Consultancy QQC AB

Dwayne Neal, Emergent BioSolutions

Phillip Ramsey, Emergent BioSolutions

Michael Rooney, Ph.D., Jazz Pharmaceuticals

Rebecca Sendak, Ph.D., Sanofi

Zoran Sosic, Biogen Idec

Earl K. Zablackis, Ph.D., Sanofi Pasteur

Contributors

Raphael Bar, Ph.D., BR Consulting

DaoTian Fu, Ph.D., Livzon Mabpharm, Inc.

Kenji Furuya, Boehringer Ingelheim

Stephan O. Krause, Ph.D., MedImmune

Nadine M. Ritter, Global Biotech Experts, LLC

Jane Weitzel, Quality Analysis Consultants

DISCLAIMER: The content and views expressed in this technical report are the result of a consensus achieved by the authorizing task force and are not necessarily the views of the organizations they represent.

Analytical Method Development and Qualification for Biotechnology Products

Technical Report No. 57-2

ISBN: 978-0-939459-74-2

© 2015 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

1.0 INTRODUCTION	1	4.2.5 Readiness to Proceed	30
1.1 Method Lifecycle	2	4.3 Method Qualification Plan or Protocols.....	30
1.2 Purpose and Scope.....	2	4.3.1 Qualification Approach	30
2.0 GLOSSARY OF TERMS.....	4	4.3.2 Qualification Characteristics	31
2.1 Abbreviations	6	4.3.2.1 Reference Standards	31
3.0 METHOD DEVELOPMENT.....	7	4.3.2.2 Specificity	31
3.1 Method Definition.....	7	4.3.2.3 Spiked Samples.....	32
3.1.1 Analytical Target Profile	9	4.3.2.4 Linearity and Range.....	32
3.2 Method Selection	11	4.3.2.5 Accuracy	32
3.2.1 Risk Assessment.....	12	4.3.2.6 Repeatability and Intermediate	
3.2.2 Selection of Platform-Based Technologies ..	12	Precision.....	32
3.2.3 Conclusion of the Selection Process.....	13	4.3.2.7 Detection Limits and Quantitation	
3.3 Method Development and Optimization.....	13	Limits	34
3.3.1 Phased Approach	13	4.3.2.8 Robustness.....	34
3.3.2 Risk Considerations	13	4.3.2.9 Stability-Indicating Assessment	34
3.3.3 Design of Experiment.....	14	4.4 Execution	35
3.3.3.1 List and Description of Experiments ...	15	4.5 Qualification Evaluation	35
3.3.4 Execution of Development Activities	16	4.5.1 Specificity.....	35
3.3.4.1 Samples and Standards.....	16	4.5.2 Accuracy, Precision, Linearity, and Range... 35	
3.3.4.2 Known or Expected Impurities.....	17	4.5.3 Detection Limits and Quantitation Limits . 36	
3.3.4.3 Forced-Degradation Samples.....	18	4.5.4 Statistical Assessments and Practical vs.	
3.3.4.4 Equipment	18	Statistical Differences.....	36
3.3.4.5 System Suitability	18	4.5.5 Qualification Excursions.....	36
3.3.4.6 Robustness.....	19	4.6 Method Qualification Report.....	37
3.3.5 Evaluation of Development Activities	20	4.6.1 Standard Operating Procedure.....	37
3.4 Method Deliverables.....	20	4.6.2 Supportive Procedures	37
3.4.1 Baseline and Best-Practice Deliverables..	21	4.6.3 Data.....	38
3.4.2 Documentation Deliverables	23	4.6.4 System Suitability and Sample	
3.4.3 Physical Deliverables.....	24	Validity Criteria	38
4.0 METHOD QUALIFICATION	26	4.7 Conclusions and Deliverables	38
4.1 Overview	26	5.0 ANALYTICAL METHOD COMPARABILITY AND	
4.2 Method Development Package Assessment ..	29	ANALYTICAL METHOD TRANSFER	45
4.2.1 Intended Use and Performance.....	29	6.0 METHOD LIFECYCLE MANAGEMENT	
4.2.2 Standard Operating Procedure.....	29	CONTINUUM	46
4.2.3 Physical Deliverables: Material and		7.0 CONCLUSION.....	48
Equipment	30	8.0 REFERENCES	49
4.2.4 Robustness.....	30		

FIGURES AND TABLES INDEX

Figure 1.1-1	Method Lifecycle and its Links to Product Development	2	Table 3.4.1-1	Baseline and Best Practices for Deliverables of a Developed Method ..	22
Figure 1.2-1	Table of Contents Map.....	3	Figure 3.4.2.1-1	Documentation Deliverables	24
Figure 3.0-1	Method Development Process.....	7	Figure 3.4.3-1	Physical Materials Deliverables	25
Table 3.1-1	Overview of Method Definition Process...	8	Figure 4.1-1	Models of Qualification.....	27
Table 3.1-2	Points to Consider for Method Definition...	9	Table 4.3.2.6-1	Sample IP Matrix.....	33
Table 3.2-1	Inputs and Outputs of Method Selection Process.....	11	Figure 4.3.2.6-1	Sample Nested Design for IP for Day 1.....	33
Figure 3.3.2-1	Risk Assessment Process Map	14	Table 4.3.2.6-2	Sample Restricted Maximum Likelihood Variance Component Estimates for IP Matrix.....	34
Figure 3.3.3.1-1	Iterative Method Development Process	15	Table 4.7-1	Evaluations and Deliverables for AMD and AMQ.....	39
Table 3.3.4.6-1	Fractional Factorial Design: Factors, Levels with Result from Each Run, and Factor Effect p-values	19	Figure 6.0-1	Development and Qualification Lifecycle Deliverables	46
Figure 3.3.4.6-1	Normal Plot Robustness Factor Assessment	20			

1.0 Introduction

This technical report provides practical, risk-based guidance for the development and qualification portions of the analytical method lifecycle for biotechnology products. It is a companion report to PDA *Technical Report No. 57: Analytical Method Validation and Transfer for Biotechnology Products*.

Method development begins with defining the requirements for the analytical method. Based on the intended use and related requirements of the method, an analytical platform is selected in concert with the appropriate materials and equipment. A method is defined through method optimization, with consideration of the final requirements of the method (e.g., sensitivity and specificity). The development of a method typically leads to, but does not necessarily finish with, its qualification, which is a documented assessment of method performance (1). This process is one means to help ensure that the method is scientifically sound (specific, sensitive, accurate, and reproducible) and is suitable and reliable for the specified purpose (2-4). Method performance may also be assessed by other means, including trending of assay controls during routine method use.

The development process depends on the use of appropriately detailed documents that describe the analytical method. Operational and maintenance procedures for equipment should be available to ensure proper functioning with respect to the intended use and phase of product development (4-7).

Analytical method development (AMD) and analytical method qualification (AMQ) are typically iterative processes whereby the method is optimized, tested for its suitability (i.e., ability to meet target criteria for performance characteristics, such as precision and accuracy) through qualification studies, and potentially further optimized based on the qualification results.

The analytical target profile (ATP) is discussed in further detail in the body of this technical report as a potential means to manage AMD and AMQ. The ATP is comprised of the concepts of intended use, expected performance; measured critical quality attributes (CQAs), identified critical performance parameters, and completed iterative performance assessments. It can, therefore, be considered the structural framework for the method development and qualification process as well as for the rest of the method lifecycle continuum, including validation and routine use (8).

Qualification of an analytical method typically proceeds in a phase-appropriate manner commensurate with the intended use of the method. In other words, a more extensive evaluation of method performance or qualification may be performed to support a Phase II clinical study than was used for a Phase I study, with both qualification activities being broadly based on the elements of ICH Q2(R1) guidance (6). The phase-appropriate guidance documents describe the qualification and validation activities recommended for release and stability methods in support of a particular clinical phase (2,3). For other methods, such as characterization methods, qualification can be the end goal in the method lifecycle. Formal method qualification is not a regulatory requirement prior to method validation, but it offers one means of ensuring method suitability and ability to satisfy the defined requirements (e.g., in the ATP) and to support a successful validation.

The intended use of analytical methods may change during the product development process and may affect the ATP, method requirements, and method performance expectations. AMQ provides an option to ensure the suitability of a method's use for the release of early-phase or midphase clinical trial material without generating formal and prospective analytical method validation (AMV) studies.

1.1 Method Lifecycle

The method lifecycle is the time from identification of the need for an analytical method through method retirement, including periodic reassessments of and updates to the method. This lifecycle is tied to the product lifecycle in that the status of the method must be assessed in the context of whether the product is in the early stages of clinical development or is commercially approved. An important part of the method lifecycle is to ensure that at each stage, the method is assessed and found ready to proceed to the next step. A schematic of the development and qualification elements of the lifecycle, which are detailed within this report, is provided in **Figure 1.1-1**, which also shows the link to validation, as detailed within PDA *Technical Report No. 57*.

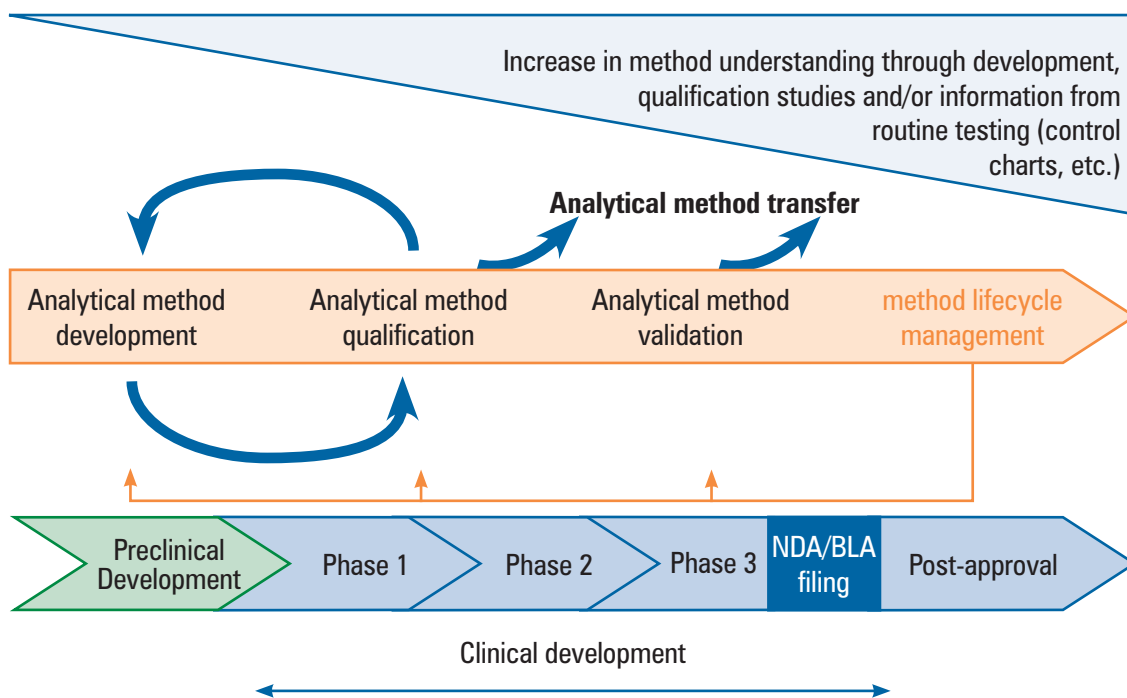


Figure 1.1-1 Method Lifecycle and its Links to Product Development

1.2 Purpose and Scope

This technical report covers method development and qualification for biotechnology products.

The content that follows describes the method development and qualification portions of the lifecycle that often lead to method validation, which is outlined in PDA *Technical Report No. 57: Analytical Method Validation and Transfer for Biotechnology Products* and ICH Q2(R1) (6,9). This report also delineates the commonalities and differences between qualification and validation, the various models for execution of qualification, and which of these models comprise the best practices of industry. The document further recognizes that terms such as “qualification” may be commensurate with phase-appropriate validation within certain company systems and regulatory environments (1). This report includes guidance for AMD and AMQ studies, such as risk-based strategies and priorities; ATP and quality-by-design (QbD) concepts; target performance criteria; and modern quality expectations, such as those presented in ICH Q8-10 guidelines (10-12).