Workshop Agenda

USP Workshops

Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation

September 24-25, 2018

Gain a better understanding of how lifecycle principles can be applied to analytical testing procedures.

Workshop Participating Organizations:

Final Agenda

DAY ONE: Monday, September 24, 2018

8:30 – 9:00 a.m.	**Registration & Coffee** *Exhibitor Tables Open*
9:00 – 9:30 a.m.	**Overview of the Analytical Procedure Lifecycle** Greg Martin, M.S., *Chair, USP Validation and Verification Expert Panel*
9:30 – 10:15 a.m.	**Method Lifecycle: From Development to Qualification** Antonio Ramos, *Group Leader, Analytical Methodologies and Method Development, Hovione*
10:15 – 11:00 a.m.	**Analytical Method Lifecycle: Current Status and Opportunities** Phil Borman, MSc, *Director, GlaxoSmithKline*
11:00 – 11:15 a.m.	**Morning Break** *Exhibitor Tables Open*
11:15 a.m. – 12:00 p.m.	**Define and Qualify: Tools for Enhanced Analytical Procedure Development** Brent Harrington, M.S., *Director, Pfizer*
12:00 – 1:00 p.m.	**Lunch** *USP Museum and Exhibitor Tables Open*
1:00 – 1:15 p.m.	**Break Out Instructions** Greg Martin, M.S., *Chair, USP Validation and Verification Expert Panel* Attendees will do 3 rotations *(see rotation chart on the following page)* *1:15 - 2:15 p.m.* *2:30 - 3:30 p.m.* *3:45 - 4:45 p.m.*

Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation

September 24-25, 2018

Gain a better understanding of how lifecycle principles can be applied to analytical testing procedures.

1:15 – 4:45 p.m.

Break Out Topics
Moderated by Members of USP's Validation and Verification Expert Panel

Development of an ATP (*Spalding Auditorium)*
Kimber Barnett, Ph.D., Pauline McGregor, Ph.D.,
Steven Walfish, M.S., MBA

Procedure Understanding & Control Strategy (*Bache/Wood Rooms)*
Elisabeth Kovacs, Greg Martin, M.S., Phil Nethercote, Ph.D., Jane Weitzel

Procedure Qualification (*Marshall/Wiley Rooms)*
Joachim Ermer, Ph.D., Rosario LoBrutto, Ph.D., David Thomas, Ph.D.

	Spalding Auditorium	Bache/Wood Rooms	Marshall/Wiley Rooms
	Development of an ATP	*Procedure Understanding & Control Strategy*	*Procedure Qualification*
Green	1:15 - 2:15 pm	2:30 - 3:30 pm	3:45 - 4:45 pm
Red	2:30 - 3:30 pm	3:45 - 4:45 pm	1:15 - 2:15 pm
Blue	3:45 - 4:45 pm	1:15 - 2:15 pm	2:30 - 3:30 pm

4:45 p.m.

Day 2 Logistics and Day 1 Concludes
USP Breakout Leaders

DAY TWO: Tuesday, September 25, 2018

8:30 – 8:45 a.m.

Registration & Coffee
Exhibitor Tables Open

8:45 – 10:30 a.m.

Summary of Breakout Sessions and Collect Feedback
Session Speakers

10:30 – 11:00 a.m.

Morning Break
Exhibitor Tables Open

11:00 – 11:45 a.m.

Analytical Method Lifecycle for Impurity Methodology: Some Strategies and Examples
Mark Argentine, Ph.D., *Senior Research Advisor, Analytical Research & Development, Eli Lilly & Co.*

11:45 a.m. – 12:45 p.m.

Lunch
USP Museum and Exhibitor Tables Open

12:45 – 1:30 p.m.

BP Investigation of AQbD Concepts
Gary Kemp, Ph.D., *Secretariat, British Pharmacopoeia*

USP Workshops

Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation

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1:30 – 2:15 p.m.	**Development of an Analytical Target Profile for 6-Sigma Capability** John Harrahy, Ph.D., *Director, Process Development, Pivotal Attribute Sciences Department*, *Amgen*
2:15 – 2:45 p.m.	**Afternoon Break** *Exhibitor Tables Open*
2:45 – 3:30 p.m.	**USP Vision for <1220> *The Analytical Procedure Lifecycle*** Horacio Pappa, Ph.D.*, Director, General Chapters, USP*
3:30 – 4:15 p.m.	**Performance Monitoring of Test Methods in Quality Control with Reference to AQbD** Ramakrishna Velicheti, Ph.D., *Validation Manager, U.S. Food & Drug Administration*
4:15 – 5:00 p.m.	**Workshop Summary** Greg Martin, M.S., *Chair, USP Validation and Verification Expert Panel*
5:00 p.m.	**Workshop Adjourns**

USP would like to thank the following vendor partners exhibiting at the event:

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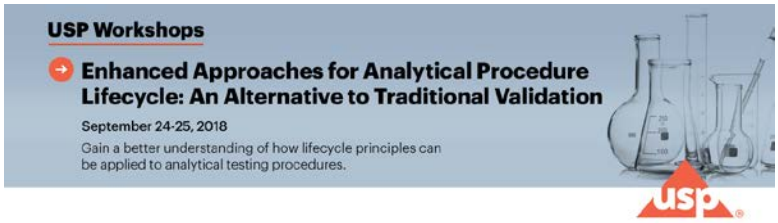
Speaker Biographies & Abstracts (listed alphabetically)

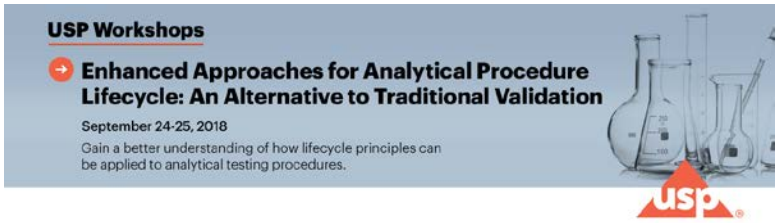


Mark Argentine, Ph.D.
Senior Research Advisor, Analytical Research & Development
Eli Lilly & Co.
Indianapolis, IN

Dr. Argentine is a Senior Research Advisor in the Analytical Research and Development division of Lilly Research Laboratories, Eli Lilly and Company. He received a B.S. in chemistry from the College of William and Mary in Virginia and a Ph.D. in analytical chemistry from the University of Massachusetts, Amherst. He joined Eli Lilly and Company in 1993 and has been involved in analytical control strategy development and commercialization of synthetic and semi-synthetic drug substance and drug product materials for the past 25 years. Current responsibilities and interests continue to include the development of analytical control strategies for pharmaceutical commercialization as well as the regulatory and quality aspects of drug development. He also currently serves as vice-chair to the Analytical Leadership Group of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium).

Presentation
Analytical Method Lifecycle for Impurity Methodology: Some Strategies and Examples
Tuesday, September 25, 2018, 11:00 – 11:45 a.m.

This presentation highlights some meaningful concepts and “tools” to develop and execute robust, effective analytical impurity methods for control. It also aims to use a few case study examples to illustrate implementation of these concepts into analytical method lifecycle concepts for impurities.



Kimber Barnett, Ph.D.
USP Affiliation: Member, Validation & Verification Expert Panel

Research Fellow
Pfizer
Norwich, CT

Kimber Barnett, Ph.D. is a Research Fellow working in Analytical Research and Development at Pfizer Inc. in Groton, CT. In her current role, Kimber serves as a technical team leader responsible for late stage analytical development of drug substances and drug products as well as the late stage LC Method Development Group. Kimber obtained her Ph.D. in Analytical Chemistry from the University of Missouri focusing on chiral separations under the guidance of Professor Daniel Armstrong.

Presentation
Breakout Session: Development of an ATP
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

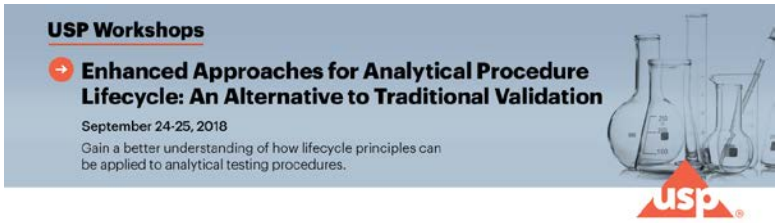
Phil Borman, MSc
Director, Quality by Design Development Lead for Small Molecules
GlaxoSmithKline
Stevenage, UK

Phil Borman is a Chartered Chemist with more than 22 years of experience in the pharmaceutical industry, having obtained a Masters in Chemistry from UMIST (Manchester) University and a Masters in Applied Statistics from De Montfort (Leicester) University. Phil is currently a Director at GlaxoSmithKline where he is accountable for the development and implementation of Quality by Design for Small Molecules. Phil pioneered the adaptation of QbD principles to Analytical methods and has published widely in the field of Analytical Chemistry. He currently co-leads the EFPIA Analytical Lifecycle Management Team.

Presentation
Analytical Method Lifecycle: Current Status and Opportunities
Monday, September 24, 2018, 10:15 – 11:00 a.m.

Phil will discuss the paper recently written by the EFPIA Analytical Lifecycle Management Team entitled: 'Analytical Procedure Lifecycle Management – Current Status and Opportunities'. This will include:

- Benefits of applying enhanced approach on analytical procedure validation & transfer
- Adoption of enhanced approach to method development and utilisation of methods across Pharma
- Future opportunities, alignment of enhanced approach with current and emerging guidance
- Q12 and our thoughts wrt Established Conditions for analytical procedures



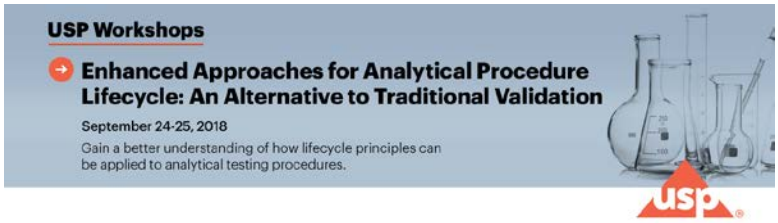
Joachim Ermer, Ph.D.
USP Affiliation: Member, Validation & Verification Expert Panel

Sanofi
Head of QC Lifecycle Management Chemistry
Frankfurt, Germany

Dr. Ermer is Head of QC Lifecycle Management Chemistry at Sanofi in Frankfurt, Germany. He studied biochemistry and has more than 25 years experience in pharmaceutical analytics including development products, global functions, and Head of Quality Control. He is member of the USP Expert Panel on Validation and Verification and of the EFPIA Analytical Lifecycle Management working group.

Presentation
Breakout Session: Procedure Qualification
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

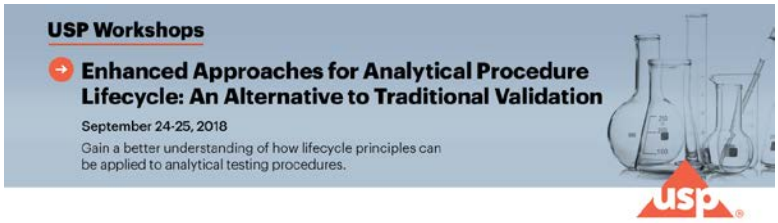


John Harrahy, Ph.D.
Director, Process Development, Pivotal Attribute Sciences Department
Amgen
Cambridge, MA

John Harrahy, Ph.D. is a Director, Process Development, in the Pivotal Attribute Sciences Department at Amgen in Cambridge, Massachusetts. His team supports late-stage clinical trial process development activities for large and small molecule modalities, helping to establish, characterize, and develop test methods for the critical quality attributes of therapeutic candidate molecules. John has also worked in coordinating Amgen's Analytical Target Profile workstream. Prior to joining Amgen in 2016, John worked at Genzyme/Sanofi for 16 years in dual roles of CMC project management and in a team supporting biochemical and biophysical characterization of therapeutic protein and gene therapy clinical candidate molecules, as well as the development, qualification and transfer of analytical methods, and GMP release testing.

Presentation
Development of an Analytical Target Profile for 6-Sigma Capability
Tuesday, September 25, 2018, 1:30 – 2:15 p.m.

The Analytical Target Profile (ATP) is a predefined set of criteria for the analytical methods used to monitor a given product's quality attributes. Given the need for critical attributes to be within a specific range, the purpose of the ATP is to ensure that attributes can be measured accurately and reliably; the manufacturing process capability can be effectively monitored only if the methods used to monitor the process are capable. This presentation will discuss the elements of the ATP – evaluation of method performance in relation to ICH Q2 parameters (including target analytical error "TAE"), performance vs. invalid rate targets, and other business considerations (attribute criticality, cost, throughput, complexity, need to use pre-existing platform technology, etc). Some examples of using ATP to evaluate drive decisions for improving method performance will be presented, along with a description of how the ATP fits into and can support a robust manufacturing process.



Brent Harrington, M.S.
Director
Pfizer Inc.
Groton, CT

Brent Harrington, M.S., is a Director in the Statistics group at Pfizer Inc. in Groton, CT. Brent received his master of science in statistics from Virginia Polytechnic Institute under the direction of Raymond H. Myers. He is responsible for providing experimental designs and statistical support for the Chemical, Manufacturing & Controls (CMC) organization, contributing to the successful filing, registration, and manufacture support of numerous products. This support includes analytical method, and drug product formulation and process development. Recently, Brent has been active in developing and promoting performance-based criteria for analytical methods through the analytical target profile (ATP) concept. Brent is an active participant with several compendia and industry organizations working on analytical quality by design concepts and case studies.

Presentation
Define and Qualify: Tools for Enhanced Analytical Procedure Development
Monday, September 24, 2018, 11:15 a.m. – 12:00 p.m.

Analytical methods are designed to measure and thus provide information concerning product quality attributes. The results produced are frequently used to make important decisions about the samples tested. When making decisions based upon analytical results, it is helpful to understand the uncertainty associated with that data and ensure that it is in line with the product specifications or other criteria. The Analytical Target Profile (ATP) has been proposed as a vehicle for the pharmaceutical industry to describe the acceptable level of measurement uncertainty for a given test and to serve as a reference point throughout the method lifecycle. The tools illustrated in this session provide pragmatic criteria to judge analytical method appropriateness and the confidence in the results generated by the method.

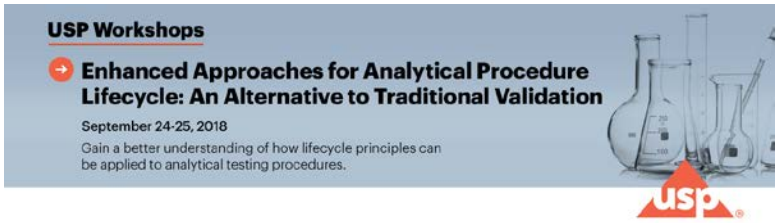
Gary Kemp, Ph.D.
Secretariat
British Pharmacopoeia
London, UK

Gary has a degree in Chemistry from the University of Reading and a PhD in peptide synthesis from UCL. Following his PhD, Gary moved into industry and spent 5 years developing novel antibody-drug conjugates for Spirogen/Medimmune/AstraZeneca.

Gary has been working for the British Pharmacopoeia (part of the UK medicines regulator, the Medicines and Healthcare Products Regulatory Agency) for the past 2 years. His responsibilities include co-ordinating the AQbD working party, supporting the Biologicals Expert Advisory Group and managing the UK's relationship with the European Directorate for the Quality of Medicines.

Presentation
BP Investigation of AQbD Concepts
Tuesday, September 25, 2018, 12:45 – 1:30 p.m.

The British Pharmacopoeia have investigated the application of QbD concepts from a compendial perspective and determined whether they can be used to create better, more robust and flexible standards. The project selected an HPLC Assay of Atorvastatin Tablets as a case study and explored several typical method development QbD concepts including structured risk assessments, DoE and MODR. The final stage of the project was to investigate ATP applications, and these were explored practically by the British Pharmacopoeia Laboratory in collaboration with the Therapeutic Goods Administration (Australia) Laboratory.



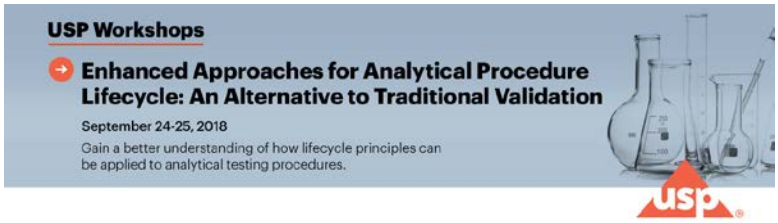
Elisabeth Kovacs
USP Affiliation: Member, Validation & Verification Expert Panel

Chief Scientific Officer, Chemistry and Analytical Sciences
Apotex Inc.
Toronto, Ontario, Canada

Elisabeth Kovacs is Chief Scientific Officer at Apotex Inc. In this role she is responsible for provision of scientific expertise and strategic direction to the organization in managing scientific advancement at all stages of product lifecycle. Elisabeth has been at Apotex for over 30 years primarily involved in analytical R&D, analytical support to new product development, especially dissolution and drug release. Member of the Leadership Team for development and implementation of QbD at Apotex, Elisabeth developed programs and provided training to Apotex staff on QbD and Life Cycle concepts. She is member of the CSPS (Canadian Society for Pharmaceutical Science) board of Directors, GPhA Sciences and Regulatory Advisory Board, GPhA USP Task Force, as well as USP Expert Panels (Validation and Verification; Residual Solvents) and USP Project Teams.

Presentation
Breakout Session: Procedure Understanding and Control Strategy
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.



Rosario LoBrutto, Ph.D.
USP Affiliation: Member, Validation & Verification Expert Panel

Head of Scientific Affairs
Sandoz
Princeton, NJ

Rosario has over 20+ years of experience developing, scale-up, transfer, and launch preparation of generic, complex generic and branded products as well as products following a 505b2 regulatory pathway at Merck, Novartis, TEVA and Sandoz. This includes development of active pharmaceutical ingredients and drug products including small molecules, polypeptides and proteins in various dosage forms (Parenterals, solid oral dosage forms, transdermals, films, etc) and drug-device combination products for a wide gamut of therapeutic areas. Currently at Sandoz, Rosario is Head of Scientific Affairs based in Princeton, NJ. Prior to joining Sandoz, Rosario worked at TEVA Pharmaceuticals as Site Head / Head of Development for Sterile Products in Pomona, New York. He also worked at Novartis as global project leader for API/drug product, Global Quality by Design Network Leader, and led various global teams: QbD training, Specification Setting Strategy and Regulatory CMC team focused on streamlining CMC processes for small molecules/ biologics development projects. Also, he worked at Merck Research Laboratories API Division supporting the development of synthetic pathways and scale-up of chemical processes for early- to late-stage drug candidates. Recognized around the world for scientific innovation: 35 research publications, 100+ presentations, and many book contributions on formulation, analytical and physical chemistry, process analytical technology (PAT), Quality by Design (QbD), and other topics. Co-Editor (Book): HPLC for Pharmaceutical Scientists.

Presentation
Breakout Session: Procedure Qualification
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

Greg Martin, M.S.
USP Affiliation: Chair, Validation & Verification Expert Panel

President
Complectors Consulting LLC
Pottstown, PA

Greg Martin is President of Complectors Consulting (www.complectors.com) which provides consulting and training in the area of Pharmaceutical Analytical Chemistry. Mr. Martin has over 25 years experience in the pharmaceutical industry and was Director of Pharmaceutical Analytical Chemistry (R&D) for a major PhRMA company for a number of years. In addition, he has volunteered for the USP for over 10 years, and currently serves on the General Chapters – Chemical Analysis Expert Committee, and serves on Expert Panels on Validation and Verification, Residual Solvents and Use of Enzymes for Dissolution Testing of Gelatin Capsules.

He has particular interest in QbD/Lean approaches to dissolution testing, impurity methods, method lifecycle (development/validation/transfer) and instrument qualification, and is passionate about using good science and sound logic to achieve high quality results, consistent with cGMPs, while minimizing resources. Mr. Martin is author of several papers in the areas of dissolution and analytical method validation, and is past chair of the AAPS In Vitro Release and Dissolution Testing Focus Group. He can be contacted at greg.martin@complectors.com.

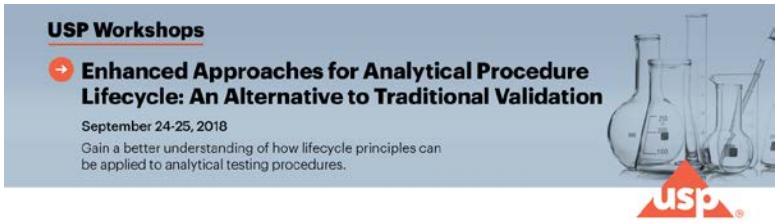
Presentation
Overview of the Analytical Procedure Lifecycle
Monday, September 24, 2018, 9:00 – 9:30 a.m.

This Workshop is the result of growing interest in the lifecycle approach to analytical procedures which integrates Quality by Design principles. The goals of this Workshop are to share some current thinking and to solicit input from the analytical community about opportunities and challenges for continued development and implementation. This talk will provide an overview of USP's progress in this area, which has been published in several stimuli articles in Pharmacopeial Forum. Other presentations in the Workshop will include case studies from industry and current thinking from several global organizations. A significant portion of the Workshop will be focused on gathering attendee input in breakout sessions. Ultimately, a compilation of the attendee input and summaries of the presentations will be published as a stimuli article in Pharmacopeial Forum.

Breakout Session: Procedure Understanding and Control Strategy
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

Workshop Summary
Tuesday, September 25, 2018, 4:15 – 5:00 p.m.



Pauline McGregor, Ph.D. CChem MRSC
USP Affiliation: Member, Validation & Verification Expert Panel

Consultant
PMcG Consulting
Toronto, Ontario, Canada

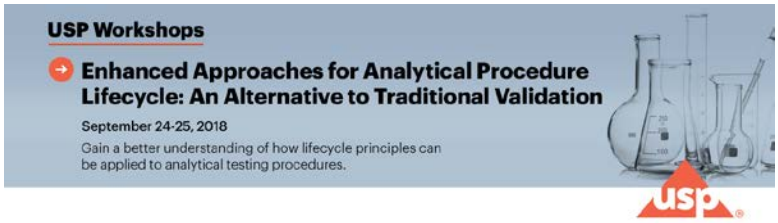
Pauline has fulfilled a variety of roles in her thirty years in the pharmaceutical industry. She is an expert in quality systems and procedures, GMP regulations and analytical chemistry. She brings the experience and ability to customize and install the quality systems required to allow new manufacturing and testing companies to operate to GMP regulations and review and improve on current quality systems to allow more efficient operations. She also brings a technical expertise to laboratories which enable her to assist them to develop analytical procedures, validate them and optimize efficiency with regards to laboratory operations and troubleshooting in an analytical development and QC environment.

She has experience in utilizing her skill set in the UK, Canada, US, Jordan, Brazil and China and has helped companies prepare for a GMP inspection to gain their European/Health Canada/FDA GMP licenses.

Pauline is a member of The Royal Society of Chemistry, UK, and is a proud member of the USP expert panel for Validation, Verification and Transfer of Analytical Procedures and a USP Chemical Medicines expert committee.

Presentation
Breakout Session: Development of an ATP
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.



Phil Nethercote, Ph.D.
USP Affiliation: Member, Validation & Verification Expert Panel

Independent consultant in Pharmaceutical Analysis
GlaxoSmithKline (Retired)
Troon, UK

Phil Nethercote has a degree in Chemistry from Herriot Watt University and a PhD in HPLC retention mechanisms from the University of Stirling. From 1987 to 2016, he worked for Glaxo, GlaxoWellcome and GlaxoSmithKline initially in an analytical development role supporting the introduction of new APIs to manufacturing sites in the UK and Singapore and laterally as Head of Analytical Technology and Standards for GSKs manufacturing division. Phil has been involved in applying QBD principles to analytical procedures since 2006 and has been a member of various pharmacopeia and industry groups looking to progress these concepts.

Presentation
Breakout Session: Procedure Understanding and Control Strategy
Monday, September 24, 2018, 1:15 – 4:45 p.m.

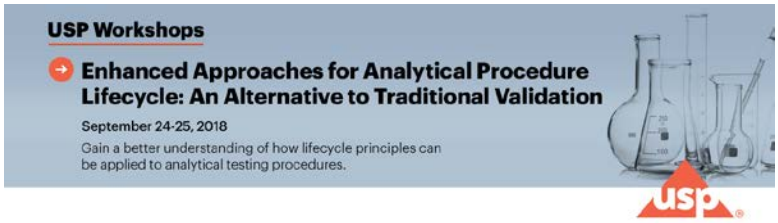
Please see breakout abstract at the bottom of this section.

Horacio Pappa, Ph.D.
Director, General Chapters
USP
Rockville, MD

Dr. Horacio Pappa has been with USP since 2003. He is currently the Director of the General Chapters Department, Global Science division of the USP. He provides scientific leadership to a team of scientific liaisons responsible for the activities of six different expert committees that cover the majority of the USP General Chapters. Horacio earned his Ph.D. in Pharmaceutical Chemistry from the University of Buenos Aires. He has authored many publications and peer-reviewed articles and is a frequent speaker and instructor on topics related to Chromatography and Validation. Prior to joining USP, he worked in the pharmaceutical industry in QA/QC. Horacio held the position of Assistant Professor of Quality Control in the Faculty of Pharmacy at Buenos Aires University, and Executive Secretary of the Argentine Pharmacopeia in the period 1997-2001. He is a Quality Engineer certified by the American Society for Quality.

Presentation
USP Vision for <1220> The Analytical Procedure Lifecycle
Tuesday, September 25, 2018, 2:45 – 3:30 p.m.

An analytical procedure must be demonstrated to be fit for its intended purpose. It is useful to consider the entire lifecycle of an analytical procedure, i.e., its design and development, qualification, and continued verification. The current concepts of validation, verification, and transfer of procedures address portions of the lifecycle but do not consider it holistically. USP is proposing the adoption of an alternative approach that fully address the entire procedure lifecycle. This approach is consistent with the concept of quality by design (QbD) as described in International Council for Harmonisation (ICH) Q8-R2, Q9, Q10, and Q11. The lifecycle approach can potentially be applied to all procedures, although the level of effort should be consistent with the complexity and criticality of the procedure.



António Ramos
Group Leader, Analytical Methodologies and Method Development
Hovione
Lisbon, Portugal

António Ramos has a degree in Chemistry by the Faculdade de Ciências of Lisbon University, and a Master degree from the Universidade Aberta, Lisbon in the field of Quality Management.

From 1998 to 2000 he worked in the Environmental area, first in the Laboratório de Análises of Instituto Superior Técnico in Lisbon and as a Technical Analytical Chemist in the Portuguese Environmental Agency in Lisbon.

From 2000 onwards António Ramos has developed his career at Hovione, first in R&D to introduce and develop Mass Spectrometry techniques (GC/MS and LC/MS/MS), and then in diverse Quality Control functions. He has been responsible for method development and validation for several projects at Hovione and also managing analytical chemistry requirements for ongoing company projects.

António Ramos is currently the Group Leader for Analytical Methodologies and Method Development in R&D area with the scope of development and evaluation of all analytical procedures that are applied at Hovione Exclusives Projects.

Presentation
Method Lifecycle: From Development to Qualification
Monday, September 24, 2018, 9:30 – 10:15 a.m.

It is currently recognized the importance of applying a lifecycle management concept to pharmaceutical analysis, that includes the application of Quality by Design (QbD) concepts on analytical development.

Known as Analytical Quality by Design (AQbD), this structured and scientific based approach for procedure development is able to increase method understanding and to identify, reduce, and control sources of variability, where Quality Risk Management (QRM) and Knowledge Management (KM) are the key enablers.

The Life Cycle Management (LCM) goes beyond AQbD and should be a continuum process. The following stage of LCM is Method Qualification. This stage should incorporate a true evaluation of Analytical Target Profile (ATP), Method Specific performance attributes and acceptance criteria as well as the established Analytical Control Strategy (ACS).

LCM is the key for a successful Pharmaceutical frame work since it can be the driver for improving partnership between Industry and Regulators and increase Patient trust and confidence in Pharma organizations.

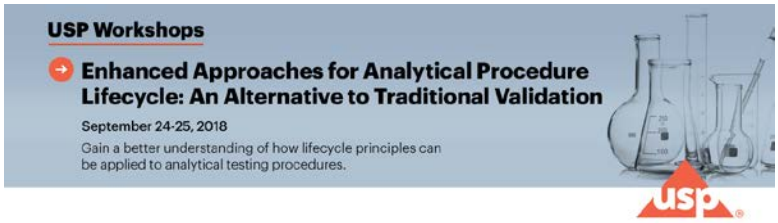
David Thomas, Ph.D.
USP Affiliation: Member, Validation & Verification Expert Panel

Scientific Director, Small Molecule Method Development
Janssen Pharmaceutical Company (Johnson & Johnson)
Titusville, NJ

David Thomas is currently Scientific Director of Small Molecule Analytical Development at Janssen R&D Pharmaceutical Companies of Johnson and Johnson. David received a B.S. in Chemistry from Loyola University of Maryland and a PhD in analytical chemistry from Drexel University in Philadelphia, PA. David joined Johnson and Johnson in 1999 and has held various analytical positions throughout his career, ranging from management of stability and quality laboratories to his current role as Scientific Director. In his current role, David and his team are primarily focused on method development, validation and transfer of new product development and life cycle management in various analytical techniques including chromatography, dissolution, moisture and spectroscopy. David has previously served on a PQRI working group for stability shelf life, the IQ Analytical Leadership Group, and currently is a member of the USP <1224> <1225> <1226>, Validation and Verification Expert Panel.

Presentation
Breakout Session: Procedure Qualification
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

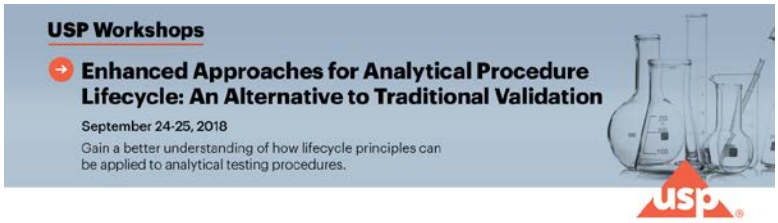


Ramakrishna Velicheti, Ph.D.
Validation Manager, Division of Biological Standards & Quality Control
Office of Compliance & Biologics Quality, Center for Biologics Evaluation & Review
U.S. Food and Drug Administration
Silver Spring, MD

Dr. Velicheti is the Validation Manager in the Division of Biological Standards and Quality Control. He received a B.Sc. and M.Sc. in Biological Sciences, and Ph.D. in Botany from Osmania University, India, specializing in microbial ecology and related chemistry. Dr. Velicheti worked as a Research Associate at the University of Illinois at Urbana-Champaign, IL, University of Minnesota at Saint Paul, MN, and Oregon State University, OR. Dr. Velicheti joined pharmaceutical industry and worked both in manufacturing and testing of generics, biotech and biologics for about 10 years. He worked at BioReliance Corporation for 6 years as Director of Validation where he supervised method validations prior to joining the FDA in 2006. Dr. Velicheti contributed as a co-author of the FDA Bioanalytical Method Validation Guidance for Industry. His current responsibilities include methods and equipment validation, process improvement, and he also serves as a Contracting Officer Representative.

Presentation
Performance Monitoring of Test Methods in Quality Control with Reference to AQbD
Tuesday, September 25, 2018, 3:30 – 4:15 p.m.

This presentation highlights development and maintenance of an analytical procedure throughout its lifecycle following the Analytical Quality by Design process, with special reference to factors that impact an analytical procedure and their mitigation strategies.



Steven Walfish, M.S., MBA
Principal Science & Standards Liaison
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Rockville, MD

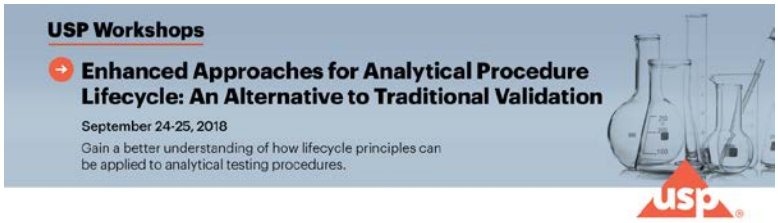
Mr. Walfish is Principal Science & Standards Liaison at United States Pharmacopeia (USP) responsible for the Statistics Expert Committee. Prior to this role Mr. Walfish was Principal Statistician at BD in Franklin Lakes, NJ responsible for supporting continuous improvement efforts and process development for worldwide operations. Mr. Walfish has held roles at GE Healthcare, Human Genome Sciences and Chiron. Steven was President of Statistical Outsourcing Services, a consulting company that provides statistical analysis and training to the FDA regulated industries.

Mr. Walfish brings over 30 years of industrial expertise in the development and application of statistical methods for solving complex business issues. Steven has experience applying statistical methods to analytical method verification and validation and stability analysis.

Mr. Walfish is a senior member of ASQ, a certified quality engineer and past chair of the Biomedical Division (2006-07). Mr. Walfish holds a Bachelors of Arts in Statistics from the University of Buffalo, Masters of Science in Statistics from Rutgers University and an Executive MBA from Boston University.

Presentation
Breakout Session: Development of an ATP
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.



Jane Weitzel
USP Affiliation: Member, Validation & Verification Expert Panel

Independent Consultant
Winnepeg, Manitoba, Canada

Jane Weitzel has been working in analytical chemistry for over 40 years for pharmaceutical and mining companies. She is currently a consultant specialising in laboratory management systems and ISO/IEC 17025, an auditor, and an educator. Jane has applied Quality Systems and statistical techniques, including the evaluation and use of measurement uncertainty, in a wide variety of technical and scientific businesses. She has obtained the American Society for Quality Certification for both Quality Engineer and Quality Manager.

For the 2015 - 2010 cycle, Jane was a member of the USP Expert Committee on Statistics and the Expert Panel on Method Validation and Verification. In 2014 she was pointed to the Chinese National Drug Reference Standards Committee and attended their inaugural meeting in Beijing. Jane is co-author for the paper on Measurement Uncertainty for the Pharmaceutical Industry USP PF 44(1).

Presentation
Procedure Understanding and Control Strategy
Monday, September 24, 2018, 1:15 – 4:45 p.m.

Please see breakout abstract at the bottom of this section.

Breakout Session Abstracts
Monday, September 24, 2018
1:15 – 4:45 p.m.

Development of an ATP

Kimber Barnett, Ph.D., Pauline McGregor, Ph.D., Steven Walfish, M.S., MBA

This session is intended to solicit feedback from audience members about the Analytical Target Profile (ATP). It will start with a brief review of the ATP concept and follow with an interactive session that includes the following:

- Discussion: What should be captured in an ATP statement?
- Exercise: Develop ATP statements for different scenarios
- Discussion: Is it clear how to translate ATP criteria into method/technique specific requirements?
- Discussion: What are the advantages and challenges related to ATPs?

Procedure Understanding and Control Strategy

Elisabeth Kovacs, Greg Martin, M.S., Phil Nethercote, Ph.D., Jane Weitzel

During this breakout session, we will discuss the analytical control strategy. Please read the following and consider your discussion points for this topic.

A robust Analytical Control Strategy (ACS) is essential in ensuring that the Critical Quality Attributes (CQAs) of the reportable result are met.

The ACS is developed during stage 1 of the Analytical Lifecycle using a systematic approach based on Quality Risk Management (QRM) principles.

The ACS reflects an understanding of the linkages between the Parameters and Material Attributes of the analytical procedure and the CQAs of the reportable result.

An effective system for Knowledge Management is a key enabler in the development and maintenance of an ACS throughout the analytical procedure lifecycle

- The goal is to develop a 'planned set of controls', which might include:
  - Laboratory controls (Instrument qualification, SOPs, analyst training, etc.)
  - Instructions in the procedure (proactive controls)
  - A system suitability test (reactive controls or 'in-process check)
  - A replication strategy (if appropriate to address variability)

During the Breakout session we will discuss the following:

- Where do you think taking a systematic risk based approach to developing and an Analytical Control Strategy will add value?
- How would you introduce Analytical Control Strategy elements to address risks which are determined to be significant and in need of control?
    - How would you identify risks (variables) in your analytical procedure, and decide which are critical or non-critical?
    - How would you evaluate the potential risks (e.g. DoE, one factor at a time, other)?
- What steps would need to be taken to fully imbed this structured risk based approach in our industry?
    - What issues do you think require further clarification?
    - What do you see as the role of the USP in facilitating this approach? What additional guidance, training or education be valuable?

Procedure Qualification

Joachim Ermer, Ph.D., Rosario LoBrutto, Ph.D., David Thomas, Ph.D.

In order to implement Analytal Lifecycle Management in practice, there are questions and details that need to be clarified. In the following workshop some topics related to Stage 2 Procedure Performance Qualification will be proposed and the audience will discuss 3 of 8 topics that are of most interest (see list below). During the workshop we will develop, discuss and share pragmatic approaches. Moreover, we will align our understanding with respect to pre-requisites and cllarify issues to be solved.

1. What are pre-requisites to use data from Stage 1 for Stage 2?
    - e.g. GMP-level, data integrity,
    - method completeness/documentation, etc.
2. How to justify and reference acceptance criteria in the Stage 2 protocol?
    - e.g. method-specific performance requirements,
    - Traceability to ATP, etc.
3. What should be performed in which Stage (1 or 2)?
    - Specificity/selectivity, linearity (calibration model), accuracy, precision levels, detection/quantitation limit)
4. Precision of the reportable value: Point estimate (calculated precision value) or statistical approach?
5. How to establish a replication strategy for the reportable value?
    - Number of repeated injections, sample preps, runs
6. Should precision for assay be determined over the range of the analyte in the respective matrix?
7. How should accuracy for assay be addressed,
    - Combined with precision or separately?
    - What sequence, accuracy first?
8. How to investigate the stability of test solutions, standard preparations, stock solutions etc. for quantitation?

Stimuli Articles
Please Read Prior to Workshop

Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification [PF 39(5)]

Fitness for Use: Decision Rules and Target Measurement Uncertainty [PF 42(2)]

Analytical target profile (ATP): Structure and application throughout the analytical lifecycle [PF 42(5)]

Analytical control strategy [PF 42(5)]

Proposed New USP General Chapter: The Analytical Procedure Lifecycle ⟨1220⟩ [PF 43(1)]

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification[a]

USP Validation and Verification Expert Panel: Gregory P Martin, MS (Chair); Kimber L Barnett, PhD; Christopher Burgess, PhD; Paul D Curry, PhD; Joachim Ermer, PhD; Gyongyi S Gratzl, PhD; John P Hammond; Joerg Herrmann, PhD; Elisabeth Kovacs; David J LeBlond, PhD; Rosario LoBrutto, PhD; Anne K McCasland-Keller, PhD; Pauline L McGregor, PhD; Phil Nethercote, PhD; Allen C Templeton, PhD; David P Thomas, PhD; ML Jane Weitzel

ABSTRACT In this *Stimuli* article, the USP Validation and Verification Expert Panel discusses how the modern concept of a lifecycle model, which is based on process validation and described in ICH guidelines Q8, Q9, and Q10, can be applied to analytical procedures. The Expert Panel proposes that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities. As a starting point or "predefined objective" according to ICH Q8, the requirements for a measurement of a critical quality attribute are established in the Analytical Target Profile. In alignment with process validation, three stages are proposed: Procedure Design (development and understanding), Procedure Performance Qualification, and Continued Procedure Performance Verification.

INTRODUCTION

Any analytical procedure must be shown to be fit for its intended purpose before use. [NOTE—The term *analytical procedure* used in this *Stimuli* article is interchangeable with the term *method* commonly used in industry and includes steps such as sample preparation, analytical technique, calibration, and definition of the reportable result.]The usual process of demonstrating this suitability in food and drug analytical laboratories takes place by way of a documented validation study and, if required, a verification or transfer process to demonstrate the procedure performs appropriately in the laboratory in which it will be used. The United States Pharmacopeial Convention (USP) has been a strong advocate of this process. General chapter *Validation of Compendial Procedures* ⟨ 1225 ⟩, which was first published in *USP XXI* (1989), served as the foundation for the development of the ICH Q2 Guidance on Validation of Analytical Procedures (*1*). More recently, USP has further led on this topic with the publication of general chapters *Verification of Compendial Procedures* ⟨ 1226 ⟩ and *Transfer of Analytical Procedures* ⟨ 1224 ⟩ (*Figure 1*).

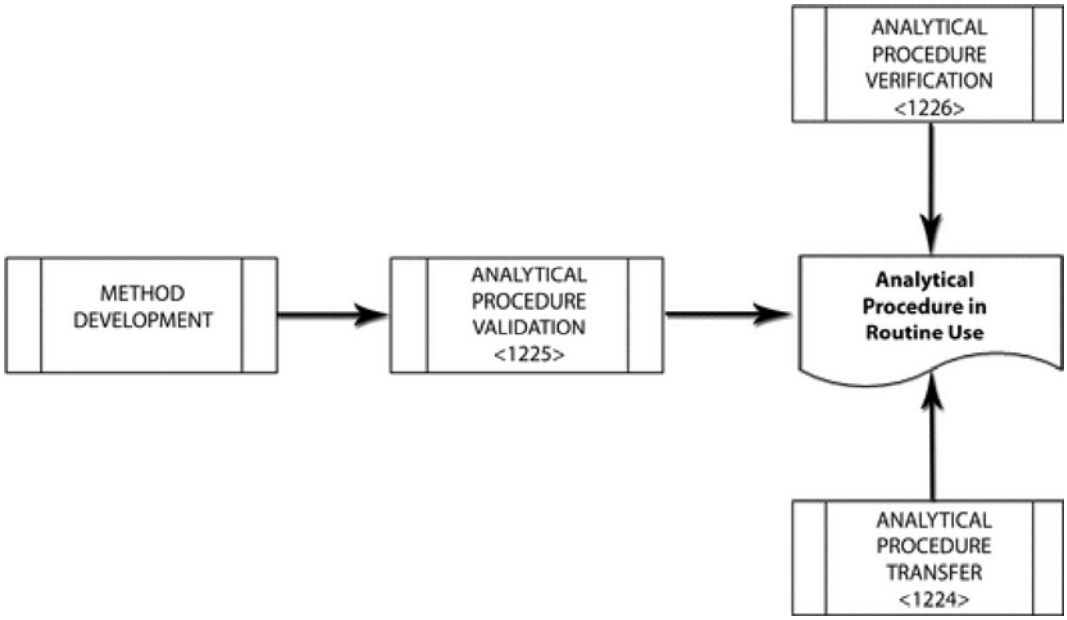


Figure 1. Current typical process for analytical procedures.

The intent of ICH Q2 and ⟨ 1225 ⟩ was to provide *guidance* to the industry about how to validate different types of analytical procedures. This guidance was intended to be used in combination with sound scientific judgment to ensure that appropriate experiments applicable to different analytical procedures and situations would be performed on a case-by-case basis. Over time, however, these documents have come to be interpreted as mandatory expectations rather than scientific guidance. Although these practices are successful in many cases, there are opportunities to further refine and improve them. The ICH and USP documents provide guidance pertaining to procedure suitability as part of the procedure validation exercise (e.g., accuracy, precision, linearity, specificity, etc.), but they do not provide a framework that allows users to reliably understand and control sources of variability. Similar observations were made in the manufacturing process development area, leading to development of the lifecycle management process described in ICH Q8, Q9, and Q10 (and more recently Q11) (*2–5*). Taking these ICH documents into consideration, the USP Validation and Verification Expert Panel has reevaluated the current validation, verification, and transfer guidelines for analytical procedures.

The lifecycle concept described in ICH Q8 is adaptable to analytical procedures if we consider an analytical procedure as a process and the output of this process as the reportable result, that is, the value that will be compared to the acceptance criterion. The purpose of applying lifecycle principles to analytical procedures is to holistically align analytical procedure variability with the requirements of the product to be tested and to improve the reliability of the procedure by understanding, reducing, and controlling sources of variability. Enhanced understanding of variables that affect the performance of an analytical procedure provides greater assurance that the quality attributes of the tested product can be reliably assessed. The lifecycle management process provides a framework for defining the criteria for and development of an analytical procedure that meets the acceptance criteria. The procedure then becomes part of a continuous verification cycle to demonstrate that it meets the predefined criteria over the life of the procedure. Implementation throughout the procedure's lifecycle of a change management process that is based on knowledge gained during the procedure's lifetime ensures that the procedure remains fit for its intended use. Key to the general approach is an understanding of overall variability, including variability arising from the manufacturing process as well as the analytical procedure. A focus of USP has been understanding the variability of its reference materials, which are part of the total variability that should be understood, controlled and, where possible, reduced.

In this *Stimuli* article, the USP Validation and Verification Expert Panel discusses how the modern concept for process validation (*6,7*), which is based on a lifecycle model, can be applied to analytical procedures (*8–11*). We propose that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities.

The Validation and Verification Expert Panel proposes that the concepts addressed in 〈 1225 〉, 〈 1226 〉, and 〈 1224 〉 should be revised and compiled into a single new general information chapter, *Lifecycle Management of Analytical Procedures* 〈 1220 〉 and a new general chapter 〈 220 〉 specifying the basic requirements.

The Validation and Verification Expert Panel seeks reader comments on the contents of this *Stimuli* article.

THE LIFECYCLE APPROACH

Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. The results are applied against Decision Rules that give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and acceptance criteria, taking into account the acceptable level of the probability of making a wrong decision (*12,13*).

The adoption of a lifecycle approach to ensure the quality of pharmaceutical products has been extensively discussed during the past several years (*2–7*). The concept of Quality by Design (QbD) is understood as a "systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (ICH Q8). Application of lifecycle management concepts to analytical procedures provides an opportunity to use the knowledge gained from the application of scientific approaches and quality risk management to continual improvement and assurance of data quality.

There should be an effective Quality Management System in place consistent with ICH Q10. The concepts described in ICH Q10 complement current GMPs, thus providing an integrated model for a pharmaceutical or similar quality system. This supports continual improvement across the entire lifecycle of the analytical procedure.

The Analytical Target Profile (ATP), risk management, control strategy, and knowledge management are cornerstone concepts in lifecycle management, which will be discussed in the following sections.

Analytical Target Profile

A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective that stipulates the performance requirements for the analytical procedure. These requirements are derived from the Analytical Target Profile (ATP). See *Figure 2* for some examples.

1. Assay: 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.

2. Impurity: The procedure must be able to quantify [impurity] relative to [drug] in the presence of components that are likely to be present in the sample within the range from the reporting threshold to the specification limit. The accuracy and precision of the procedure must be such that the reportable result falls within ± *D*% of the true value for impurity levels from 0.05% to *0.15*% with *80*% probability with *95*% confidence, and within ± *E*% of the true value for impurity levels > *0.15*% with *90*% probability determined with *95*% confidence.

Figure 2. Examples of Potential Analytical Target Profiles. [NOTE—Items in brackets and italics (variables listed as capital letters and numerical values) are placeholders to be replaced by specific items for an ATP.]

The concept of an ATP parallels the concept of a Quality Target Product Profile described and defined in ICH Q8. The ATP defines the requirements for the "product" of the test procedure, which in this case is the reportable result. Criteria defined in the ATP refer to the quality data attributes of the reportable result, i.e., accuracy and measurement uncertainty, which include all sources of variability, including precision. Identifying the output of the analytical procedure as the reportable result provides a target for development and helps to ensure the procedure is developed toward predetermined performance requirements that are directly linked to the quality of the data. In other words, the ATP defines the objective of the test and quality requirements, including the expected level of confidence, for the reportable result that allows the correct conclusion to be drawn regarding the attributes of the material that is being measured. It is essential to reach a high degree of confidence that an analytical procedure will consistently generate reportable results that meet the ATP requirements under all conditions of use and as the material progresses through the lifecycle.

The ATP is based on the understanding of the target measurement uncertainty, which is the maximum uncertainty that the data should have in order to maintain acceptable levels of confidence in data quality. This introduces key performance attributes and changes the way we currently define and evaluate analytical performance characteristics. The ATP serves as a reference point for assessing the fitness of an analytical procedure not only in the development phase but also during all changes within the analytical lifecycle and is not linked to a specific analytical method. It is conceivable that more than one analytical procedure can meet the requirement of an ATP. Any analytical procedure that has been demonstrated to be capable to generate data that conform to the performance requirements established in the ATP would be regarded as acceptable (*USP* general chapter *Elemental Impurities—Procedures* ⟨ 233 ⟩ and *USP Medicines Compendium* general chapter Assessing Validation Parameters for Acceptable Procedures ⟨ 10 ⟩).

Existing procedures also can be evaluated in terms of their ability to meet an ATP. When using a compendial procedure for the first time, an ATP can be derived from monograph specifications, a performance-based monograph, and any existing knowledge of the product.

In assessing new or existing procedures for their capability to meet an ATP, analysts can use statistical methods for analyzing prospectively designed studies (*14*). In the case of existing procedures for which significant historical data are available, statistical procedures for retrospective evaluation of historical data such as stability data, laboratory investigations, check samples/controls, release data, and others are available (*15,16*). The level of variability present in the historical data may trigger additional studies that aim to understand and reduce or eliminate sources of variability and improve the data quality to meet ATP.

Risk Management

A high degree of confidence is needed that the analytical method will generate reportable results that meet the ATP requirements under all conditions of use as the method progresses through the lifecycle. Application of Quality Risk Management (QRM) concepts and tools (ICH Q9) can be valuable in providing a mechanism of achieving this. QRM for analytical procedures can be defined as a systematic process for the assessment, control, communication, and review of risks to the quality of data across the product lifecycle. Process mapping tools and Ishakawa diagrams can be employed to ensure a rigorous approach is used in identifying all potential variables that may affect data quality. The variables should include all aspects of the full analytical procedure (*Figure 3*), i.e., sampling, sample preparation, standards, reagents, facility, and equipment operating conditions. The identified variables then should be evaluated using appropriate risk-assessment tools and prioritized experimentation to understand, eliminate, or mitigate areas of risk. An approach known as

CNX (Control, Noise, Experimental) can help classify all identified variables. A decision can be made concerning which variables should be controlled (C), which are potential noise factors (N), and which should be examined experimentally (X) to determine acceptable ranges. As part of this exercise analysts should provide and document justifications (prior knowledge, scientific rationale, or others) for the assignments made. Risk-analysis tools can then be used to screen experimental (X) variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies then provide justification of the critical variables and their acceptable ranges (from the risk assessment and experimental work), are inputs in the Analytical Control Strategy, and are explicitly specified in the analytical procedure (*Figure 4*).

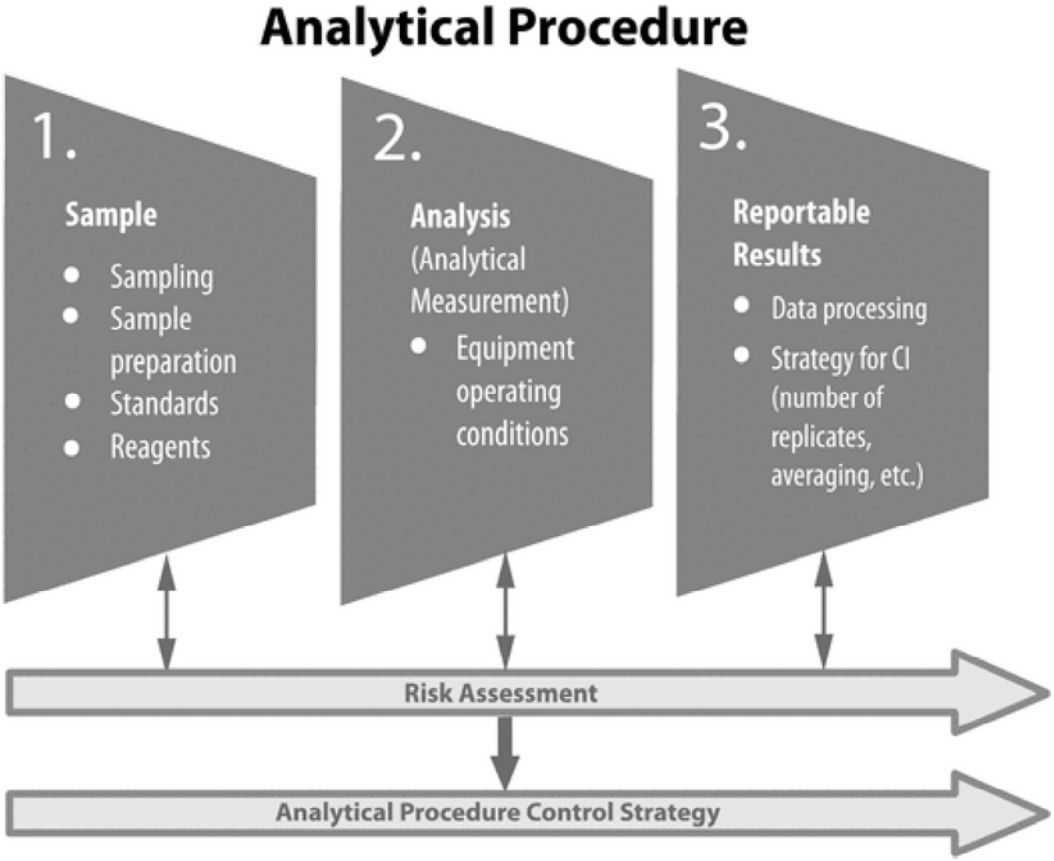


Figure 3. Analytical procedural variables to consider for risk assessment and control strategy.

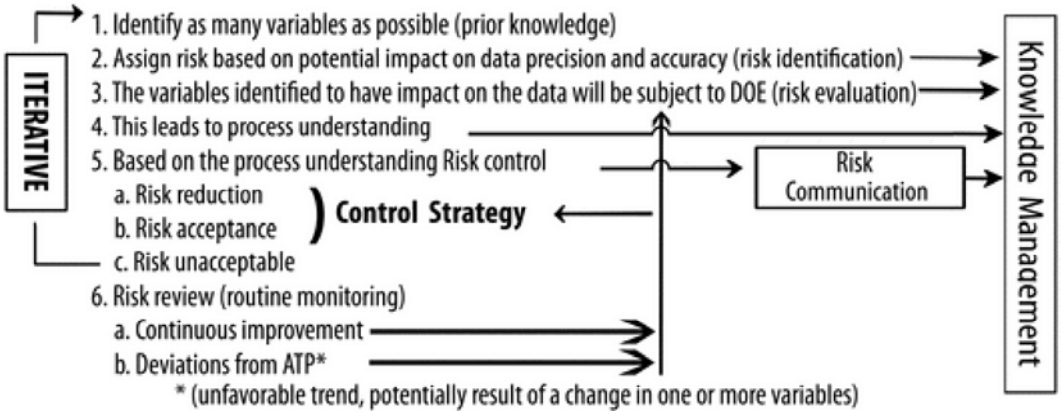


Figure 4. Quality risk management, control strategy, and knowledge management: how they work together.

Analytical Control Strategy

A well-developed control strategy, i.e., a planned set of controls, is derived from current product and process

understanding. The variables and their acceptable ranges (from the risk assessment or experimental work) should be explicitly specified in the procedure. The controls can include variables and aspects related to the sample, sample preparation, standards, reagents, facility, equipment operating conditions, historical experience (prior knowledge), the format of the reportable value (e.g., number of replicates), and frequency of monitoring and control. The Analytical Control Strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle and also should be considered throughout the lifecycle as part of development, continual improvement, and change management. Different control strategies may be required at different sites. A scientific risk-based approach can be applied to the assessment of a control strategy's suitability across different sites, and quality risk management tools should be used to guide these activities. As an integral part of the laboratory qualification to execute a compendia procedure, the process of quality risk management should be carried out, and the control strategy of the compendia procedure should be verified or expanded in order to ensure that the requirements of the ATP are met.

Knowledge Management

Knowledge management can be defined as a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Knowledge management is an important factor in ensuring the ongoing effectiveness of the control strategy. Knowledge management should include but is not limited to development activities, technology transfer activities to internal sites and contract laboratories, validation studies over the lifecycle of the analytical procedure, and change management activities. The knowledge gathered to develop the method understanding should be collected in a repository and shared as needed to support implementation of the control strategy across sites that use the analytical procedure. Changes and improvements to an analytical procedure should be made with reference to the method knowledge repository, which contains the information from the various stages of the method lifecycle.

We believe that applying a lifecycle approach (*Figure 5*) to analytical procedures will better ensure that quality objectives are met on a consistent basis.

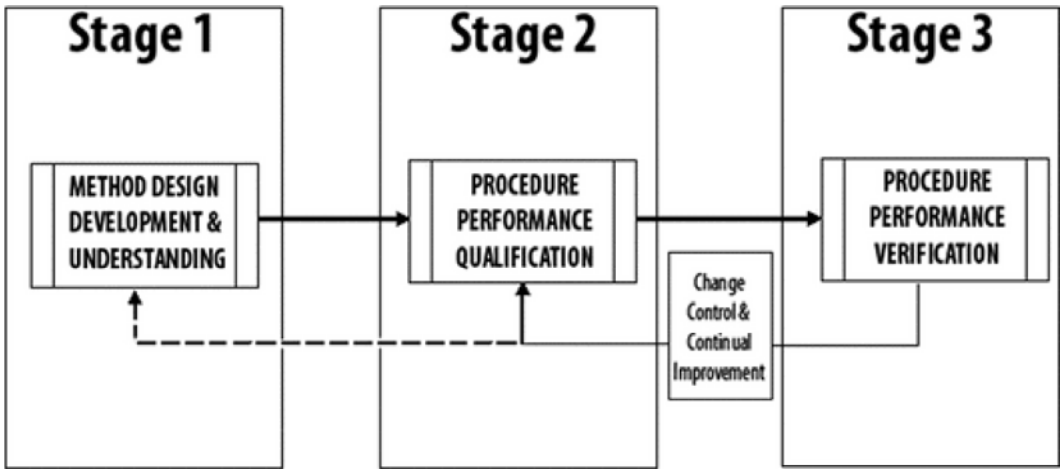


Figure 5. Summary of proposed analytical procedure lifecycle approach.

Lifecycle Stages

In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, we propose a three-stage concept that is aligned with current process validation terminology:

- Stage 1—Procedure Design (development and understanding)
- Stage 2—Procedure Performance Qualification
- Stage 3—Continued Procedure Performance Verification.

These steps are illustrated in *Figure 6* and are discussed in the following text.

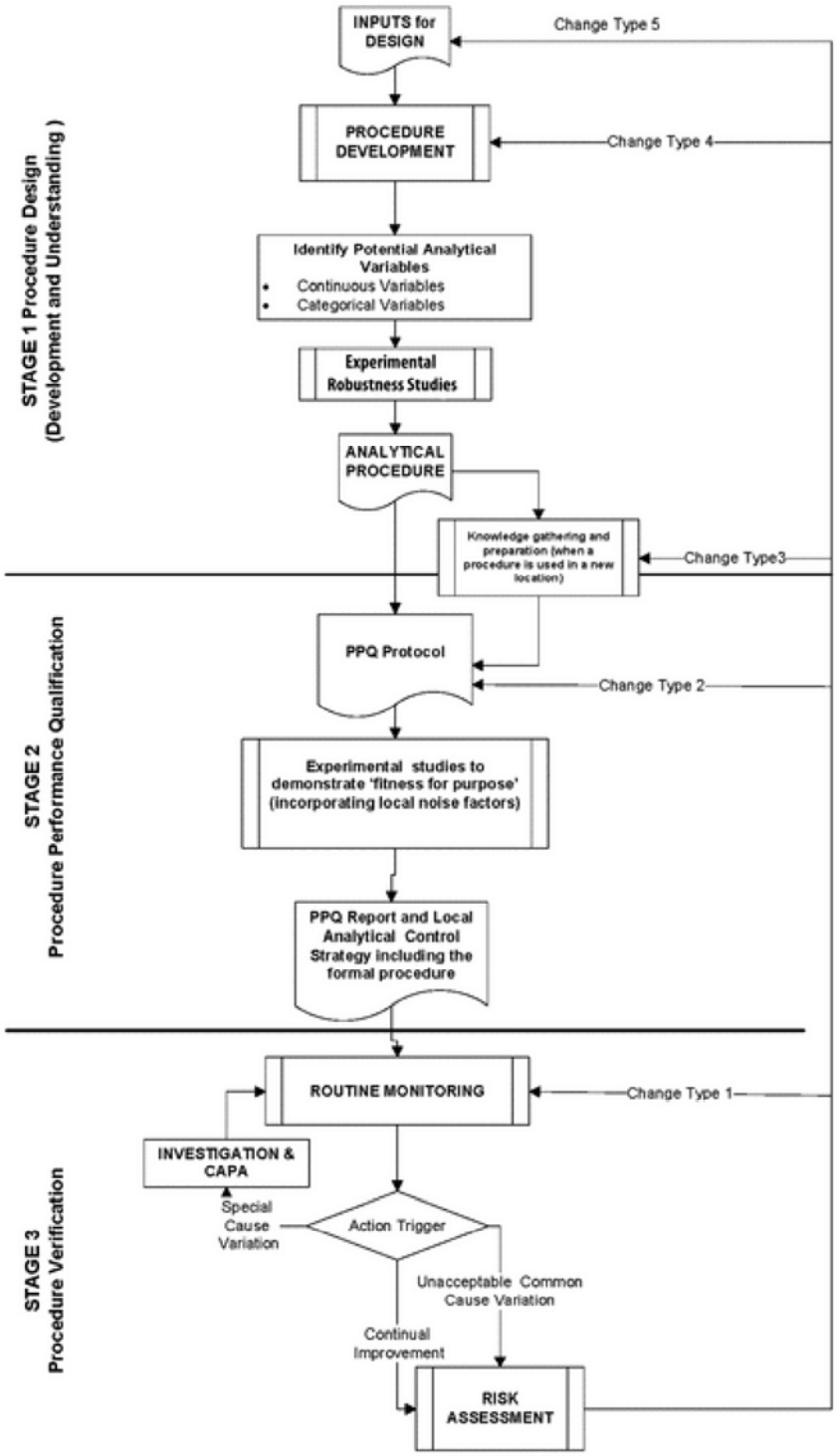


Figure 6. Three stages in the proposed lifecycle approach.

[NOTE—Refer to *Continual Improvement* (below) for a description of the different types of change.]

STAGE 1—PROCEDURE DESIGN

Procedure Development and Understanding (Identify and Study Potential Analytical Variables)

Once the ATP is established and the requirements for data quality (accuracy and uncertainty) of the reportable

result are defined, it is the responsibility of the analyst to select an appropriate technology and analytical procedure likely to meet the requirements of the ATP. Consequently, the ATP will be translated into the key performance characteristics of the intended analytical procedure.

The next step is to gain an understanding of how potential sources of variability in the proposed analytical procedure affect the performance characteristics of the procedure. Tools such as process maps and Ishikawa diagrams (fishbones) can be used to provide structure to a brainstorming and information-gathering exercise. Risk-assessment tools (see ICH Q9 for examples) then can be used to identify potential procedural variables that may need to be controlled to ensure procedure performance and to prioritize experimentation to eliminate or mitigate areas of risk. CNX can help classify all the variables. As part of this exercise it is important to provide justifications (for example, prior knowledge or scientific rationale) for the assignments made.

Based on historical knowledge and an assessment of risk, analysts can make and document decisions about which variables will be classified as C and fixed and which variables will be classified as X and investigated experimentally. During the procedure-development phase, analysts identify certain variables that are fundamental to the procedure design, e.g., detector or column type. These are classed as control variables and are not further explored during the procedure-understanding phase of Stage 1.

Experimental Robustness Studies

Experimental robustness studies address the variations that may occur as the procedure is performed on different occasions. These studies consider both continuous and categorical X (eXperimental) variables. Continuous variables (e.g., temperature, pH, or flow rate) typically are studied via design of experiments (DoE). For these continuous variables, the output of the DoE study could be a procedure design space within which the procedure performance is ensured. For categorical variables (like column packing batch, type of instrument, etc.) the DoE study attempts to highlight variables that could have a significant effect on procedure performance regarding accuracy and precision, although these variables may have an even greater effect later in the life cycle. During this study, variables may be identified and may be considered too difficult or expensive to control. These are defined as Noise (N) variables in the CNX scheme. Although N variables are not directly studied at this stage, they are assessed indirectly as part of the Stage 2 activities when a laboratory has to confirm that the analytical control strategy is adequate to allow the procedure to produce reportable results that meet the requirements of the ATP in a particular environment. Example N variables include environmental and routine operating conditions.

As a result of the robustness study, a set of operational procedure controls with respect to the C and X variables are defined as part of the Analytical Control Strategy.

When uncontrolled categorical variables may result in unacceptable procedure performance, analysts should consider including a check or system suitability test (e.g., chromatographic resolution, symmetry factors, etc.). When such a check is included, it is good practice in the analytical procedure to explain the purpose of the check and the specific categorical variables it is designed to monitor.

Knowledge Gathering and Preparation

This step focuses on ensuring that any location where the procedure is intended to be operated is adequately prepared to use the procedure. It is the transition step between Stage 1 and Stage 2 where effective communication channels need to exist between the laboratories. The knowledge gathered to develop the procedural understanding should be shared as needed in support of the implementation of the control strategy across sites that intend to use the analytical procedure.

The extent of the knowledge required should take into account the level of preexisting knowledge of the analysts at the new location with respect to the product, analytical method, or procedure. The analytical procedure conditions and detailed operating controls, along with all of the knowledge and understanding

generated during the design phase and any performance history should be conveyed to or summarized for staff at the location where the analytical procedure will be used.

STAGE 2—PROCEDURE PERFORMANCE QUALIFICATION

The objective of this stage is to demonstrate that the procedure is fit for purpose. This stage confirms the analytical procedure is capable of delivering reproducible data that consistently meet the performance criteria defined in the ATP while operated subject to the noise variables that may be experienced. Therefore, procedure performance qualification must be performed before routine application of the analytical procedure by the user laboratory.

Procedure performance qualification is carried out either to qualify a new procedure or to revise the conditions or operating environment of an established procedure.

Showing an analytical procedure is fit for purpose involves demonstrating that the defined analytical procedure will, under routine operating conditions, produce data that meet the target measurement uncertainty defined in the ATP. The procedure performance qualification experiments, e.g., precision studies, should be designed to challenge analytical performance characteristics that relate to the ATP requirements and should be based on sound science and risk as well as prior knowledge and understanding.

The analytical procedure used in the procedure performance qualification study should be based on available knowledge and understanding. The analytical control strategy will be refined and updated as a consequence of any learning from the study. For example, further controls may be added to eliminate sources of variability that are identified in the routine operating environment in an analytical laboratory, or replication levels (multiple preparations, multiple injections, etc.) may be increased to reduce the overall uncertainty in the reportable result (format of the reportable result).

When analysts believe there may be a residual risk of variation in the performance of the procedure, they may add appropriate checks to detect any unacceptable levels of variation in the performance of the procedure. These system suitability checks should focus on analytical performance characteristics that may be affected by noise and should be controlled to ensure the requirements of the ATP are consistently met. For example, if there is a residual risk of variation in separation performance due to the risk of batch-to-batch variation in column packing material and the degree of separation is known to have an effect on the uncertainty of the data, a check may be included to ensure that peak resolution is sufficient to meet the ATP requirements. Examples of system suitability tests for chromatographic systems are described in general chapter *Chromatography* ⟨ 621 ⟩.

When end users do not have access to knowledge and understanding acquired during procedure development, e.g., for compendial procedures, users should recognize this additional risk and ensure the procedure performance qualification study and local or compendial analytical control strategy adequately mitigate associated risks. End users also must ensure that an appropriate control strategy for the procedure is applied.

STAGE 3—CONTINUED PROCEDURE PERFORMANCE VERIFICATION

The purpose of this stage is to provide ongoing assurance that the analytical procedure remains in a state of control throughout its lifecycle.

This stage includes both routine monitoring of the analytical procedure's performance and evaluation to determine if the analytical procedure, as a result of any change, is still fit for purpose.

A system or systems for detecting unplanned departures from the analytical control strategy is essential to accomplish this goal. Adherence to cGMP requirements, specifically, the collection and evaluation of information and data about the performance of the procedure, allows detection of undesired variability.

Evaluating the performance of the procedure identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the procedure remains in a state of control.

Routine Monitoring

Trend analysis using methodologies such as control charting can be conducted on the main performance indicators to confirm that the analytical procedure remains in a state of control.

This stage should include an ongoing program to collect and analyze data that relate to analytical procedure performance, for example, from replication of samples or standards during the analysis or by trending system suitability data. This activity aligns with the guidance in *Analytical Data—Interpretation and Treatment* ⟨1010⟩ on system performance verification. Close attention should also be given to any out of specification or out of trend results generated by the analytical procedure once it is being operated in its routine environment.

If, during routine monitoring of the procedure, data indicate the procedure is out of control or there is an opportunity or need for improvement, then further action is taken. There are three action triggers (see *Figure 6* for examples):

- special-cause variation (e.g., new, unexpected phenomenom)
- unacceptable common cause variation (e.g., expected variability inherent in the procedure)
- continual improvement.

Observed Variations

During the investigation, particular attention should be given to special cause variation (shifts, drift, and deviation) and common cause variation (unacceptable noise) (*Figure 7*). Variation may result when a particular procedure variable is not adequately controlled. This variation may arise for a number of reasons:

- A variable was not identified or adequately studied during the procedure understanding study (Stage 1), and therefore no proper control was defined.
- A variable was not identified or adequately studied during Stage 2 (precision study), and therefore no proper control was defined.
- Series member of a set of categorical variables (not included in the DoE, Stage 1) has been found to have an effect on performance (e.g., a new batch of column packing results in unacceptable performance).
- A control strategy was defined but not followed.
- A noise variable has been found to have an impact on routine performance.

Investigations into inadequate performance should be thorough and well documented and should aim to reach a conclusion about the variable that is truly the root cause. Corrective and preventive action should be taken to ensure the analytical control strategy is updated in the analytical procedure.

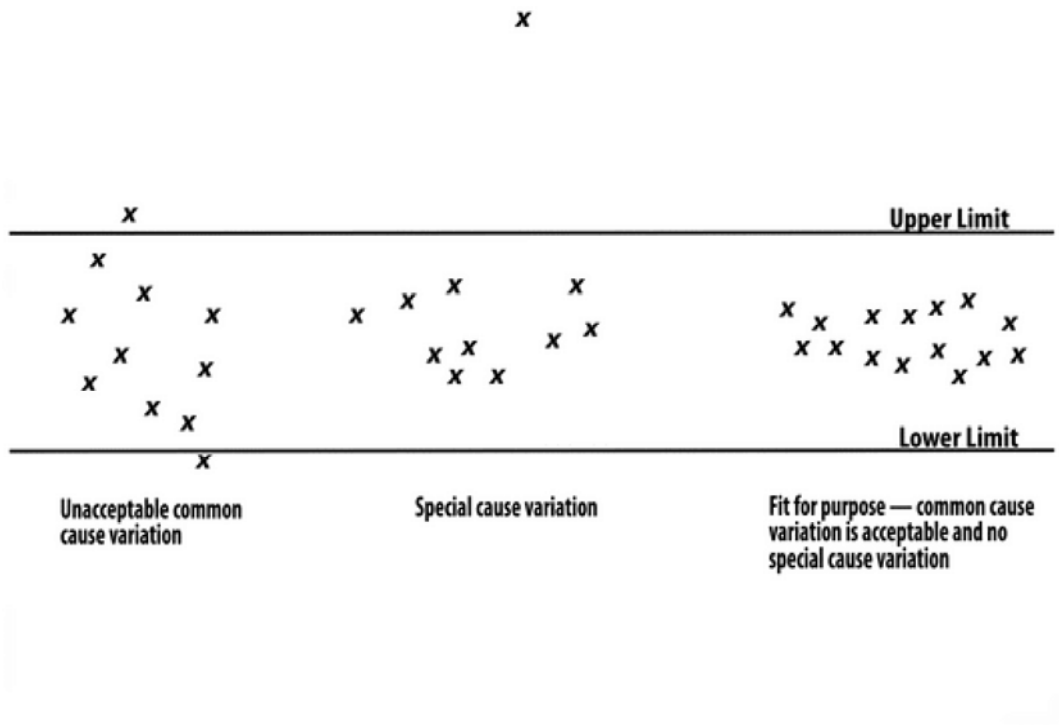


Figure 7. Common variation and special variation.

Continual Improvement

Throughout the procedure's lifecycle, changes may be required to improve the operational performance or the control strategy (continual improvement). Changes may include but are not limited to: inclusion of an additional control, introducing a new method or technology, changing the intended purpose to incorporate a new impurity or tighten specifications, or alignment with a procedure in a compendial monograph that has been updated. The nature of the change dictates the action that should be taken, and a risk assessment should be performed to identify what action is required, and the change should be documented. When the risk assessment identifies a change that requires qualification, the activities described in Stage 2 are performed. This stage also applies to modifications of compendial procedures.

EXAMPLES OF CHANGES AND APPROPRIATE ACTIONS

Change Type 1: Changes that are within already proven ranges (within the procedure's design space) are considered adjustments and do not require a procedure performance qualification study to be performed before returning to routine monitoring.

Change Type 2: These are changes that are outside the already proven ranges but require only confirmation that the procedure continues to generate data that meet ATP requirements. Full procedure redevelopment is not required.

Change Type 3: These are changes that involve the need to operate the analytical procedure in a different environment. These types of changes traditionally have been treated as a procedure-transfer exercise (or procedure verification when a pharmacopeial procedure is used for the first time in a new environment).

Change Type 4: This is a change that may require a new analytical procedure, but the ATP remains the same. The procedure will return to the procedure development stage.

Change Type 5: This change involves tightening a specification limit or a change to the intended purpose of the procedure to measure additional attributes. These changes result in a new ATP being defined.

CONCLUSION

The Expert Panel recommends adoption of a lifecycle approach for the management of analytical procedures. This approach builds on and enhances the current information contained in several *USP* general chapters and ICH guidance documents. Adoption of this approach would introduce new concepts to the *USP*: the Analytical Target Profile and associated predefined acceptance criteria, evaluation of the uncertainty associated with the analytical procedure, incorporation of risk analysis strategies, and consideration of the potential effect of changes to an analytical procedure in the context of the analytical procedure's lifecycle. *Table 1* shows the key advantages of adopting a lifecycle approach.

Table 1. Advantages of Adopting a Lifecycle Approach for Managing Analytical Procedures

Current Approach	Lifecycle Approach
Focus is showing that various procedure performance characteristics meet criteria—but may not consider how these relate to the overall uncertainty in the data and whether they are acceptable or not	The driver is understanding the target measurement uncertainty, which is the maximum level of measurement uncertainty that represents fitness for purpose (i.e., ensures decisions from data are made with a predefined confidence) and to demonstrate the procedure will meet this uncertainty requirement
Tendency to perform validation in a check box manner against the general analytical performance characteristics described in ⟨ 1225 ⟩ and ICH Q2	Specific ATP for each measurement requirement defining the characteristics and criteria that the procedure should meet
Limited understanding of effects of variation on performance	Structured and methodological approach to identify and explore variables
Validation, verification, and transfer are seen as separate exercises	All are integrated as part of the analytical procedure lifecycle, and success is demonstrated by generating reportable results that are consistent with the ATP
Confusion about the differences among procedure validation, procedure transfer, and procedure verification	Improved clarity and holistic view with the ATP as the focal point
Separate guidances in *USP* covering validation, verification, transfer of analytical procedures, and system performance verification	A single guidance for a lifecycle approach for analytical procedures

As a result of these recommendations, the Validation and Verification Expert Panel proposes that the concepts addressed in ⟨ 1225 ⟩, ⟨ 1226 ⟩, and ⟨ 1224 ⟩ be revised to integrate the processes for demonstrating that an analytical procedure is fit for purpose throughout its lifecycle and that these three chapters be compiled into a single general information chapter ⟨ 1220 ⟩ and a new general chapter ⟨ 220 ⟩ that specifies the basic requirements.

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Fitness for Use: Decision Rules and Target Measurement Uncertainty

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ABSTRACT The *Stimuli* article *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification*, published in *Pharmacopeial Forum* 39(5), discussed the application of the modern lifecycle model to an analytical procedure. The article introduced several topics: decision rules, target measurement uncertainty, analytical target profile, and the control strategy for continued verification of the analytical procedure. The present article addresses several of these topics in detail: what are decision rules, how are they developed, and how is the target measurement uncertainty determined. The Validation and Verification Expert Panel seeks reader comments on the contents of this *Stimuli* article.

INTRODUCTION

Decisions Made with the Reportable Result

A major, if not the most important, driver for adopting the lifecycle approach to an analytical procedure is to ensure that the reportable result is fit for use. It is important, therefore, to understand what the result will be used for and to have a way of defining criteria that can be used to assess the fitness of results for their purpose or use. Reportable results are generated in order to make decisions; however, the challenge is clearly defining the decision being made with the reportable result. Currently, there is no clear, commonly used, and internationally agreed upon process to follow that defines whether a reportable result is fit for use. The development of decision rule (DR) (*1*) concepts provides an approach that can be helpful for determining fit for use.

There is a long history behind DRs, which have been used to provide organizations with procedures for accepting and rejecting products. Guidelines (*2*,*3*) have been written to plainly and unambiguously define the theory behind DRs, and these guidelines can include situations when two or more bodies are involved in accepting or rejecting a product, such as purchaser/supplier relations or manufacturer/regulatory relations. Some regulatory bodies in other industrial sectors are already using DRs in formulating laws and regulations for dealing with commodities, including the food (*3*) and nuclear (*4*) industries, environmental regulations (*5*), and highway traffic laws (*6*).

The analytical target profile (ATP) concisely defines the requirements for a reportable result to be fit for use. The DR defines the use of the reportable result, and can provide the information, such as acceptable probabilities, needed to set the target measurement uncertainty (TMU), which is defined in the *International Vocabulary of Metrology* (*7*) as a "measurement uncertainty (MU) specified as an upper limit and decided on the basis of intended use of measurement results."

The TMU can become part of the ATP, which is valuable to the pharmaceutical industry because it provides a mathematical proof that reportable results are suitable for use.

Fit for Use and the Measurand

The DR approach allows the defining of any decision that will be made with the reportable result; this is the use of the reportable result. The process for defining the DR must include the end user of the reportable result. End users may include the lead in a clinical study, the production manager, the stability study coordinator, the regulator releasing a lot of drug product (DP), or other positions. The DR must clearly state the measurand as defined in VIM (*7*). The measurand helps to determine the intended use for the procedure and should include important aspects and conditions, such as the following:

- Description of the quantity to be measured, more commonly known as the units;
- The analyte, which is the entity actually being measured;
- The matrix, if relevant;
- Whether the reportable result refers to the laboratory sample or to the "parent body";
- If relevant, the measurand may include information on the analytical procedure itself. For operationally defined (empirical) procedures, this is often relevant. For example, experimental conditions, such as the temperature for loss on drying, may be specified.

More information on the measurand can be found in *Eurachem Guide: Terminology in Analytical Measurement* (*8*).

Another challenge in defining fit for use is that there may be more than one use for a reportable result. Thus, when developing criteria for the reportable result, we need to consider all possible uses, including release, stability, and others, as each has its own need for the data. The required quality or tolerance for MU (bias and uncertainty) associated with the reportable result may be different for each use. The uncertainty that is acceptable for the reportable result to release a lot may be larger than that required for the stability study of that lot. Following a defined process using knowledge management, risk analysis, and process mapping helps define the uses of the reportable result and its required quality. Each use will require its own DR and ATP because the measurand and acceptable risks may be different.

THE LINK OF DECISION RULES WITH SPECIFICATIONS

Any discussion on introducing the concept of DRs in the pharmaceutical industry inevitably must also consider the process by which specifications are set. In present practice, pharmaceutical specifications are established to ensure safety and efficacy and are in fact generally tighter than the specifications required for safety and efficacy. This is because of quality rationales related to the capability of processes and analytical procedures. These rationales may not involve the actual performance of the DP in the clinical environment, or this connection is not always apparent. With quality by design (QbD), there is a desire to more closely link the acceptance criteria in specifications to the clinical effect (*9*,*10*). The importance of a scientific, risk-based approach to specification setting, and its link to analytical QbD and the lifecycle approach to analytical procedures, are discussed in Borman et al (*9*). Work by Yu (*10*) discusses the attributes and quality system controls needed to ensure clinical performance of the DP. By ensuring that specifications are based on clinical relevance, as shown in *Figure 1*, DRs can act as the link between the reportable result and the clinical effect of the DP.

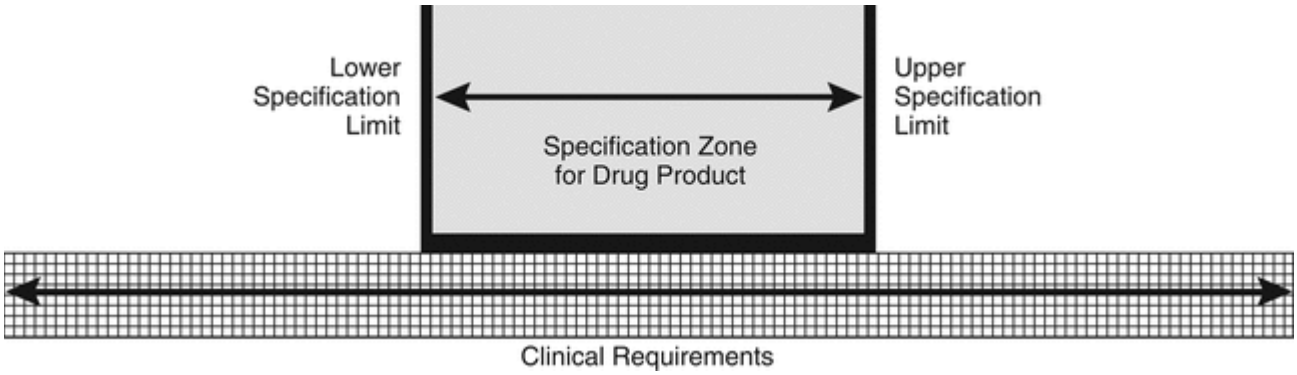

Figure 1. This figure shows that the requirements for the clinical use of a DP may be much wider than the specifications of the DP. This relation between clinical requirements and product specifications may not be apparent. A DR based on the intended use of the reportable result can be used to make this relationship apparent.

THE RELATION TO THE ANALYTICAL PROCEDURE

A DR can provide an understanding of the maximum variability or maximum uncertainty (or TMU) that can be associated with a reportable result, and whether that reportable result may still be fit for its intended use. The next section introduces DRs, the different types of DRs, and how they use probability in order to calculate the TMU.

DECISION RULES

DR References, Guidance, and Standards

This section describes DRs and draws upon approaches discussed in consensus standards documents (*1*,*2*,*9*). The concept of DRs has been described in detail elsewhere (*1*).

A DR is a documented rule that describes how the MU will be allocated with regard to accepting or rejecting a product according to its specification and the result of a measurement (*1*). DRs are developed using risk—assessed by considering the potential harms and hazards—and probability. DRs give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and the specification limit or limits. Additionally, DRs can take into account an acceptable level with regard to the probability of making a wrong decision. The wrong decision can lead to accepting an out-of-specification (OOS) reportable result which is not true or rejecting an OOS reportable result which is true, or a false failure or a missed fault, which are discussed below. The DR guidances use the word “product”, which can mean many things, such as a lot of drug substance, an in-process sample, a raw material, an environmental control sample, or others. The product is essentially any pharmaceutical material that is being tested.

THE DR AND COMPLIANCE

When the reportable result and its uncertainty are compared to the specification limit or limits, there are four possible outcomes, illustrated in *Figure 2*. [NOTE—The figure uses an upper limit, but the same four outcomes exist for a lower limit.] For each of the four possible outcomes, the DR defines the compliance judgment.]

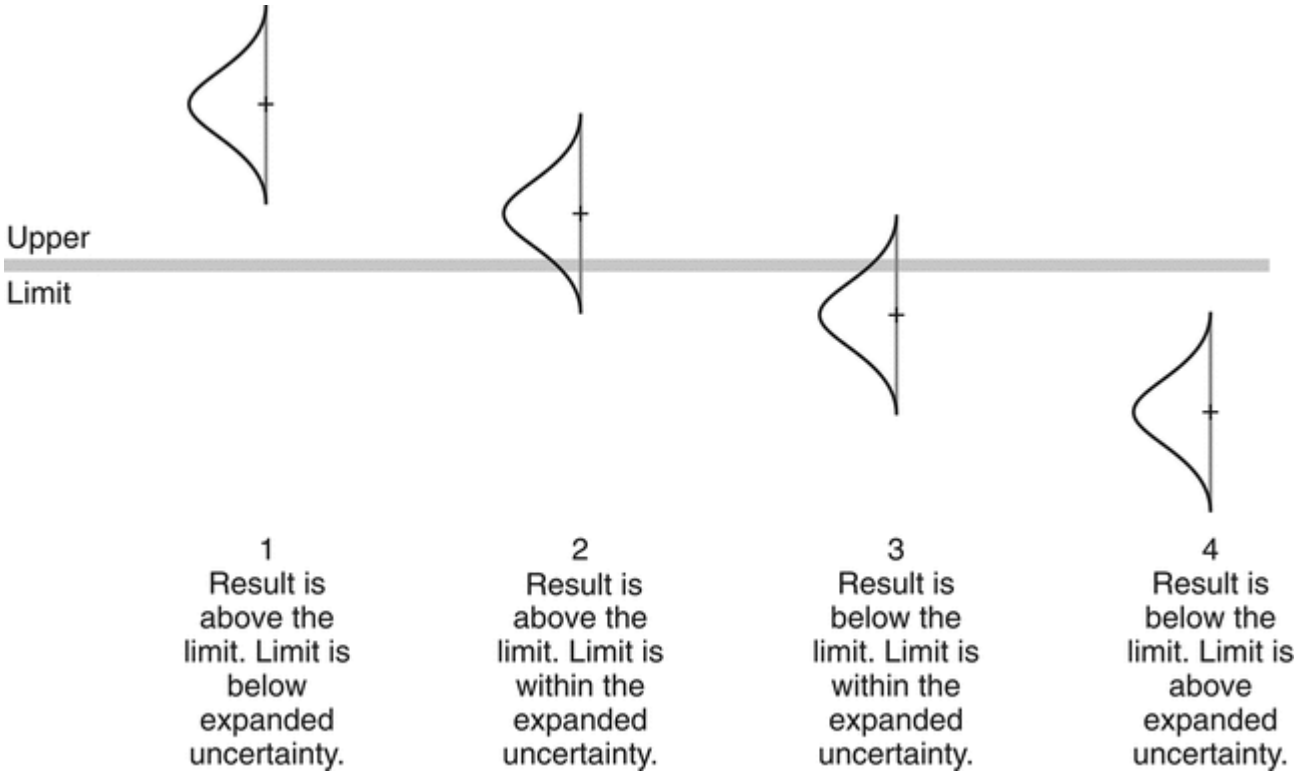

Figure 2. The four possible outcomes when a reportable result and its expanded uncertainty are compared with a specification. Each outcome shows a normal distribution curve with the reportable result at the center and the width of the distribution determined by the uncertainty.

Expanded uncertainty and coverage factors: MU is standard uncertainty, u, which is expressed as a standard deviation. The guides on uncertainty recommend that an expanded uncertainty, U, should be used and normally reported by the laboratory, because it provides an interval within which the true value is believed to lie with a higher level of confidence. The expanded uncertainty is calculated using a coverage factor, k, chosen based on the acceptable probability of making a wrong decision. A coverage factor is similar to the z factor for a standard normal distribution and is typically in the range of two to three (e.g., for a 95% level of confidence, a $k = 2$ is used). For the example shown in *Figure 3*, when assessing compliance with an upper limit—using a coverage factor of $k = 1.65$ with a 95% level of confidence—it can be interpreted that the probability of making a wrong decision is 5%. This is for a reportable result that is 1.65 times standard uncertainty ($1.65u$) below the upper specification limit.

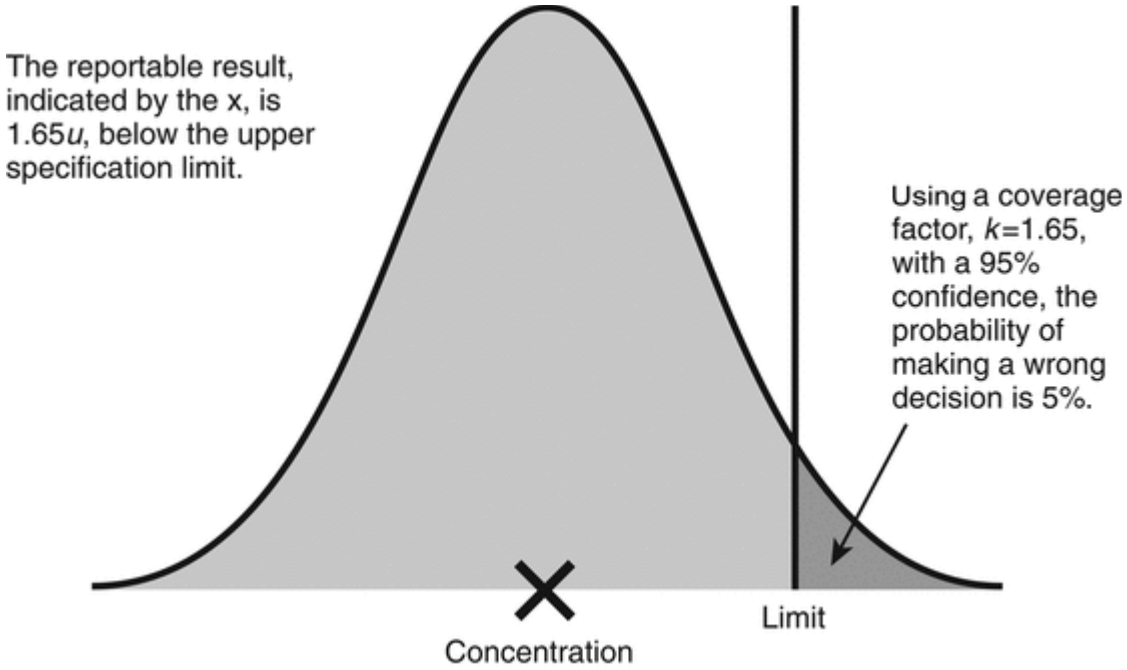

Figure 3. A normal distribution curve centered on the reportable result shown by the x. For this reportable result, using a coverage factor of 1.65 with a 95% level of confidence, the probability of making a wrong decision is 5%. This is for a reportable result that is 1.65 × standard uncertainty below the upper specification limit.

The end user of the data can judge the impact of being wrong 5% of the time. If the impact is not acceptable, a different level of probability can be chosen, the uncertainty can be reduced, or the specification limits can be changed.

ASSUMPTION OF NORMAL DATA DISTRIBUTIONS

This *Stimuli* article and many discussions on MU assume a normal distribution for the reportable result, and Annex G in the *Guide to the Expression of Uncertainty in Measurement* (*11*) provides the rationale and conditions needed to make the assumption that the probability distribution is normally distributed. These assumptions are fulfilled for many, if not the majority, of procedures in pharmaceutical analysis. In the case of a non-normal distribution, the estimation of the standard uncertainty is not impacted, and only the calculation of the expanded uncertainty may require different coverage factors. This information is fully covered in section G 5.3 of GUM (*11*). Regardless of the distribution, the same process of multiplying the uncertainty by a coverage factor is used to create and follow the DR.

Types of DRs

DRs use acceptance zones to define the range within which the product will be accepted and rejection zones to define the range within which it will be rejected. A transition zone defines a range within which the product is not immediately accepted or rejected; instead, other activities may be performed, such as additional testing, testing using a different technique, or an investigation. These zones may or may not align with the specification ranges.

Different types of DRs use different acceptance, rejection, or transition zones to fully define the subsequent decision. The zones for a simple DR are illustrated in *Figure 4*.

Simple acceptance or rejection zone: Product conformance is verified if the measurement result is in the specification zone; otherwise rejection is verified. The specification and acceptance zones are aligned, so the acceptance zone is called the simple acceptance zone and the range outside the specification zone is called the simple rejection zone.

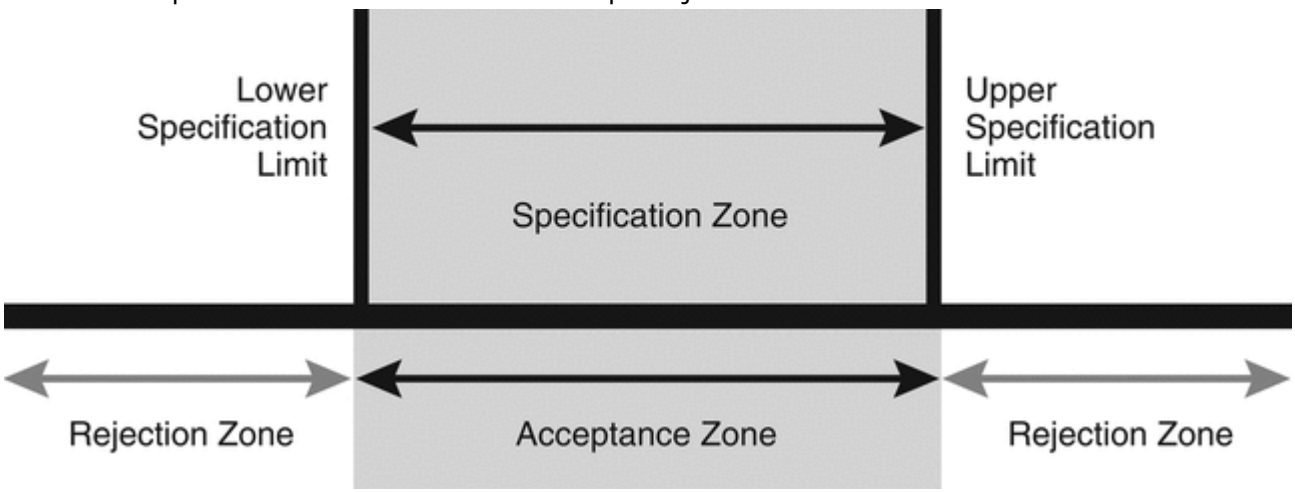

Figure 4. The various zones used in a simple DR. The acceptance zone and the rejection zone are termed "simple" because they align with the specification zone.

Based on the risk, the acceptance and rejection zones may be different from those of the specification. These DRs use guard bands, which is the magnitude of the offset from the specification limit to the acceptance or rejection zone boundary (*1*).

Stringent acceptance zone: A specification zone that is reduced from the upper and lower specification limits by a guard band (often called an "alert" or "internal release limit" in the pharmaceutical industry).

Relaxed rejection zone: The rejection zone is increased and is inside the specification zone by the amount of a guard band (g_L and g_U). This is shown in *Figure 5*.

Relaxed acceptance zone: The acceptance zone is increased beyond the specification zone by a guard band. This is shown in *Figure 6*.

Stringent rejection zone: The rejection zone is increased beyond the specification zone by a guard band.

Transition zone: Area between the acceptance zone and rejection zone. This is shown in *Figure 7*. If a reportable result were obtained in the transition zone, additional activities would be prescribed. For example, an investigation may be initiated to determine the reason for obtaining a value in the transition zone and additional tests may be prescribed, or a different procedure with a lower uncertainty may be used.

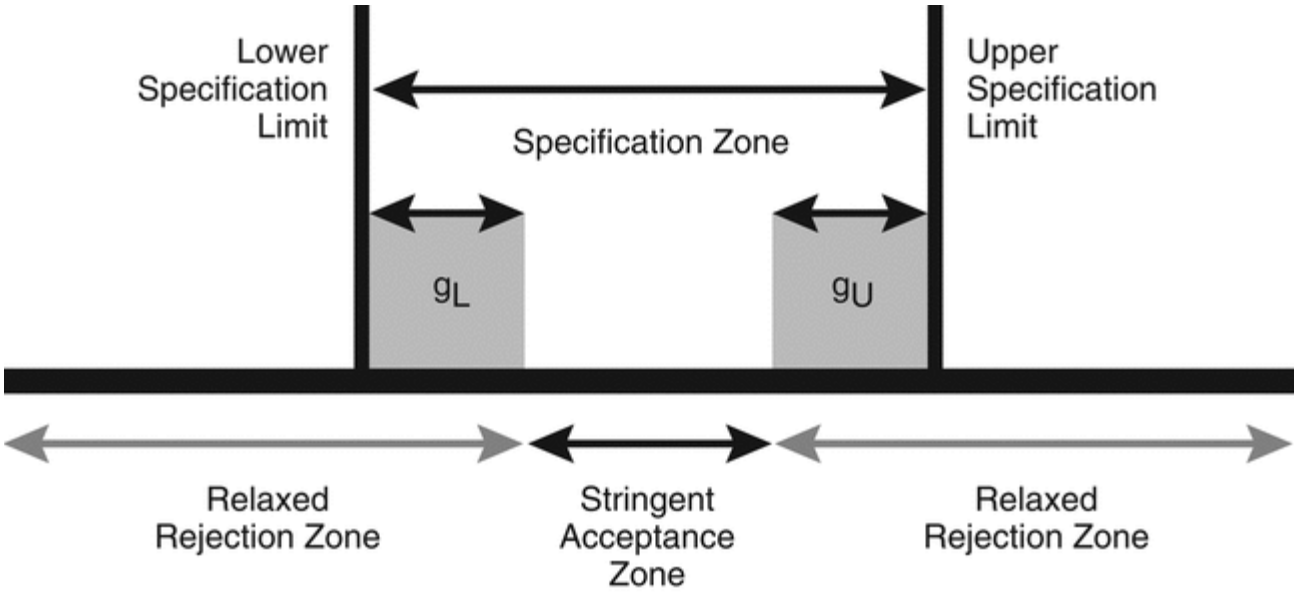

Figure 5. A DR that uses a stringent acceptance zone and relaxed rejection zones. The guard bands, g_L and g_U, are within the specification zone. For this DR, a product will be accepted if the risk of being OOS is low.

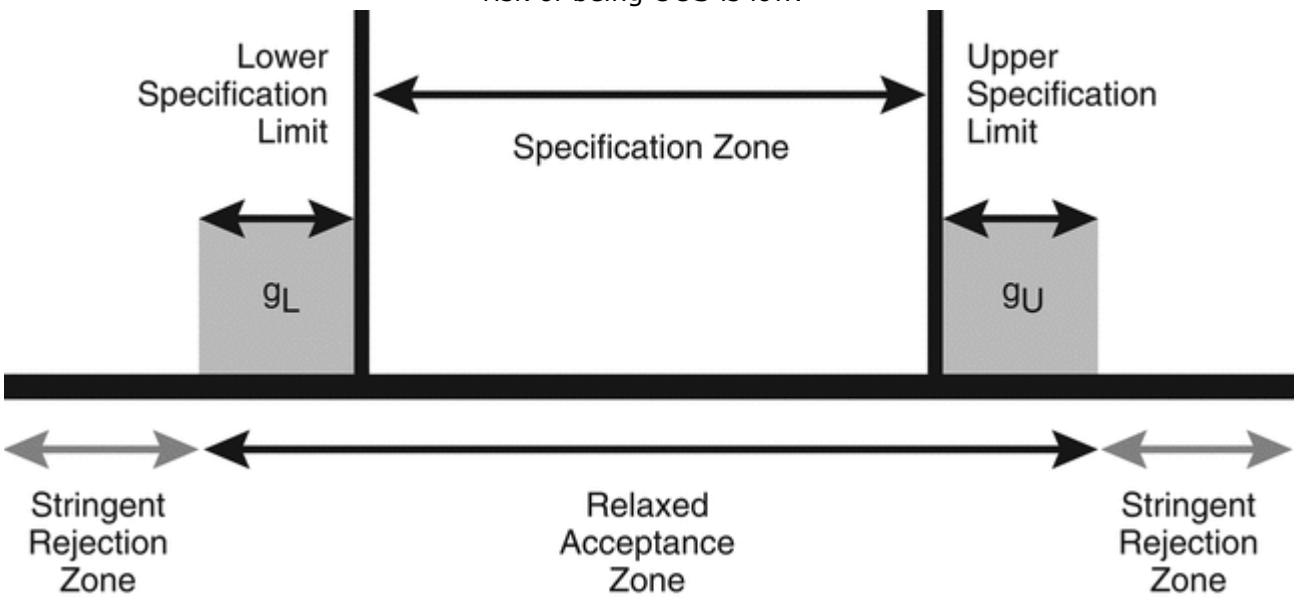

Figure 6. A DR that uses a relaxed acceptance zone and stringent rejection zones. The guard bands, g_L and g_U, are outside the specification zone. For this DR, a product will be rejected only if the risk of the product being OOS is high.

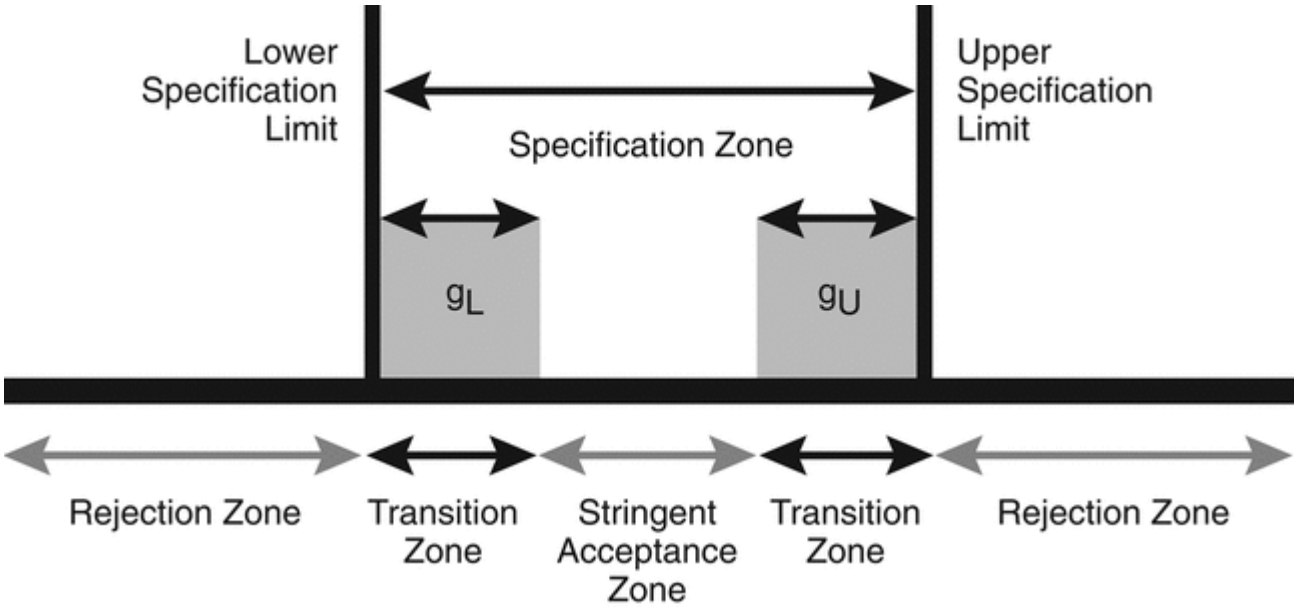

Figure 7. A DR that uses a transition zone. If a reportable result is obtained within the transition zone, additional activities prescribed in the DR can be undertaken.

The MU should meet the requirements of the acceptance zone. The TMU is set using the acceptance zone and the acceptable probability of obtaining reportable results within the transition zone or rejection zone. Setting the TMU in this way ensures that the reportable result will be fit for purpose, and allows the TMU to become part of the ATP.

Present Practice in the Pharmaceutical Industry

Current practice in the pharmaceutical industry may be described as using two types of DRs: "simple" DRs and DRs that use transition zones. Applying DR theory to present practice allows for a better understanding of risk and probability and can also define additional criteria, such as the TMU, for the ATP. A majority of *USP* monograph specifications are simple DRs. When a reportable result is obtained that is at the specification limit, there is a 50:50 probability that the true value is OOS as shown in *Figure 8*. If this probability may not be acceptable, a transition DR that uses a guard band and transition zone can be used. In current practice these are called internal release or alert limits. The transition DR, shown in *Figure 7*, uses a transition zone. If a reportable result is obtained within the transition zone, additional activities prescribed in the DR can be undertaken. The transition zone is determined by the guard band. Work by Burgess (*12*) details how the requirements for generating a scientifically sound reportable value can be met using DRs and guard bands.

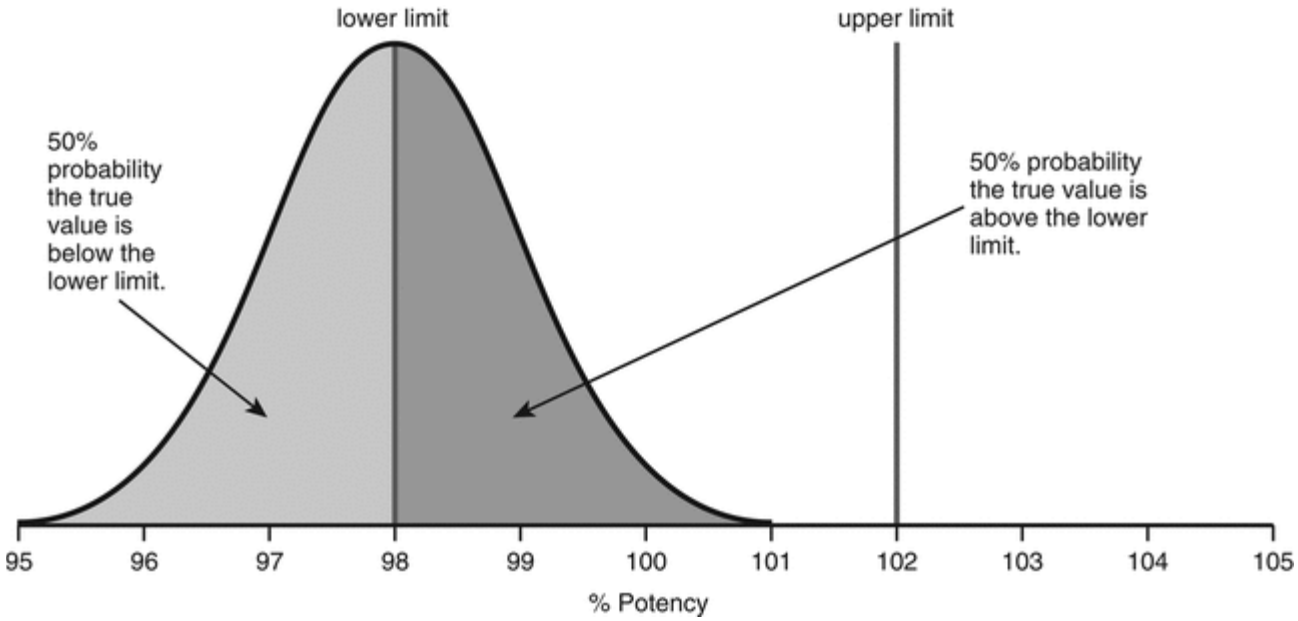

Figure 8. A USP specification of 98.0%–102.0%. If a reportable result is at or close to 98.0%, there is a 50:50 probability that the true value is below the lower limit.

TARGET MEASUREMENT UNCERTAINTY

As stated above, the DR can also be used to set the TMU, which then becomes part of the ATP. Two approaches can be used to calculate the TMU: use of misclassification rates or use of the coverage factor.

Calculating TMU Using Misclassification Rates

MISCLASSIFICATION THEORY AND REFERENCES

Misclassification rates and their use in assessing whether a measurement system, in this case an analytical procedure, is capable have been described in detail previously (*13*,*14*) and will not be repeated here. The reader should refer to these references for the detailed discussion of misclassification theory.

TRUE VALUE VERSUS MEASURED VALUE

In the discussion of misclassification rates, it is useful to understand what is meant by the terms "true value" and "measured value." The reality is that each measurand has an actual value, called a true value, which cannot be known. For example, each lot of DP has a true potency that is "truly good" if it is within specification and "truly bad" if it is outside the specification. In practice, a measurement is made to obtain a measured value, which is an indication of the true value. The measured value and the uncertainty associated with it are subsequently used to make a decision. For each true value that is inside the specification, there is a probability the measured value will be outside the specification. Alternately, for each true value that is outside the specification, there is a probability the measured value will be inside the specification. The misclassification approach allows the estimation of these probabilities, which can then be used to set a TMU.

[NOTE—GUM (*11*) states that the true value is, in practice, unknowable. Trueness is defined in VIM (*8*) as "closeness of agreement between the average of an infinite number of replicate

measured quantity values and a reference quantity value." Since an infinite number of measurements is not possible, a conventional value is used. It may be a best estimate of the value. The reader is referred to Annex D in the GUM (*11*) for a detailed discussion on the term trueness.]

TYPE OF RISK OF MAKING A WRONG DECISION

When deciding on the use of the reportable result, the risks of making a wrong decision need to be considered. There are two types of risks:

False failure: A false failure (FF) is a lot whose true value (measurand quantity or lot mean) is within product limits, but it is assigned an OOS potency and is rejected. This decision is based on applying the DR to the measurement result from a laboratory sample of the lot in question. This type of risk can be serious for the manufacturing company but is usually of little consequence to a patient. However, it could be serious to the patient if urgently needed product is not available.

Missed fault: A lot with a true value (measurand quantity or lot mean) that is outside product limits, but the lot is judged acceptable; this is known as a missed fault (MF). This decision is based on applying the DR to the measurement result from a laboratory sample of the lot in question. This risk is serious for the patient, and is also serious for the company because there is a higher probability that a laboratory sample taken from the lot would be OOS.

Consider each type of risk separately: Risk is defined in International Council on Harmonization (ICH) Q9, Quality Risk Management (*15*) as the "combination of the probability of occurrence of harm and the severity of that harm." The acceptable probability for each risk needs to be determined. The process described in ICH Q9 (*15*) can be used to assess the risks and assign an acceptable probability for the risks, FF and MF. The development and implementation of this risk assessment process, however, is outside the scope of this paper.

Classify Product Based on Measurements

From the risk assessment, acceptable probabilities are decided for an MF and FF error. The probabilities for these misclassification errors can be calculated using a Monte Carlo simulation. This is done by simulating 100,000 true values (i.e., 100,000 simulated production lots) from the production process normal distribution, using expected values for the production mean and standard deviation. These 100,000 true values are presented as a histogram in *Figure 9*. The product lots that have a true value within the specification are shown in blue bars and those with a true value either above or below the specification are shown in red bars.

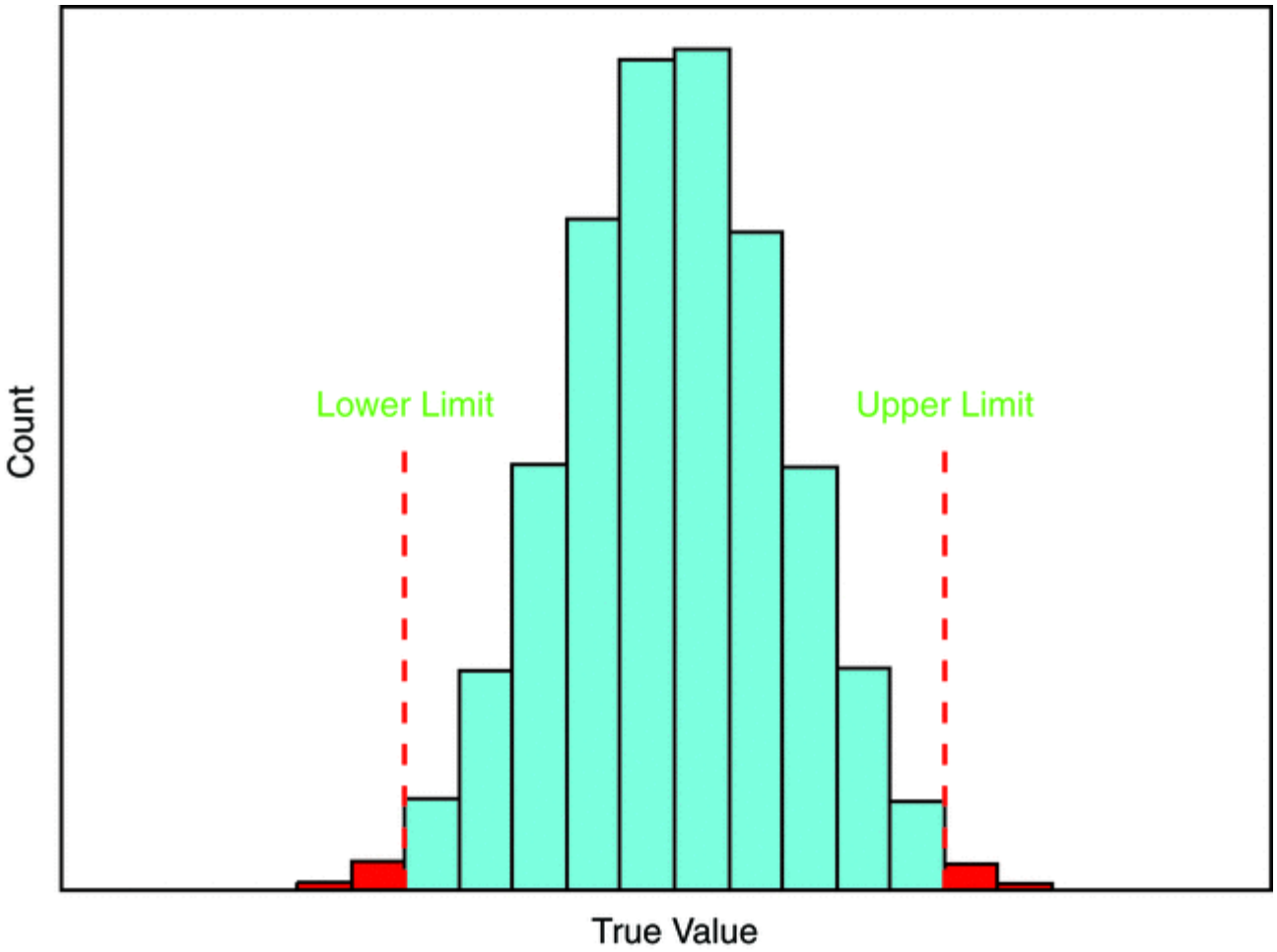

Figure 9. This histogram illustrates the true state of product determined by comparing true values to product limits. Good product is shown in blue and bad product is shown in red.

In reality, we cannot know the true values. Instead we must estimate the true values using an analytical procedure that measures the potency for each lot. We can simulate the results of testing the 100,000 lots using the characteristics, bias, and standard deviation of the analytical procedure. The distributions of the measurement results or measured values are shown in *Figure 10*.

The top chart, in blue, shows the measured values for the lots with true values within the product limits. As a result of the variability in the measurement process (or the analytical procedure), there are FF that are shown outside the specifications. These occur when a measured value outside the acceptance zone is obtained for a good product lot.

The lower chart, in red, shows the measured values for the lots with the true value outside the product limits (or a bad product lot). Again, as a result of the variability in the analytical procedure, there are MF. These occur when a measured value inside the acceptance zone is obtained for a bad product lot.

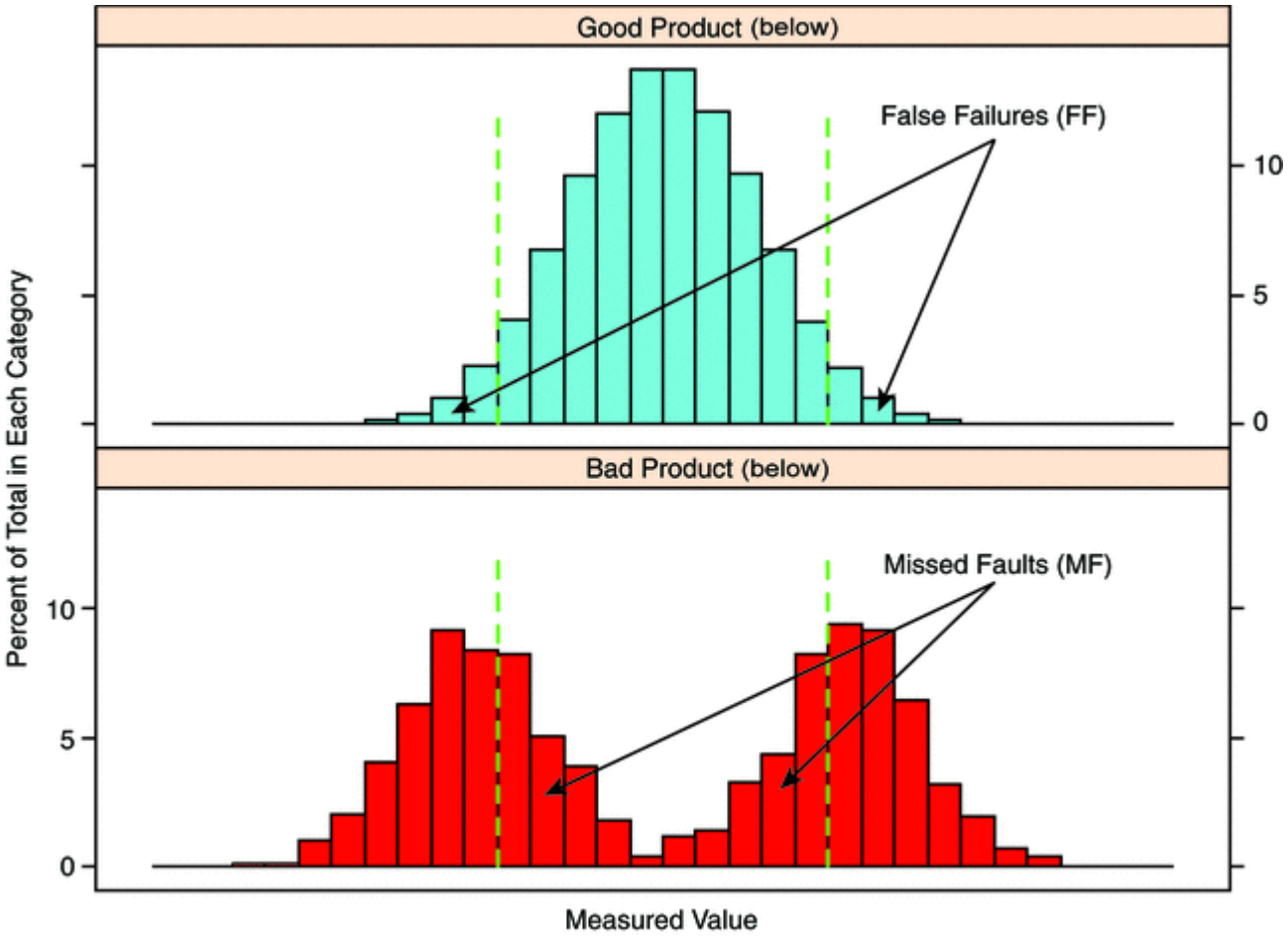

Figure 10. The measured values obtained for the 100,000 true values for the production process. The top chart, in blue, shows the measurement results for the good true lots. The lower chart, in red, shows the measurement results for the bad product lots.

Another way to visualize the MFs and FFs is shown in *Figure 11*.

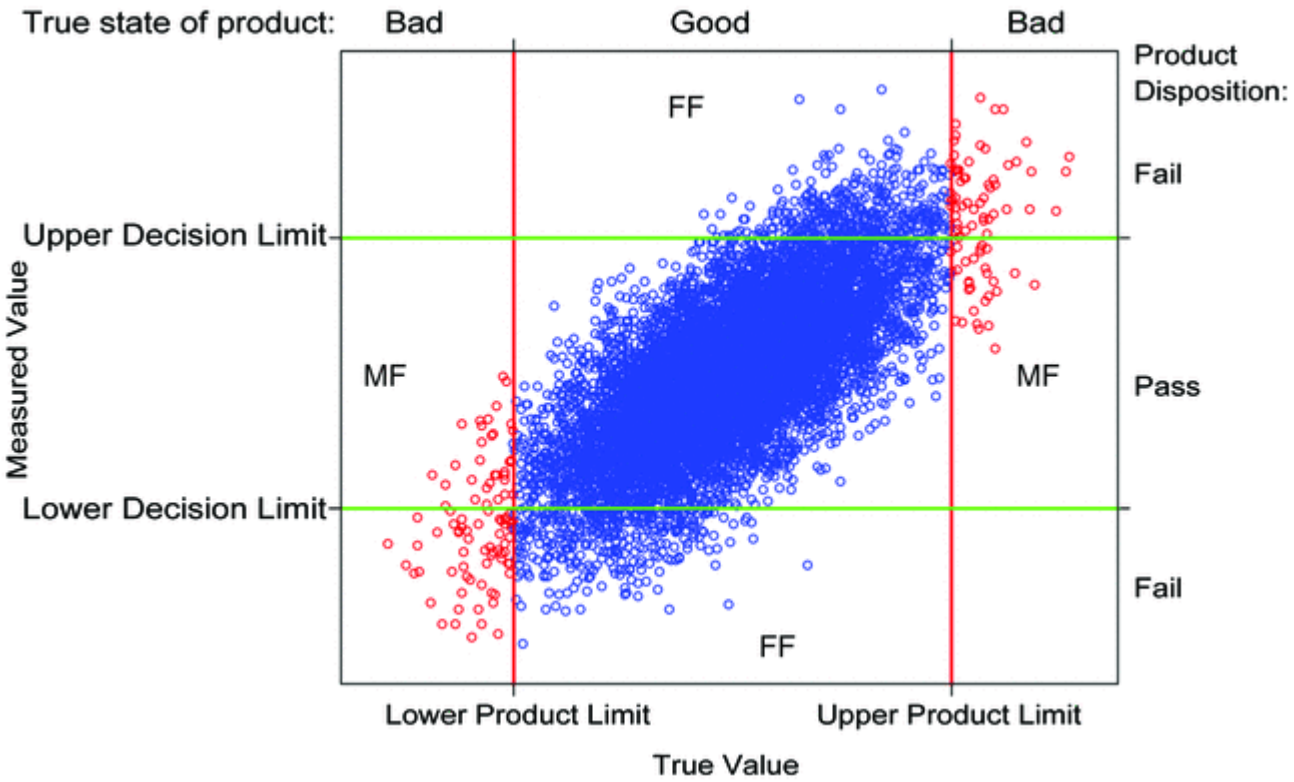

Figure 11. This graph shows 10% of the 100,000 simulated values are outside the production limits. Only 10,000 simulated tests are shown so the figure is clear. The misclassifications are shown in the areas labeled MF and FF.

The TMU for the analytical procedure can be determined by varying the analytical procedure standard deviation used in the Monte Carlo simulation until satisfactory probabilities for FFs and MFs are obtained.

USING MISCLASSIFICATION TO DETERMINE THE TMU

There are a number of assumptions upon which the FF and MF misclassification scheme is based. These are:

If...

- We know (or can estimate) the true product distribution (i.e., this can be achieved by using process capability).
- We have product limits to distinguish truly good from truly bad product. These are not the limits against which a measurement result is compared. These are "a priori" limits that unambiguously discriminate "good" from "bad" lots in terms of potency. These limits apply to the measurand quantity true value which we can never know.
- We know the maximum allowable MF and FF probabilities.

Then...

- We can conduct simulations such as those described above.
- We can vary the MU and DR and predict the MF and FF probabilities.
- We can find ranges for MU and DR that provide acceptable MF and FF probabilities.
- We can specify the maximum MF and FF probabilities in the DR and determine the TMU.

It is important to recognize that the FF and MF rates will depend not only on the uncertainty of the analytical procedure, but also on the variability in the production process.

USING MS EXCEL

MS Excel can be used for the Monte Carlo simulation. It can also be used to illustrate the production and analytical procedure distributions, both individually and combined. Also, the probability of MF and FF can be calculated in MS Excel. Therefore, all the required calculations associated with fitness for use can be made in MS Excel.

MISCLASSIFICATION AS AN EFFECTIVE TOOL TO ASSESS RISK

The misclassification approach allows us to quantify the risks so they can be effectively understood, evaluated, and communicated. The acceptable levels of risk can then be decided upon by the decision makers and become part of the DR.

Calculating TMU Using the Coverage Factor

The use of FF and MF probabilities to determine a TMU is valuable when the variability of the manufacturing process and/or product is known or can be estimated. When this is not available or it is known that the variability of the product is insignificant, the coverage factor can be used to calculate the TMU. This may be the case for a drug substance that is very pure, as shown in the *Appendix*, *Example 5*. Since the expanded uncertainty is calculated using a coverage factor, the TMU is calculated by dividing the expanded uncertainty range by the coverage factor, *k*. This is shown in *Figure 12*.

$$TMU = U/k_p \qquad \text{Equation 1}$$

U = expanded uncertainty
k = coverage factor
p = acceptable probability of making a wrong decision

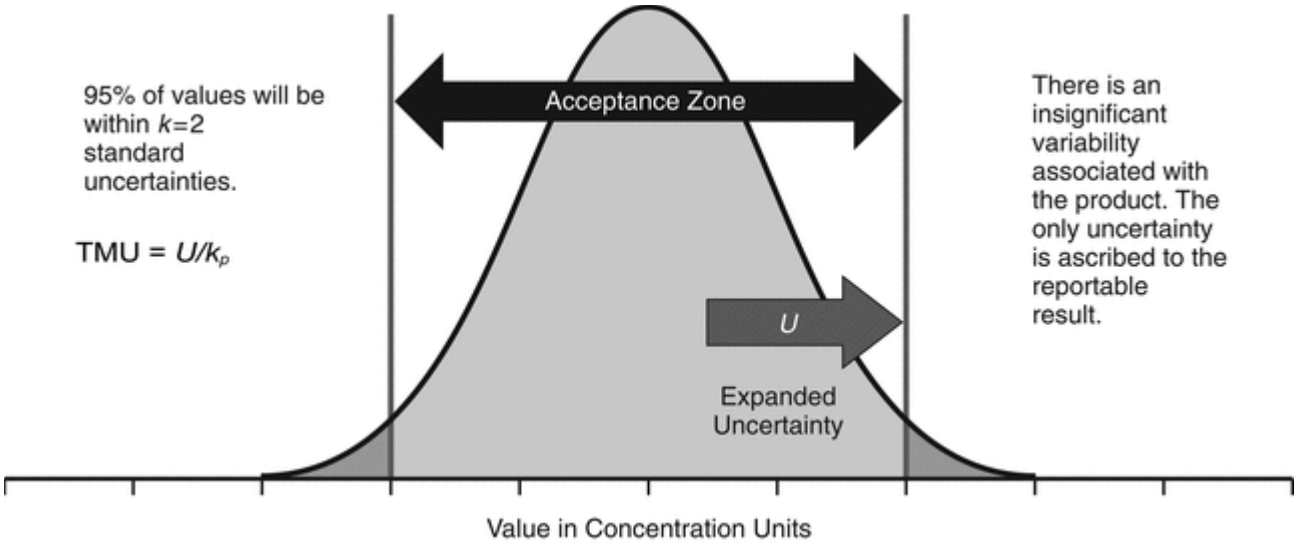

Figure 12. This figure shows the situation in which the variability of the product value is insignificant. In this case, the TMU can be calculated using the coverage factor.

For example, the standard uncertainty (u) for a potency assay is estimated to be 0.9%. The expanded uncertainty is reported for a level of confidence of 99.7%, using a coverage factor, k, of 3. A reportable result of 99.8% would be reported as "99.8 ± 2.7% where the reported uncertainty is calculated using a coverage factor of 3."

Bias and TMU

The TMU is calculated using the model of a normal distribution that has a central value. In reality, this value may not be centered on the midpoint in a specification range. The commercial manufacturing range may not be centered or the analytical procedure may have a bias and not be centered. Both of these cases will impact the setting of the TMU.

The production range can be considered part of the measurand. The measurand will be for a DP produced by a manufacturing process with a centered value and a spread or standard deviation. An illustration of this is given in *Example 2*.

If an analytical procedure has a significant bias, that bias needs to be addressed. During analytical procedure development, the bias should be eliminated if possible. If not, a correction for the bias should be adopted. If neither of these options is possible, the TMU must be adjusted to account for the bias.

CONCLUSION

There are many advantages to using DRs and TMU. They are widely used in other industries, so the theory and guidance for their use have been established. They also provide a mechanism for setting acceptance criteria when observing the performance of the analytical procedure. Therefore, any compliance decisions related to that analytical procedure will be based on sound science and good metrology. With clinically based specifications and fit-for-use analytical procedures, there is a major benefit for the patient, who will receive medications that are shown to be fit for their intended use through a well understood, standardized approach.

There are, however, challenges with the proposed adoption of DRs and TMU. The process for setting specifications will need to change, and alteration to these specifications will require additional education and training. The level of statistical knowledge will need to increase, not only for analysts, but also for any other employee who uses the data generated by these new DRs and TMU.

APPENDIX

Examples

EXAMPLE 1

DR and TMU determined for a DP using the MF and FF approach:

Example background and constraints: This example uses the potency test for a DP. The specification comes from an individual USP monograph.

In an effort to keep the example simple so we can focus on the misclassification topics (MF and FF), no bias was assigned to the production or analytical processes. The approach still works if there is a bias, which is illustrated in *Example 2*.

Clinical: The usual adult dose for a DP is 40 mg orally every 4 h as needed, not to exceed 1 g/day. The USP monograph for a DP defines the specification for assay as 95.0%–105.0%. This is the label specification.

The upper specification limit (USL) is 105.0% and the lower specification limit (LSL) is 95.0%. The target specification limit (TSL) is 100.0% (see *Table 1*).

Table 1

Potency Specification for a Lot of DP	USP Monograph Specifications (%)	USP Monograph Specifications (mg)
LSL	95.0	38
TSL	100.0	40
USL	105.0	42

DR: The probability of harm (making a wrong decision) assigned for the DR was the acceptable probability for the individual FF and MF events. The decision makers assessed the acceptable level of risk and assigned the value of the FF as 2.5% (0.025) and the value of the MF as 1.5% (0.015).

The DR is therefore "the lot of DP will be considered compliant if the probability of the FF is less than 2.5% and the probability for an MF is less than 1.5%."

Sampling, laboratory sample considerations, and caveats: The specification applies to the entire DP lot, which in sampling terminology is called the parent body. The development process has to take into account that samples will be taken for analytical testing, and these samples, called "laboratory samples" must be representative of the parent body. It is important to note that for a *USP* monograph product, the specification relates to the sample. The company must develop a product for which the laboratory sample will pass the USP specification.

Commercial manufacturing: The pharmaceutical development has resulted in a process that will produce 95% of the product with an assay value centered on 100.0% with the standard deviation of 2.0%. This is determined from the formal experimental designs in the manufacturing process development program, including manufacturing robustness studies.

To find analytical uncertainty that meets the DR requirements, use an MS Excel spreadsheet with Monte Carlo formula, and the "true SD (uncertainty)" is varied until the maximum value that yields the DR requirements is found. The true SD (uncertainty) values used for this example are shown in *Figure 13*.

Variables for Calculation of Misclassification Probabilities Using Monte Carlo Simulation		
Instructions: Enter values into cells shaded blue.		
Product limits	Lower limit	95.0
	Upper limit	105.0
Production distribution	True mean	100.0
	True SD	2.0
Analytical uncertainty	True bias	0.0
	True SD (uncertainty)	1.2
Decision rule	Lower limit	95.0
	Upper limit	105.0

Figure 13. The analytical uncertainty was varied in the Monte Carlo simulations until acceptable FF and MF probabilities were obtained. The various scenarios or analytical uncertainties are listed in *Figure 14*. The MF is much lower than 0.015 because the manufacturing capability results in a low number of lots outside the specifications.

Scenario	Goal	1	2	3	4	5	6
Analytical true SD (uncertainty)		2.0	0.5	1.0	1.5	1.2	1.3
Probability of an FF	<0.025	0.0682	0.0054	0.0172	0.0372	0.0235	0.0297
Probability of an MF	<0.015	0.0042	0.0020	0.0040	0.0041	0.0041	0.0047

Figure 14. The values given by the simulator for various analytical uncertainties. The probabilities are expressed as %. The "analytical true SD (uncertainty)" of 1.2% meets the goal or DR requirements of FF < 0.025 and MF < 0.015.

TMU determined using misclassification approach: An uncertainty of 1.2% met the goal or DR requirements of FF < 0.025 and MF < 0.015. This becomes the TMU. The target uncertainty can also be expressed using a coverage factor to calculate a coverage interval. Using a coverage factor of 2 for a 95% coverage interval, the TMU is 2.4%.

EXAMPLE 2

The impact of bias: In this example we will consider what happens when there is a bias in the manufacturing process. The scenario is the same as *Example 1*, except that the pharmaceutical development has resulted in a process that will produce 95% of the product centered on 99.0% with the standard deviation of 2.0%. The DR in this example is the same as what was established in Example 1. Using the misclassification spreadsheet, the true SD (uncertainty) is varied until the DR requirements are met. The scenarios are shown in *Figure 15* and the TMU is 1.0%.

Scenario	Goal	1	2	3
Analytical true SD (uncertainty)		1.2	1.1	1.0
Probability of an FF	<0.025	0.0321	0.0260	0.0221
Probability of an MF	<0.015	0.0057	0.0075	0.0050

Figure 15. The scenarios used to determine the TMU for the case when the commercial manufacturing is centered on 99.0%. The TMU is 1.0%.

The expanded uncertainty is calculated using a coverage factor of 2 for a 95% coverage interval. The expanded uncertainty is 2.0% using a *k* of 2.

$$U = k \times u = 2 \times 1.0\% = 2.0\%$$

U = expanded uncertainty
k = coverage factor
u = standard uncertainty = TMU

EXAMPLE 3

When there is no knowledge of requirements from pharmaceutical development and commercial manufacturing: The laboratory may have no knowledge of the pharmaceutical development or commercial manufacturing requirements. This can occur early in development or for a testing laboratory that is qualifying a USP procedure.

In this example, a DP is being developed. There is little knowledge about the manufacturing process and product. The decision makers and experts in pharmaceutical development and analytical can use their knowledge, experience, and industry standards for process capability to make some presumptions about the expected product limits. With these presumptions, different simulations can be run and the FF and MF probabilities estimated, leading to identification of the ranges for the TMU. These can then be used to formulate a DR. As development of the product, manufacturing process, and analytical capabilities progress, or as more information is obtained for the commercial product, the presumptions can be revisited. The DR can be adjusted if required.

Consider the following example: the manufacturing process is introducing the use of methanol and must meet the ICH requirements for residual solvents. The relevant specification is ≤ 3000 ppm. Pharmaceutical development presumes that the concentration of the methanol will be about 1000 ppm. The decision makers expect this to be reproducible, and presume a standard deviation of 500 ppm. The analytical capability is expected to be about 500 ppm, based on experience with other similar products. The decision makers have stated they will accept an FF probability of 5% (0.05) and an MF failure of 1% (0.01).

These presumed parameters are entered into the FF and MF spreadsheet and the estimates are shown in *Figure 16*.

Variables for Calculation of Misclassification Probabilities Using Monte Carlo Simulation		
Instructions: Enter values into cells shaded blue.		
Product limits	Lower limit	0.0
	Upper limit	3000.0
Production distribution	True mean	1000.0
	True SD	500.0
Analytical uncertainty	True bias	0.0
	True SD (uncertainty)	500.0
Decision rule	Lower limit	0.0
	Upper limit	3000.0
The effect on the probability of misclassification is:		
Type of Misclassification	**Probability**	**%**
Probability of an FF	0.0079	0.79%
Probability of an MF	0.0639	6.39%

Figure 16. The FF probability is found to be too high. The analytical experts state they may be able to reduce the analytical uncertainty and will use replicates if needed. A second simulation is run using a lower analytical uncertainty of 400 ppm, shown in *Figure 17*.

Variables for Calculation of Misclassification Probabilities Using Monte Carlo Simulation		
Instructions: Enter values into cells shaded blue.		
Product limits	Lower limit	0.0
	Upper limit	3000.0
Production distribution	True mean	1000.0
	True SD	500.0
Analytical uncertainty	True bias	1000.0
	True SD (uncertainty)	400.0
Decision rule	Lower limit	0.0
	Upper limit	3000.0
The effect on the probability of misclassification is:		
Type of Misclassification	**Probability**	**%**
Probability of an FF	0.008	0.80%
Probability of an MF	0.0410	4.10%

Figure 17. FF and MF probabilities that are now acceptable. Development can continue, with the knowledge that the development goals for both pharmaceutical development and analytical are attainable.

EXAMPLE 4

Using the coverage factor to establish the DR: This example illustrates a stringent acceptance DR using the ICH requirements for the residual solvent, methanol. Although there are safety factors considered in the limit, the laboratory decides to use a stringent acceptance DR using a guard band.

Using ICH Option 2, based on permitted daily exposure and a maximum daily dose of 7 g/day, the upper specification limit is methanol ≤4285 ppm. In other words, methanol content of NMT 4285 ppm will correspond to NMT 30 mg of methanol daily intake.

Table 2 lists data that are known from development information.

Table 2

Parameter	ppm
Analytical uncertainty expressed as standard uncertainty	470
Analytical bias	0
Production process is described by a normal distribution with a center value	2661
Production process has a standard deviation significantly less than analytical so it is assigned a value of 0	0

The decision makers assign an acceptable probability of making a wrong decision as 5%. For a one-sided coverage interval, the coverage factor is 1.645 for a 95% confidence level. The guard band is calculated as

$$1.645 \times 470 \text{ ppm} = 773 \text{ ppm}$$

The stringent acceptance zone is ≤ 3512 ppm and is illustrated in *Figure 18*.

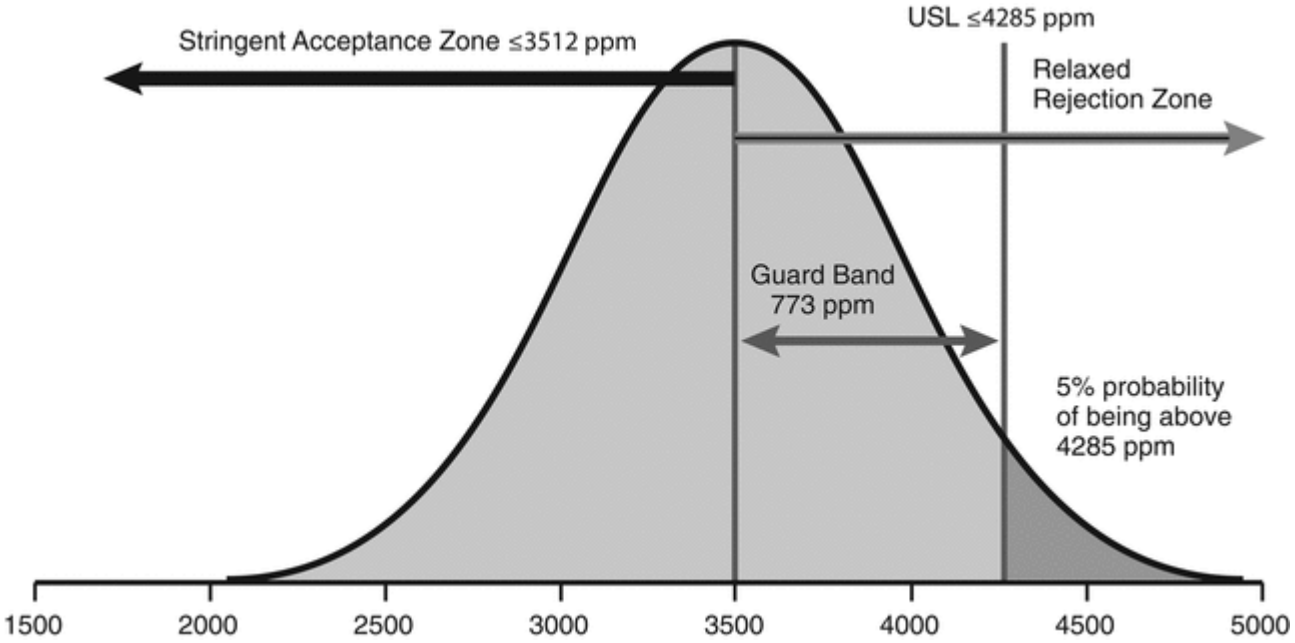

Figure 18. The stringent acceptance zone DR for methanol in a lot of drug substance. The dark shaded area shows that the probability of making a wrong decision is 5% for a lot that has a true concentration of 3512 ppm when analyzed with the analytical procedure that has a standard uncertainty of 470 ppm.

The DR can be stated as "the lot of DP will be considered compliant with the specification of methanol ≤ 4285 ppm if the probability of being above 4285 ppm is less than 5%, and noncompliant otherwise."

EXAMPLE 5

In this example, the coverage factor is used to calculate the TMU according to *Equation 1*. This is applicable when the product and production variability is insignificant.

A quality control laboratory needs a method to confirm the potency of a purchased drug substance. The drug substance is pure, and the producer of the drug substance characterized only two known impurities, with concentrations below 0.01%. The potency is determined by the

supplier using multiple definitive, state-of-the-art methods, so the uncertainty of the assigned potency is low. For these reasons the variability of the potency of drug substance, as stated on the Certificate of Analysis issued by the suppler, is negligible. The true value of the potency can be taken as 100.0%, with the specification at 98.0%–102.0%. The decision makers assign an acceptable probability of being wrong as 5%. This means that the probability the result is between 98.0% and 102.0% is 95%. For this, the coverage factor is 2. The range between the center value and the limit is 2.0%. The TMU is calculated as 1.0%.

$$\text{TMU} = U/k_p = 2.0\%/2 = 1.0\%$$

U = expanded uncertainty
k = coverage factor
p = acceptable probability of making a wrong decision

The simple DR is that "the lot of drug substance will be considered compliant if the probability the result is within the specification limit is ≥ 95% and considered noncompliant otherwise."

The analytical procedure should have no bias and an associated standard uncertainty of ≤1.0% to meet this requirement. This is shown in *Figure 19*.

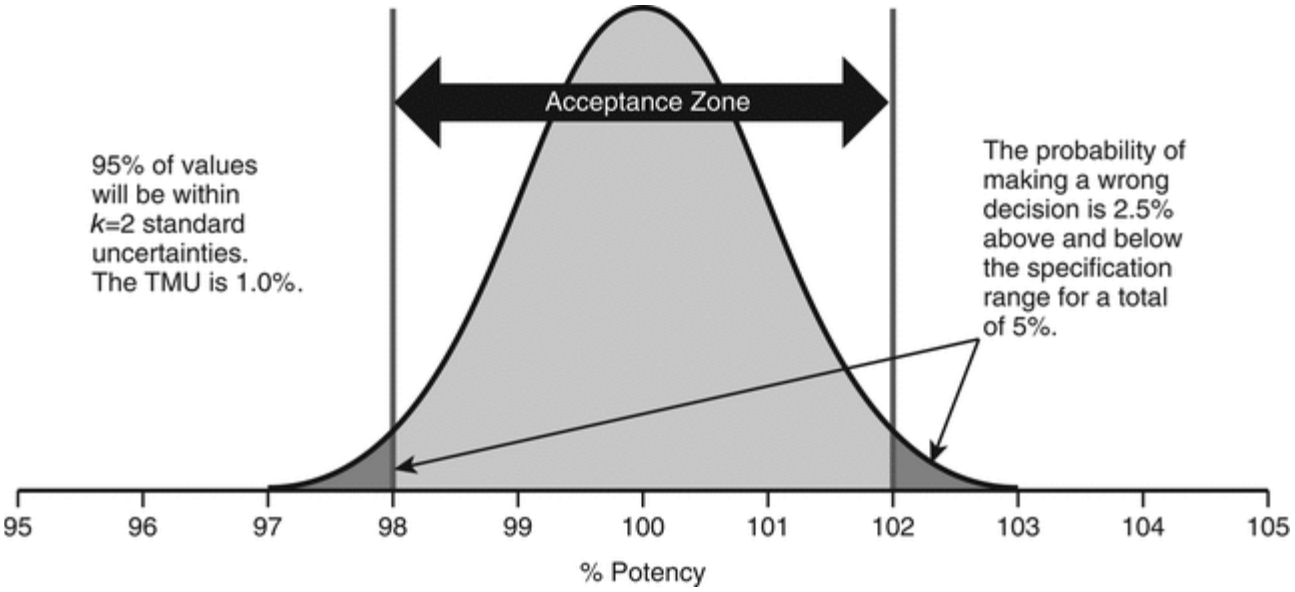

Figure 19. The distribution of the probability for a drug substance sample with a true value of 100.0% and a 95% probability the reportable value is within the acceptance zone.

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Analytical Control Strategy

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ABSTRACT The concepts of quality risk management (QRM), analytical control strategy (ACS), and knowledge management (KM) were briefly introduced in a previous *Stimuli* article titled *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification*, published in *PF* 39(5). In this *Stimuli* article, the USP Validation and Verification Expert Panel provides a more in-depth discussion on how an ACS that has been developed, maintained, and updated using the QRM process described in ICH Q9 (*1*) can improve the decision-making methodology during the lifecycle of the analytical procedure. This article explains how the ACS needs to be maintained in order to stay current and ensure that the analytical procedure will deliver a reportable value that meets the analytical target profile (ATP) requirements continuously throughout the analytical procedure lifecycle. A comprehensive discussion is also provided on the development of the ACS, how it applies to sample preparation and measurement, and how a suitable replicate strategy can be developed to ensure that the ATP is met. The Expert Panel would appreciate any feedback on the suggested approach, as well as any alternative approaches for consideration.

In this article, the following questions are considered:

- What is the ACS?
- What is the relationship between the ACS and the ATP?
- What is the QRM process and how can it be applied to an analytical procedure?
- How does the ACS apply to the product lifecycle?

Examples of the following are provided:

- How to develop an ACS using the QRM process
- How to develop and apply a risk-based replicate strategy to minimize variability (*Appendix*)

This article is intended to be a companion to a separate *Stimuli* article discussing the ATP, appearing in the same issue of *PF*.

INTRODUCTION

Fundamental to the concept of quality by design (QbD) is to start with the end in mind. When a QbD approach is applied to a pharmaceutical manufacturing process, the initial step is to develop a quality target product profile, which defines the design criteria for the product and forms the basis for the development of the product critical quality attributes (CQA) and control strategy. The same QbD concepts can be applied to the design and development of analytical procedures by considering the reportable value as the product of an analytical procedure. In this case, an

analytical target profile (ATP) is prepared, which forms the basis for development of the analytical control strategy (ACS).

To ensure that the requirements defined in the ATP (*2*) are met, one must identify those analytical procedure variables that have the potential to impact the reportable value (accuracy and precision). It is important to understand how variations in these variables impact the results and to define controls that ensure the target criteria are met.

WHAT IS THE ANALYTICAL CONTROL STRATEGY?

In alignment with ICH Q10 (*3*), the ACS is a planned set of controls, derived from an understanding of the requirements for fitness for purpose of the reportable value, an understanding of the analytical procedure as a process, and the management of risk, all of which ensure the performance of the procedure and the quality of the reportable value, in alignment with the ATP, on an ongoing basis. Once it has been derived from management of risk, the ACS should lead to assurance of consistent quality of the output of the analytical procedure in alignment with the ATP. Theoretically, each and every step in the analytical procedure, from sampling to the final reportable value, can potentially be a contributor to the measurement uncertainty of the reportable value.

The evaluation of the risk posed by each variable and how it may impact the reportable value should be based on scientific knowledge, prior experience, and experimentation. Using quality risk management (QRM) proactively will lead to an understanding of the linkage between procedure variables and the accuracy and precision of the reportable value as well as interdependencies of the different variables. Strategies for the analytical procedure controls can be designed to reduce input variation, adjust for input variation to reduce its impact on the output, or combine both approaches. This systematic approach should ensure that the performance of the analytical procedure can be explained logically and/or scientifically as a function of procedure parameters/inputs, and is most effective when supported by good knowledge sources. The sources of knowledge can include: prior knowledge (public domain or internally documented); expertise (education and experience) or experience with similar applications; and product-/process-specific knowledge developed and/or acquired with each application as it becomes available. QRM and knowledge management (KM) are enablers and support the ACS throughout the analytical procedure lifecycle, from development through qualification and routine commercial use. The linkages between ACS, QRM, and KM are illustrated below in *Figure 1* (*4,5*).

Figure 1. Linkages between the ACS, QRM, and KM.

Analytical Unit Operations

Development of the ACS requires consideration of all aspects of an analytical procedure that might impact the reportable value. A unit operation is any part of a potentially multiple-step process that can be considered to have a single function with clearly defined boundaries. For an analytical procedure, three distinct unit operations can be identified, as shown in *Figure 2*. The unit operations for an analytical procedure are illustrated and described below.

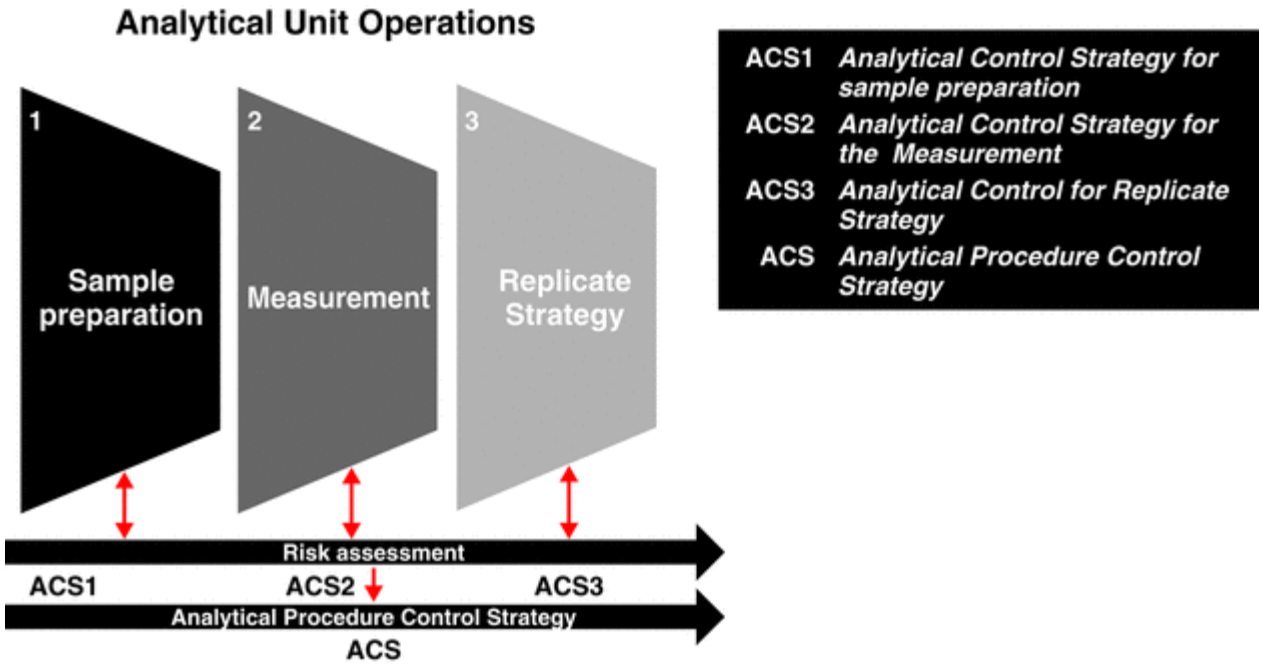


Figure 2. Three distinct unit operations of the analytical procedure.

TEST SAMPLE PREPARATION

The objective of the sample preparation unit of operation is to convert the laboratory sample into a test preparation suitable for measurement. This analytical unit operation includes all steps starting from sampling the batch to provide a representative laboratory sample for the testing lab; to laboratory handling, sub-sampling, splitting, and sample preparation procedures such as weighing, extraction, and dilutions; to the final analytical test preparation or solution. Although the sampling and representativeness of the laboratory sample are essential elements, and their potential impact on measurement uncertainty cannot be ignored, these will not be discussed in this article (*6*).

The sample preparation step needs to ensure that the analyte does not undergo any significant changes in its properties from the moment of sampling to the time when the actual analysis is carried out. These changes can be chemical, microbial, enzymatic, or physical. Depending on the technique used, this step can take a large variety of forms. It can be as simple as dissolving a known amount of drug substance in a known volume of solvent, or as complicated as complex extractions or derivatization. In all cases, the objective of this step is to maintain the integrity of the analyte in the sample (*7*). For example, where the test sample is a solution, there are two aspects that need to be considered: completeness of the dissolution/extraction and stability of the analyte from the time of preparation until the measurement. For an infrared identification test, the preparation of the pellet should not induce form changes; for a dissolution test, it is important to maintain the amount dissolved from the time of sampling from the dissolution vessel to the measurement [high-performance liquid chromatography (HPLC) or ultraviolet].

MEASUREMENT

This is the step where a relationship between the analyte in the test sample and a signal that can be detected or measured is established. This relationship can be qualitative (e.g., identification tests), or quantitative, where a mathematical relationship between the

concentration of the analyte in the test solution or test sample and the measurable signal can be established. The analysis can be instrumental or classical (wet chemistry) and can employ a large variety of techniques. Classical quantitative analysis is achieved by measurement of weight or volume, while instrumental procedures use a detector to measure physical or chemical quantities of the analyte such as light absorption, fluorescence, or conductivity.

For this step, it is important to ensure that the signal measured or observed is specific to the analyte, and the signal response and concentration are defined by a known relationship over the concentration range of interest.

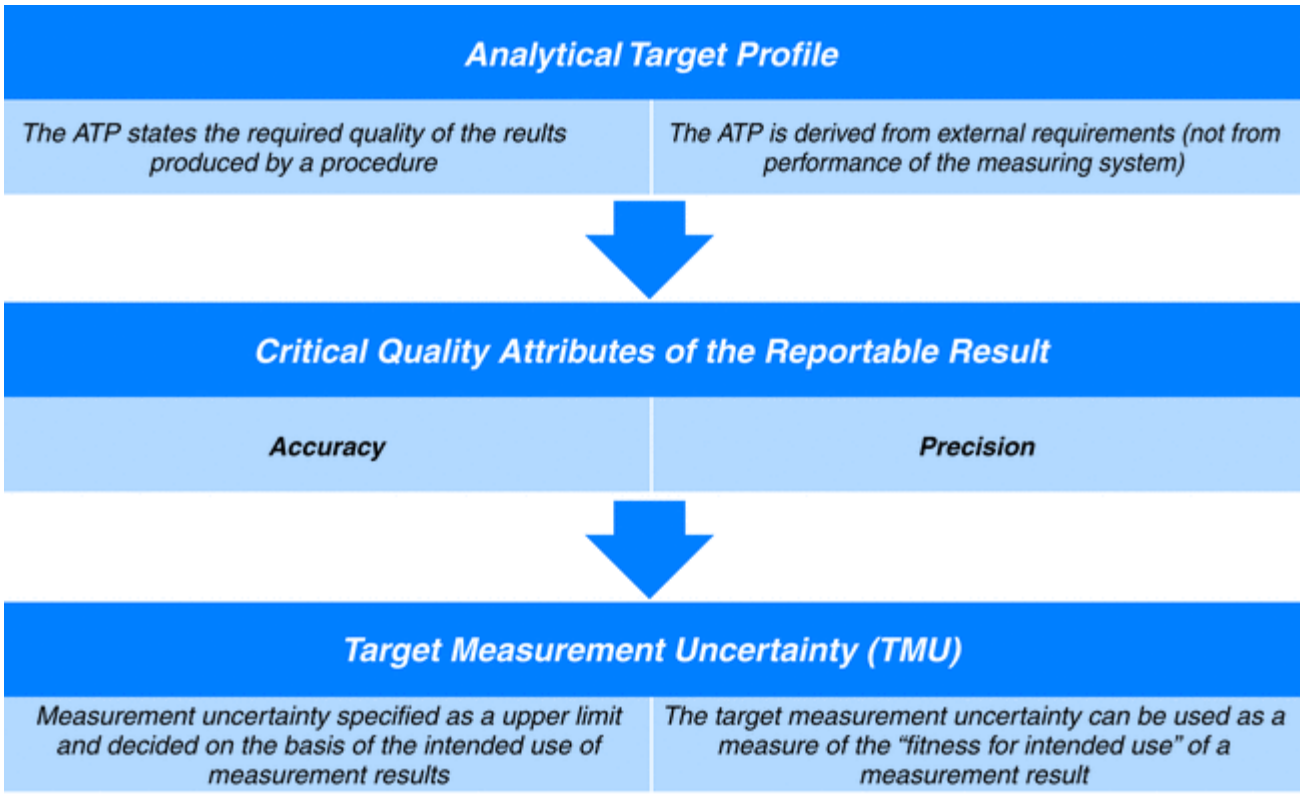
REPLICATE STRATEGY

USP General Notices, 7.10. Interpretation of Requirements, states, "The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented." Depending on the analysis unit operation, these individual determinations—or "format of the reportable value" (see *Biological Assay Validation* ⟨1033⟩) —may include several replicate levels, such as injections and sample preparations in liquid chromatography, or applications of the same test solution, several test solutions, and several titer plates (independent series) in the case of bioassays. The impact of increasing the replicates on the precision of the reportable value depends on the corresponding variance contribution, because increasing the number of injections will have no impact on the variance of the sample preparation, for example. Therefore, it is the objective of precision studies to achieve a reliable estimate of the variance contributions of an analytical procedure as the basis of a scientifically sound definition of the replicate level (see *Appendix*).

Because the unit operations are sequential, and some of the process steps are linked by input-output relationships, it is important to consider controls for unit operations that have an impact on downstream processing and/or end-product quality. For example, the output of the sample preparation unit of operation is input in the measurement unit. Therefore, aspects and attributes of the test sample preparation may affect the measurement. For example, for an HPLC procedure, a suitable control strategy has been developed and optimized to ensure stability and extraction of the analyte. However, if the sample solvent is not compatible with the mobile phase, or the concentration of the analyte in the test sample does not afford adequate detection or is out of the detector's linear range, this will introduce bias or increase variability, and ultimately the accuracy and precision of the reportable value will be compromised and the requirements of the ATP will not be met. It should be noted that some of these variables tend to be applicable on a general basis, and controls for these have already been implemented. Examples of variability can originate from weighing, pipetting, volumetric flasks, HPLC flow rate, or injection volume, just to name a few. These are controlled by the instrument/equipment qualification/calibration programs that are an integral part of a firm's good manufacturing practices. Other variables are specific to the product, technique, and/or analytical procedure.

What is the relationship between the ATP and ACS?

The relationship between the ATP, CQA of the reportable value, and the target measurement uncertainty (TMU) are illustrated in *Figure 3* below.



International Vocabulary of Metrology the International Vocabulary of Metrology–VIM editi VIM edition 3 Guide JCGM 200:2008 [ISO/IEC Guide 99:2007]
www.bipm.org/en/publications/guides/vim.html

Figure 3. Relationship between the ATP, CQA, and TMU.

The ATP considers the acceptable level of risk of making an incorrect decision with the reportable values. Setting decision rules (*8*) may assist in this area but they are not always necessary. As a first consideration, the acceptable level of risk should be linked to patient safety and efficacy and the risk of erroneously accepting a batch that does not meet specifications. Manufacturer risk—i.e., the risk of erroneously rejecting a lot that meets specifications [a false out-of-specification (OOS) result]—can also be considered when criteria for risk are established. Accuracy and precision are CQAs and are described by the measurement uncertainty and bias associated with the reportable value generated by the analytical procedure. The TMU is the maximum acceptable uncertainty for the reportable value in order to meet the ATP and therefore accomplish the fitness-for-purpose requisite for the analytical procedure. The TMU (if stated in the ATP) can be used as a target for development criteria for the analytical procedure qualification and standard for monitoring the performance of the analytical procedure during routine use. The role of the ACS is to ensure that the TMU is met on a consistent basis over the entire lifecycle of the analytical procedure, and therefore the reportable value conforms to the ATP.

A detailed discussion on accuracy, bias, total error, and TMU is provided in the *Analytical Target Profile: Structure and Application throughout the Analytical Lifecycle Stimuli* article intended to be a companion to this article.

It is not the intent of this paper to discuss the theory and provide guidance on calculation of measurement uncertainty and TMU. Detailed guidance on these concepts is available (*9–11*).

What is the QRM process and how can it be applied to an analytical procedure?

The path to an effective ACS is the QRM process. The QRM for an analytical procedure is a systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the analytical procedure lifecycle (see *Figure 4*). Although ICH Q9 (*1*) refers to the risk to the quality of the pharmaceutical product, and ultimately the impact on the patient, in the context of the analytical procedures the risk refers the quality of the reportable value, which is the product of the analytical procedure.

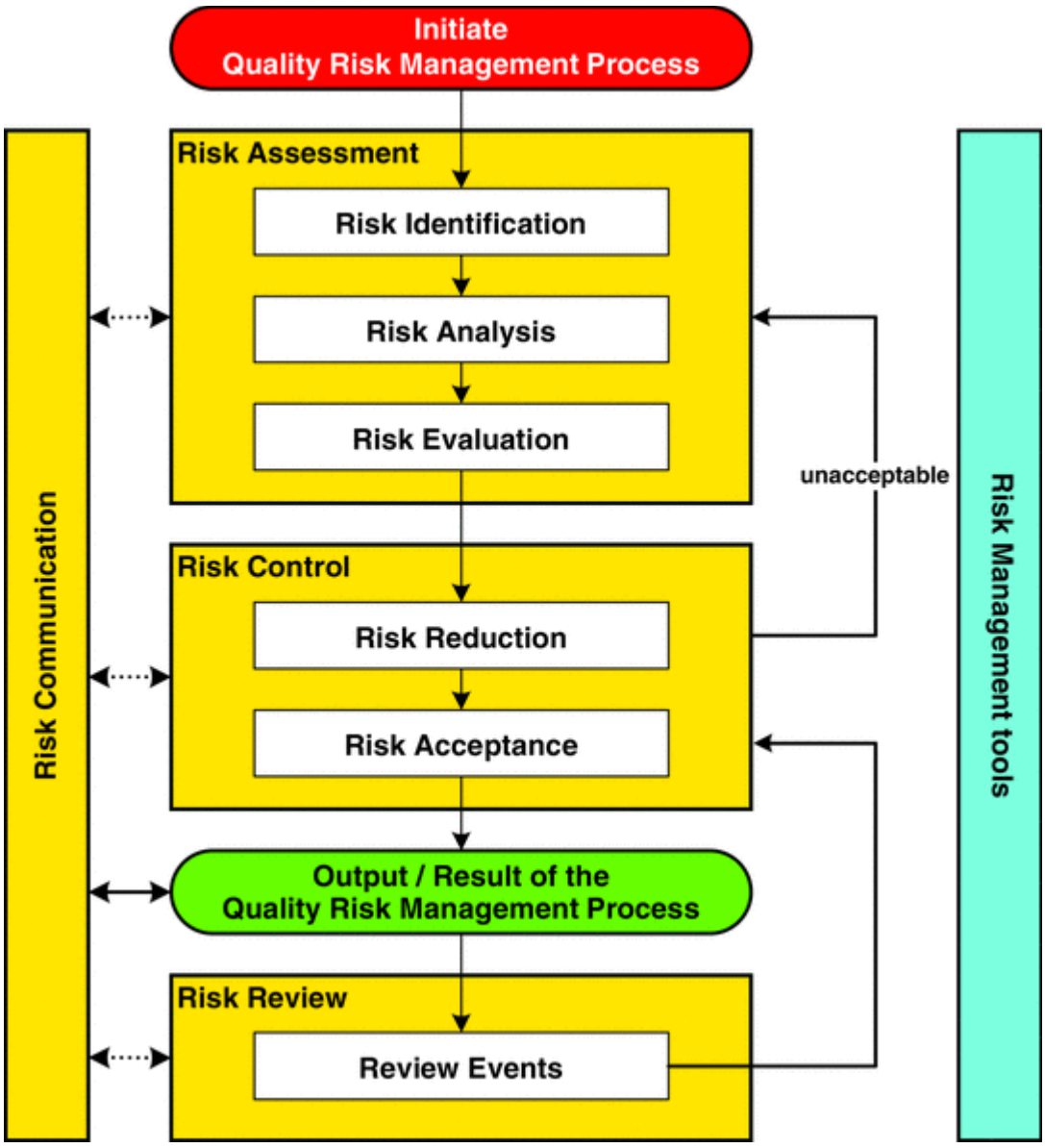


Figure 4. Overview of a typical QRM process (ICH Q9).

The ACS is the totality of steps taken to eliminate the risk or control it at an acceptable level. The risk is a combination of severity, probability, and detectability. The severity rating relates to the actual impact on the CQA, and it will not change as result of the QRM process. However, reducing the probability of occurrence and increasing the detectability are steps that will reduce the risk to an acceptable level.

Risk Assessment

This is the stage of learning and developing understanding about which analytical variables, such as material attributes and analytical procedure parameters, affect the quality attributes of the reportable value and how they have these effects. Based on scientific principles, experience, and prior knowledge, the following types of variables may be considered for analytical procedures: 1) variables related to materials (e.g., reagents, solvents, or reference standards); 2) procedure variables (e.g., equipment/instrument settings); and 3) environmental variables (e.g., light, moisture, or temperature). Not all variables need to be studied. At this stage, decisions can be made as to which of these variables can be controlled and which ones do not represent risk (therefore, they will not be subject to further consideration). By completing the risk assessment step, one will be able to answer the following questions: What might go wrong? What is the likelihood (probability) it will go wrong? What are the consequences (severity)?

1. Risk identification is the first step in the risk assessment process. It requires a systematic use of information to identify hazards referring to the risk question or problem description. Risk identification addresses the question, What might go wrong?
2. Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors into the estimation of risk. Risk analysis addresses the question, What is the likelihood (probability) it will go wrong?
3. Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluation considers the strength of evidence for all three of the fundamental questions. Risk evaluation addresses the question, What are the consequences (severity)?

Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Risk control might focus on the following questions: Is the risk above an acceptable level? What can be done to reduce or eliminate risks?

1. Risk reduction focuses on processes for mitigation or avoidance of risk to quality when it exceeds a specified (acceptable) level. The risk assessment step provides the knowledge and understanding as to which of the variables studied impact the accuracy and precision of the reportable value and will ultimately result in increasing the measurement uncertainty to an unacceptable level (i.e., exceeding the TMU). These will then be the variables that will be subject to controls developed at this stage. It is also important to note that this process is iterative; if some of the critical variables cannot be controlled adequately, the analytical procedure development/design stage may need to be revisited and adequate changes implemented. Once a preliminary ACS is developed, it is recommended to carry out a verification step to ensure that all critical variables have been studied and the sources of variability and bias have been eliminated or reduced to an acceptable level so the analytical procedure will generate a reportable value that meets the ATP.
2. Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not

specified. Risk cannot be completely eliminated. The objective of the ACS is to reduce and maintain the risk at an acceptable level. An analytical procedure may be used over a long period of time, and it can be expected that materials, equipment, or other factors may change. An example that most analytical chemists are familiar with is the column-to-column variability. Although incorporating column age as a variable in the risk assessment process is reasonably feasible, the performance of the column over a number of years cannot be predicted or assumed. The risk associated with using a different batch of packing material cannot be controlled, but the risk can be reduced by including a system suitability check, such as resolution, as a mechanism for detecting unacceptable variation. There may be other potential sources of residual risk such as changes in reagents or equipment.

There are several examples of publications on risk assessment and applications of QRM methodology to analytical procedures (*12–14*).

Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Any learnings gained during the QRM process as described above should be documented in order to communicate shared knowledge. KM is an important component of risk communication.

Risk Review

Risk review should be an ongoing part of the quality management process. The performance of the procedure should be reviewed on a regular basis. This is part of the routine monitoring process and is discussed later in this document.

QRM Methodologies

Risk assessment tools are used to support science-based decisions. It should be noted that no single tool is appropriate for all cases, and specific risks do not always require the same tool. A great variety of tools is listed below, but other existing or new ones might also be used. It is recognized that different companies, consultancies, and competent authorities may promote the use of different tools based on their culture and experiences; some of these are listed below. It is important to select the most appropriate tool for a given process, with the understanding that the level of formality and extent of documentation will be dictated by the risk in question. Results of the risk assessment can be presented either qualitatively or quantitatively. Some examples of risk management methodologies are provided below.

Basic risk management facilitation methods include flowchart, check sheets, process mapping, cause and effect diagrams (Ishikawa/fishbone).

Better-known risk evaluation and analysis methods include failure mode effects analysis (FMEA), failure mode effects and criticality analysis (FMECA), fault tree analysis (FTA), hazard analysis and critical control points (HACCP), hazard operability analysis (HAZOP), and risk ranking and filtering. It is not within the scope of this article to detail these, but excellent sources of information are available in several publications. An outstanding summary on the tools and how they are applied is provided in “Quality Risk Management ICH Q9; Annex I: Methods & Tools” (*15*).

Design of Experiments

Design of experiments (DoE) is a fundamental methodology for the QRM process. It is a systematic method to determine the relationship between potential variables of an analytical procedure and their impact on the output (i.e., the reportable value). In other words, it is used to find cause-and-effect relationships. In a properly constructed DoE, variables that could potentially impact a procedure will be identified and varied simultaneously in a carefully planned manner such that their individual and combined effects on the output can be identified. Fractional factorial designed experiments can be used to efficiently screen variables to determine which have the greatest impact on the output, whereas full factorial designed experiments will help to reveal significant interactions among the variables. This methodology allows for a significant reduction in the number of experiments needed, compared with the classical one-variable-at-a time approach where the rest of the variables are held constant. Furthermore, DoE is more robust and feasible for a complicated process. DoE also utilizes statistical data treatment, which allows clear determinations regarding the significance of a variable and/or its interactions with regard to the output.

DEVELOPMENT OF AN ACS USING THE QRM PROCESS: STAGE 1

In this article, an example is provided in which a few variables were selected to illustrate how the principles of QRM can be applied. Using these principles, a comprehensive ACS can be developed by considering possible variables and systematically applying the QRM approach to each of these. The example uses a simplified scenario and significantly fewer variables than is typical in real cases. The development of an ACS can be more complex when the number of variables is significantly greater than in this example. However, the example is useful in providing a "walk through" of the process, including the steps involved, the scientific considerations, and the use of risk management tools.

The QRM process begins once an appropriate analytical technique has been selected and tentative procedure conditions have been chosen. At this time, as a result of the preliminary screening, major sources of bias may also be identified and reduced or eliminated by the choices of technology and procedure conditions. The aim of the QRM process is to take the proposed procedure conditions and identify appropriate controls on the process inputs that will ensure the desired process output (i.e., a reportable value that meets the requirements stipulated in the ATP).

The first step in the QRM process is the risk assessment, which starts with the risk (hazard) identification. At this time, the question is, What might go wrong? The risk identification step begins by developing a process flow chart highlighting the key steps involved in the analytical procedure. For an HPLC procedure, an example of a process flow chart is shown in *Figure 5*.

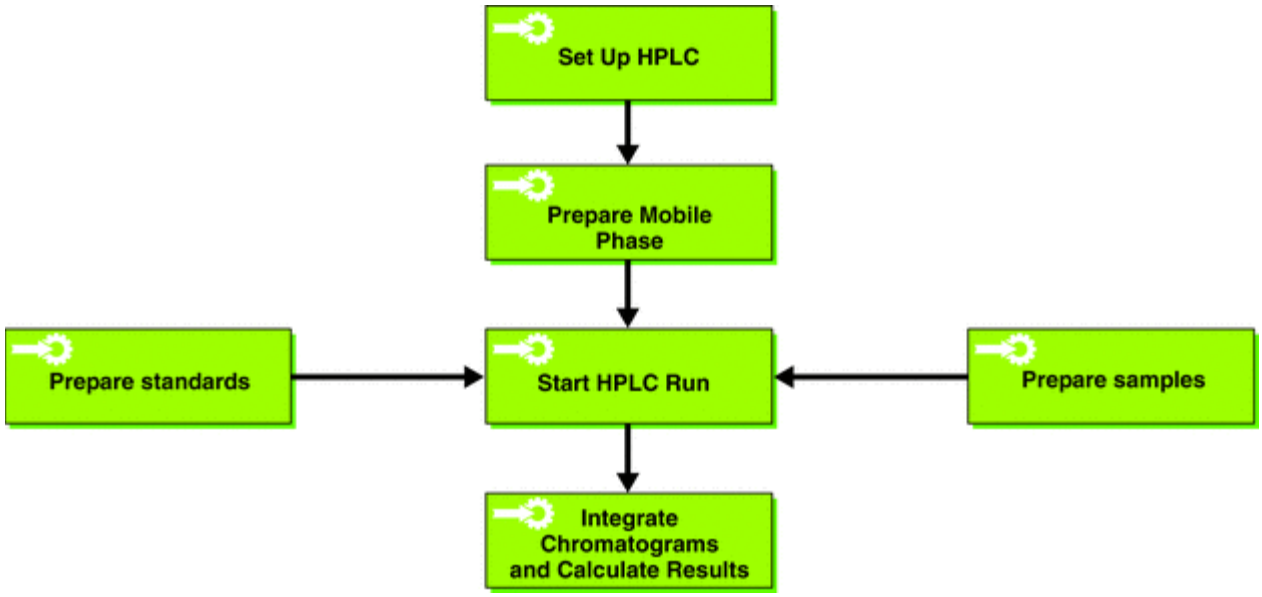


Figure 5. An example of a process flow chart for an HPLC procedure.

Each high-level step in the process can be further broken down using process mapping tools. For example, the sample preparation step can be broken down into a number of detailed sub-steps, as shown in *Figure 6*.

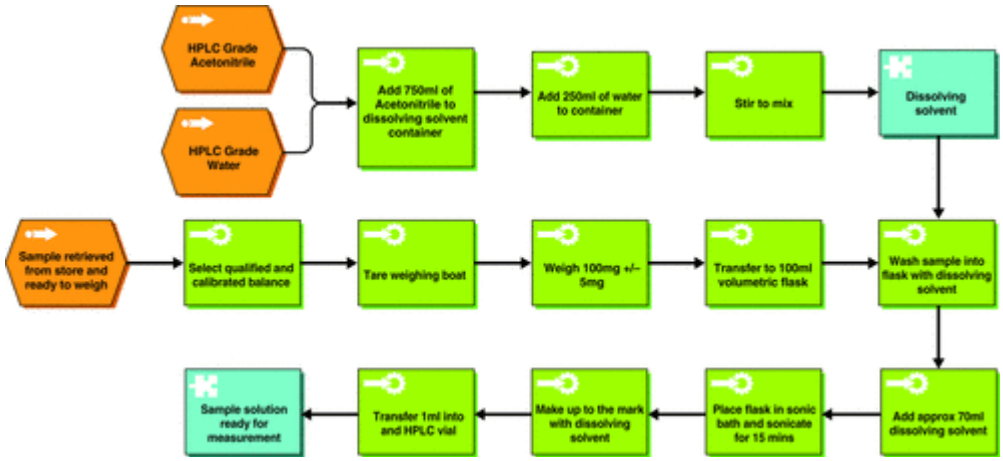


Figure 6. The sample preparation step, broken down into detailed substeps.

This detailed process map can then be used to identify the variables associated with the process. Ishikawa diagrams (fishbone diagrams) can be used in conjunction with the detailed process maps to identify the potential variables. In the example below (*Figure 7*), a range of potential variables associated with the use of the sample preparation step is illustrated.

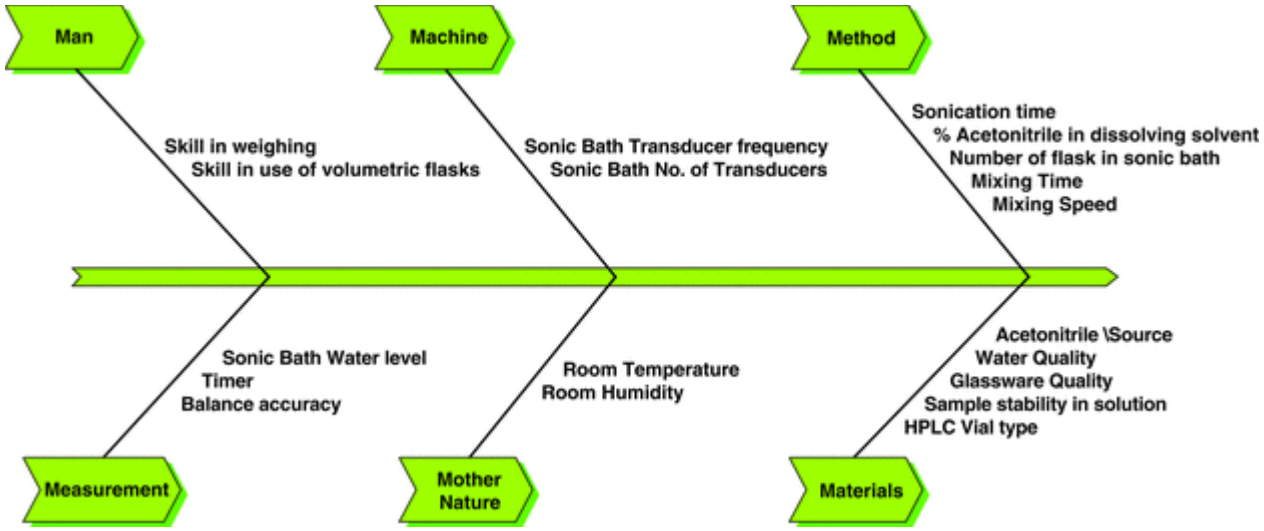


Figure 7. Ishikawa (fishbone) diagram, used to identify potential variables.

Note that the Ishikawa diagram is used in helping to brainstorm potential variables and, as with any type of brainstorming, no judgment should be made at this stage on whether a variable is likely to be critical or not. The aim is simply to ensure that the list of variables is as comprehensive as possible.

Risk Assessment

1. RISK IDENTIFICATION

The first step in the assessment is risk identification. It answers the question, What can go wrong?

To illustrate this and the subsequent steps in the QRM process, we will focus on a small selection of variables associated with the sample preparation and HPLC setup steps in the process flow diagram. This is a subset of the total list of variables that may need to be examined.

Variables for sample preparation unit of operation:

- % Acetonitrile in the sample solvent
- Sonication time
- Analyst skill in sample preparation
- Humidity of the laboratory
- Quality of acetonitrile used in the dissolving solvent
- Variables for the measurement unit of operation (HPLC setup):
- Column temperature
- % Acetonitrile in the mobile phase
- Batch of packing material used in the HPLC column
- Quality of the acetonitrile

For most samples, the relative organic/aqueous composition of the mobile phase is likely to be important in ensuring complete dissolution of the sample, which if not achieved would lead to an inaccurate result. Also, where the solution composition is critical to dissolution, there is an increased likelihood that minor variation in the preparation of the dissolving solvent could lead to accuracy and/or precision issues when different batches of sample solvent are prepared.

Similarly, sonication time may be important if the sample does not dissolve easily. The humidity of the laboratory may be important if the sample is impacted by humidity (e.g., it degrades or absorbs moisture). Analyst skill is important, as mistakes in sample preparation can impact both accuracy and precision.

The column temperature may affect retention time, resolution, and peak shape, potentially affecting resolution (accuracy). Effects on peak shape can potentially lead to inconsistent integration (precision). The percent acetonitrile in the mobile phase may impact the accuracy as it may be critical to achieving resolution of interfering peaks and may also impact precision by affecting the peak shape. The batch of packing material can be important to the quality of the separation and hence the accuracy of the results.

2. RISK ANALYSIS

The next step in the assessment is the risk analysis. The risk analysis answers the question, What is the likelihood (probability) it will go wrong?

Once all the potential hazards have been listed, the risk identification step is complete and the process then moves to the risk analysis step. At this step we are trying to estimate the risk associated with each of the variables. When considering the variables identified in the risk identification step, it will be possible to identify certain variables which, from prior knowledge, will be important to control within a certain range (controlled variables). Some of these variables will be difficult or impractical to control or are known to be of low risk (noise variables), whereas some will require the performance of experiments to understand how critical they are and to determine the range over which they need to be controlled. The risk analysis process aims to identify, from the many variables in the output from the risk identification step, those for which an understanding of their impact on the reportable value is required in order to establish appropriate control limits.

A “heat map” can be a valuable tool to support a preliminary qualitative assessment of risks. The heat map provides a visual indication of which variables are considered to have a potentially strong impact (red), medium impact (amber), or minor impact (green) on the procedure performance in terms of accuracy and precision that can be related to the requirements of the ATP. Heat maps are dependent on previous knowledge and expertise of the chemist and the intended purpose of the analytical procedure. Readers may disagree with the assignment of the colors in the example but should consider this representative of the author’s procedure, and may adapt the theory illustrated here to suit their own scenario. Based on the nine variables above, the heat map in *Table 1* was created.

Table 1. Example of a Heat Map

Analytical Unit of Operation	Variable	Potential Hazard	Accuracy	Precision
	% Acetonitrile in the sample dissolution solvent	Completeness of the Dissolution of the sample		
Sample preparation	Sonication time	Completeness of the Dissolution of the sample		
Sample preparation	Analyst skill	Incorrect sample preparation Weighing, dilutions, use of volumetric flask		
Sample preparation	Humidity of the laboratory	Moisture absorption can lead to inaccurate weighing or degradation		
Sample preparation	Grade of acetonitrile used in the dissolving solvent	Potentially can impact if contaminants interfere with the analyte		
Measurement (HPLC SetUp)	Column temperature	Column performance, resolution, peak shape		
Measurement HPLC SetUp	% Acetonitrile in the mobile phase	Column performance, resolution, peak shape		
Measurement (HPLC SetUp)	Batch of packing material used in the HPLC Column	Column performance, resolution, peak shape		
Measurement (HPLC SetUp)	Quality of acetonitrile	Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength		

The rationale for the risk level assignments is as follows. At this stage it is useful to separate the variables into those that can be controlled, those that cannot be controlled, and those that will be subject to further experimentation. An uncontrollable variable is one that may have an impact on the accuracy or precision of the data, but it is not possible to directly measure the relationship between the variable and the response in an experiment. In our example, it is not possible to understand and control how potential variability of column packing of future batches might impact the chromatography. Although these variables are not directly controllable and therefore not included in a DoE, they are still potential hazards that need to be considered in the ACS (see the example ACS below for how this risk might be mitigated).

The quality of acetonitrile used can be important for ensuring that no contamination is observed in the chromatography. An adequate control of the quality of the acetonitrile can be implemented by specifying the grade (HPLC) or HPLC and low-UV cut off, depending on the analytical wavelength, so further assessment of this variable will not be carried out.

Analyst skill is controlled by the good manufacturing practice (GMP) requirement in the form of mandatory training and demonstration of competence. Therefore, this variable is considered low

risk. (Analyst-to-analyst or laboratory-to-laboratory performance of the analytical procedure will be evaluated as part of the intermediate precision study).

Humidity for both the sample preparation (the material is not hygroscopic or moisture sensitive) and the HPLC measurement step was assessed as low risk for this application, thus there was no need for it to be studied further.

Batch-to-batch variability of the column packing cannot be studied. Adequate performance of the column will be verified by the system suitability requirements to ensure performance of the analytical procedure. This risk has been mitigated by increasing detectability of the variation. The column-to-column variability, however, needs to be accepted as residual risk (see *Risk Acceptance* below).

This leaves four controllable variables that are considered to present potential risk. They are then studied in a DoE to determine the sensitivity of the variables, eliminate bias, and determine ranges where the quality requirement of the reportable value established in the ATP will be met. (When a significant number of variables requires an experimental study to understand their impact, a "screening DoE" may be performed first, to identify those with the greatest impact on the quality of the reportable value). The four selected variables and ranges for study are presented in the table below. The mid level is presented as the proposed condition of the analytical procedure. At this time, the range (high to low) needs to be expanded beyond values expected as normal fluctuations typically encountered during routine use. This is done to afford understanding and indisputably identify relationships if they exist between the variation and impact on the CQA of the reportable value. DoE experiments can easily be run using software to analyze a series of samples under the conditions stated in *Table 2*.

Table 2. Conditions for the DoE Experiment

Variable	High Level	Mid Level	Low Level
% Acetonitrile in sample solvent	80	65	50
Sonication time (min)	20	12	5
Column temperature (°)	45	35	(ambient; 25)
% Acetonitrile in mobile phase	80	70	60

The information from a DoE study indicated that all four of these variables (% acetonitrile in the sample solvent, sonication time, column temperature, and % acetonitrile in the mobile phase) have a strong correlation with the accuracy and/or precision of the data (i.e., the "severity of harm" from these variables is high). The risk assessment needs to consider not only the severity of harm (or strength of the relationship between the input variable and the desired output) but also the likelihood of occurrence—i.e., what is the probability that this variable will vary to the extent that quality of the reportable value will be impacted? The assessment of the severity can be combined with the assessment of probability of variation to give an overall risk score, and the resulting risk score can be further reduced by incorporating analytical procedure performance checks in the system suitability (as described earlier in *Risk Control*).

Risk Evaluation

Risk evaluation compares the risk versus the given risk criteria. The risk acceptance criteria (or the risk protection threshold) for this step is the TMU. Therefore, a risk target of 10 will correspond to the TMU. Any variable or combination of variables that equal or exceed the risk target of 10 will need to be controlled in ranges that will ensure the required performance of the procedure. If the above example is evaluated against the criteria, it would be concluded that all four of the variables exceed TMU and therefore should be subject to ACS (*Table 3*).

Table 3. Example of Risk Evaluation

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in sample solvent	4	3	12
Sonication time (min)	4	3	12
% Acetonitrile in mobile phase	5	4	12
Column temperature (°)	5	2	10

Risk Control

RISK REDUCTION

Risk reduction can include actions to reduce the risk, reduce the probability, or improve the detectability. The DoE essentially can establish a quantitative relationship between the variable studied and the response (i.e., the TMU). Therefore, the DoE can also be used to predict ranges for the variables studied where the TMU will be met. The DoE results suggest that, in the ranges specified in *Table 4* below, the criteria will be met.

Table 4. Conditions for the DoE Experiment

Variable	High Level	Mid Level	Low Level
% Acetonitrilein sample solvent	70	65	60
Sonication time (min)	15	12	10
Column temperature (°)	40	35	30
% Acetonitrile in mobile phase	75	70	65

At this time, a verification step confirms that the ranges predicted are acceptable for three of the four variables studied. The % acetonitrile in the mobile phase, while it meets the risk threshold, is still marginal. As previously stated, because these variables affect the CQA, the severity component of the risk does not change; the risk can be reduced to an acceptable level by decreasing the probability of variation and increasing the detectability needed to reduce the risk (see *Table 5*).

Table 5. Example of Risk Evaluation

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in sample solvent	4	1	4
Sonication time (min)	4	1	4
% Acetonitrile in mobile phase	5	2	10
Column temperature (°)	5	1	5

Adding a system suitability requirement to detect the hazard, before the harm occurs to the reportable value, reduced the risk from 10 to 2.5, which is well below the risk acceptance threshold (see *Table 6* and *Table 7*).

Table 6. Risk Assesment

Variable	Severity (from DoE) (1 low, 5 high)	Probability of variation (1 low, 5 high)	Detection	Risk Score (SxP)/D*
% Acetonitrile in mobile phase	5	2	4	2.5

*S: Severity; P: Probability; D: Detectability

Table 7. Risk Assessment After Implementation of the ACS

Analytical Unit of Operation	Variable	Potential Hazard	Control Strategy	Accuracy	Precision
Sample preparation	% Acetonitrile in the sample dissolution solvent	Completeness of the dissolution of the sample	Specify% acetonitrile in the sample solvent 65% +/– 5%		
Sample preparation	Sonication time	Completeness of the dissolution of the sample	Sonication time between 10 and 15min		
Sample preparation	Analyst skill	Incorrect sample preparation: weighing, dilutions, use of volumetric flask	Controlled by training mandated by GMP		
Sample preparation	Humidity of the laboratory	Moisture absorption can lead to inaccurate weighing or degradation	No impact		
Sample preparation	Quality of acetonitrile used in the dissolving solvent	Potentially can impact if contaminants interfere with the analyte	Specify grade of acetonitrile		
Measurement (HPLC Set Up)	Column temperature	Column performance, resolution, peak shape	Specify column temperature, 30 +/– 5°		
Measurement (HPLC Set Up)	% Acetonitrile in mobile phase	Column performance, resolution, peak shape	Specify % acetonitrile in the mobile phase 70% +/– 5%. Add system suitability requirement		
Measurement (HPLC Set Up)	Batch of packing material used in the HPLC column	Column performance, resolution, peak shape	Add system suitability requirement		
Measurement (HPLC Set Up)	Quality of acetonitrile	Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength	Specify grade of acetonitrile		

RISK ACCEPTANCE

Risk cannot be completely eliminated but it can be reduced to an acceptable level. As discussed earlier, the variability of the column packing for future columns cannot be controlled; and while the risk is reduced to an acceptable level, it cannot be eliminated completely. The composition of the sample solvent was established and verified using drug substance samples available to the

laboratory at the time of the analytical development qualification, and it is not likely to change during the product lifecycle. Therefore, the probability that the polymorph will vary from one lot to the next is negligible because the polymorph control is typically part of the drug substance specifications. However, because different polymorphs may have very different solubilities, in the case of a compendial procedure the suitability of the sample solvent should be verified as part of the procedure installation.

Although it is recognized that these types of studies are not new and an analytical chemist charged with developing an analytical procedure knows that important parameters need to be studied and optimized, historically these parameters have been evaluated in isolation, with no or little ability to fully understand the interactions between them. The USP Expert Panel believes that providing target acceptance criteria, linked holistically to the quality of the output, will trigger a systematic science- and risk-based strategy for development, qualification, and performance monitoring during routine use. This will improve overall performance of the analytical procedures by placing focus on the output. The output is held to the standard established in the ATP and directly linked to the fitness for purpose of the analytical procedure.

Today, computer-simulated experiments have prompted the development of new types of experimental designs and methods of analysis. These not only facilitate rational experimental designs, but also are able to assess a large number of variables with minimal experimentation and predict, based on data generated, the optimal ranges that will meet the target performance. This approach greatly facilitates the development of an ACS that, by design, is intended to be proactive. In other words, variables that are known or found to impact the quality of the reportable value are eliminated or limited to ranges where the impact is reduced to an acceptable level.

This is an important point in line with the QbD philosophy, which requires that quality be built into the product rather than relying solely on end-product testing. An ACS, in addition to placing controls on input variables, will also include a selection of system suitability tests that are intended to provide a means of verifying that the procedure is performing as expected. The combination of input controls and performance indicators, in the form of system suitability checks as components of a control strategy, is consistent with the principles described earlier in the QRM section. Thus, the input controls are aimed toward decreasing the probability of hazard occurrence, and the performance indicators in the form of system suitability are aimed toward increasing the detectability of hazards, thus minimizing the risk of harm to the quality of the reportable value.

Measures used to verify the adequate performance of an analytical procedure are, for example, %RSD for calibration standards and replicates, system suitability for chromatographic procedures, and resolution, plate count, or tailing factor. For an HPLC procedure, for example, replicate injections may be used to provide assurance that the system precision is satisfactory. Replicate sample or standard preparations provide assurance of the precision of the sample/standard preparation step, and a resolution check may be used to provide assurance that the accuracy of the procedure is not adversely affected by interference from other components in the sample. Ideally, system suitability checks should be designed to detect variation in the performance of a procedure in routine use. They should be based on an understanding of the risk and impact of variation, and the acceptance criteria used should be chosen to ensure that the measurement uncertainty does not exceed the TMU. A control sample (i.e., a homogenous and

stable sample with a defined value for the attribute being measured) can also be used to provide confidence in the accuracy of the data generated.

How the ACS Applies to the Product Lifecycle

STAGE 2: QUALIFICATION

The second stage in the lifecycle approach to validation of analytical procedures involves confirming (or qualifying) that the procedure meets the requirements of the ATP (typically, the accuracy and precision of the reportable value), in the facility where the procedure will be routinely operated. Note that many of the important analytical characteristics, such as linearity, range, specificity, and sensitivity, will have been evaluated and characterized during stage 1. This qualification activity takes place once the initial ACS has been defined. Note that the result of the qualification activity may indicate that the ACS needs to be extended. An example of this could be a change to the replication strategy for samples and standards (see *Appendix*).

STAGE 3: CONTINUAL VERIFICATION

Once an ACS has been established and qualified as part of the analytical procedure, it is important that the performance of the procedure is maintained throughout the lifecycle (*16*). It is important therefore to have mechanisms for:

- Routine monitoring of the performance of the analytical procedure
- Controlling changes made to the analytical procedure

Routine Monitoring

It is beneficial to have a system for the collection and evaluation of information and data about the performance of the analytical procedure. This allows for detection of undesirable variability and trends. Many of the concepts and approaches described in *FDA Guidance for Industry: Process Validation: General Principles and Practices* (*17*) can also be applied to analytical procedures to ensure that the data they produce is valid throughout their lifecycle of use, as discussed in *FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics* (*18*). In addition, *Analytical Data—Interpretation and Treatment* ⟨1010⟩ (*19*) states that "Verifying an acceptable level of performance of an analytical system in routine or continuous use can be a valuable practice. This may be accomplished by analyzing a control sample at appropriate intervals, or using other means such as variation among the standards, background signal-to-noise ratios, etc. Attention to the measured parameter, such as charting the results obtained by analysis of a control sample, can signal a change in performance that requires adjustment of the analytical system" (*19*).

The aim of introducing a system for routine monitoring of procedure performance is to ensure that the analytical procedure is continuously producing reportable results that are fit for intended use. An analytical procedure can be considered fit for purpose when the requirements of the ATP are met. A routine monitoring program therefore needs to be designed to:

- Continually ensure that the reportable results produced by the procedure are fit for purpose
- Provide an early indication of potential procedure performance issues or adverse trends

- Ensure that any new understanding of the impact of variables on procedure performance is addressed in an updated ACS

Although system suitability checks are useful in establishing that a method is performing satisfactorily at time of use, having a mechanism for trending method performance over time is important in order to verify that the key variables impacting a procedure's performance are adequately understood and controlled. A program based on statistical process control techniques (*20,21*) is useful in order to trend the key indicators of procedure performance. However, it should be noted that the objective is conformance to the ATP requirements, not necessarily to statistical rules. Trend plots of critical procedure performance indicators—such as resolution values, RSDs from system precision checks, results from routine testing, control or stability samples, or OOS or out-of-trend (OOT) investigations—can be established.

If the procedure is found to be producing inconsistent reportable values that do not meet the performance requirements defined in the ATP, or the root cause of performance issues identified from lab investigations indicates that a critical variable has not been identified or adequately controlled, the QRM process ACS should be reviewed and updated to reflect this new information.

Change Control

Effective qualification and monitoring of an analytical procedure provides confidence that the data generated are fit for purpose. In practice, however, during the lifecycle of a pharmaceutical product both the manufacturing process and the analytical procedure are likely to experience a number of changes through continuous improvement activities or the need to operate the method and/or process in a different environment. There are many drivers that may result in a change in the procedure. These include:

- Changes driven by the need to address new requirements for data quality (e.g., the tightening of specification limits or the need to control potential impurities from new suppliers of materials)
- Changes made to improve the quality of the data produced (e.g., where the measurement uncertainty is no longer acceptable or where new critical variables are identified)
- Changes that allow the data to be generated more quickly, more cost effectively, or by using more sustainable methods

These changes can range from small changes to the control strategy for the procedure to the development of a new analytical procedure based on a completely different technology. In order to ensure that any changes introduced during the lifecycle have no adverse impact on the fitness for purpose of the data, it is important to have effective processes in place to assess and control change.

A system of change control should be established and should provide the means for ensuring that all changes are recorded, evaluated, and approved prior to being implemented. In order to assess the impact of a change, it is important to first understand the requirements of the data. The ATP that defines the maximum acceptable TMU should be used as the basis against which to assess the change. The change control system should ensure that any changes are re-qualified as being able to meet the TMU requirements in the ATP, that work is completed, and that supporting documentation is updated and approved before the procedure is returned or

introduced to routine use. Depending on the degree of change, the actions required to qualify the change will be different. Some examples are as follows:

a. A change in a method variable to a value that is within a range that was previously proven to produce fit-for-purpose data (e.g., changing an HPLC flow rate from 1.0 mL/min to 1.5 mL/min for an analytical procedure where a range of 1–2 mL/min was qualified during the method design stage). In this case, no additional experimentation is required to qualify the change.
b. Where the change is simply adding additional controls to an existing procedure (e.g., adding extra impurities to a test mix to help with peak identification). Again, this would not typically require any experimentation to qualify the change.
c. A change in a procedure variable to a value outside the range that was previously proven to produce fit-for-purpose data (e.g., changing a flow rate to 0.8 mL/min for the method used in the previous example). Changing to a method noise variable (e.g., a critical reagent source) would require a risk assessment. This should consider which procedure performance characteristics may be impacted by the change and then should perform an appropriate method performance verification study to confirm that the change does not impact the method's ability to meet the ATP.
d. A change to a new procedure/technique would require performance of appropriate development, understanding, and qualification activities to demonstrate conformance of the new procedure to the ATP.
e. A change impacting the ATP (e.g., a specification limit change or the need to apply the procedure to measure levels of analytes not considered in the original ATP) would require an update to the ATP and a review of the existing procedure qualification data to determine whether the procedure will still meet the requirements of the new ATP. If not, a new or optimized analytical procedure or technology will be required and actions similar to those for example d. above would be required.
f. Sometimes it may be necessary to use the method in a new location (i.e., analytical transfer or implementation of compendial procedures). This type of change should be treated similarly to example c above. In this case, however, it is particularly important that effective knowledge transfer takes place between the established and new locations.

The level of qualification required to confirm a changed analytical procedure is producing fit for purpose data will depend on an assessment of the risk associated with the change. It is recommended that, for all changes, a risk assessment should be carried out to determine the appropriate level of (re-)qualification activities required. The aim of the (re-)qualification exercise is to provide confidence that the modified method will produce results that meet the criteria defined in the ATP. This may be assessed by considering the risk that the change in the method will have on the accuracy and the precision of the reportable result. Risk assessment tools can be used to provide guidance on what actions are appropriate to verify that the method is performing as required.

ACS for Different Sites

When an analytical procedure is going to be used at a new site, the laboratory will have to demonstrate that it can execute the procedure in a fit-for-purpose manner. Thus, the lab will have to show that when the analytical procedure is executed, the reportable result will meet the criteria established in the ATP. The preparation for the implementation of the new procedure will

differ depending on how much knowledge is available—for example, an in-house method where the development findings, risk assessment conclusions, and subsequently established ACS are all known, compared with a compendial method where knowledge may not be available.

In the latter case, some of the QRM steps need to be verified, and as a result the ACS may need to be expanded. For example, additional environmental controls such as impact of exposure to light, temperature, and humidity; sample solution stability; or establishment of the site-specific replicate strategy need to be developed. The extent of the additional development/verification work will depend on how much knowledge is available to the receiving laboratory at the time of the qualification. Once the verification is complete, the new site will develop a qualification protocol or execute the existing qualification protocol to demonstrate that it is capable of generating a reportable result that meets the criteria established in the ATP, thus validating the original or the expanded ACS. After implementation, the new site should develop and implement the *Stage 3: Continual Verification* procedure as described earlier in this article.

CONCLUSION

The USP Validation and Verification Expert Panel believes that adopting a systematic approach to developing an ACS, in combination with the ATP (which is the driver for the development of the control strategy), will improve the performance of an analytical procedure. The use of KM and QRM tools will ensure that all work carried out during method design and development (stage 1) is value added, and should ensure a successful qualification exercise at stage 2. Maintaining the control strategy when the method is in routine use (stage 3) through continually monitoring the performance of the procedure and applying good change control practices will ensure that the procedure maintains its "in-control" status.

This *Stimuli* article has described how an ACS can be developed and implemented to ensure that analytical procedures are robust throughout their lifecycle. The expert panel would appreciate any feedback on the suggested approach, as well as any alternative approaches for consideration.

APPENDIX

Replication Strategy

FORMAT OF THE REPORTABLE RESULT

By increasing the number of replications, one can reduce the variability of the mean (*19*), also known as the standard error. However, only the variance linked to the corresponding analytical step [precision level; ICH Q2 (*22*)] can be influenced (i.e., increasing the number injections and sample preparations will reduce the injection variance and sample preparation variance, respectively). Therefore, the level of replications, or format of the reportable result [see *Biological Assay Validation* ⟨1033⟩ (*23*)] can be used to optimize the precision of the reportable result as part of the ACS. On the same basis, the format of the calibration (i.e., the number of replications of the reference standard), can be optimized. An essential prerequisite for such an optimization is a precision or ruggedness study to estimate the relevant variance contributions with sufficient reliability. With respect to the format of the reportable result, the variance contributions linked to the replicate levels are the primary objective (i.e., injection/analysis variance, sample preparation variance, and between-run variance).

It is preferable to calculate the variance contributions using an analysis of variance (ANOVA). Two precision levels can be addressed by a one-way (or one-factor) ANOVA, such as repeatability and intermediate precision in the case of an intermediate precision study, or injection precision and repeatability in the case of a repeatability study with replicate injections. By applying multiple-factor ANOVA, one can separate the variances of multiple steps of an analytical procedure, or of several variation factors. For example, if duplicate injections are performed in an intermediate precision study, three precision levels (i.e., system precision, repeatability, and intermediate precision) can be calculated by using a two-factor ANOVA [see Koller (*25*), or statistical textbooks].

OPTIMIZING THE PRECISION OF THE REPORTABLE RESULT

As mentioned above, one can reduce the variability of the reportable result by increasing the number of replicates, but only for the corresponding variance contributions (*19*). *Equation 1* below has been extended to include all precision levels. In contrast to bioassays, in chemical analysis the number of runs (k) is usually one. In the case of a single determination (injection), $k = n = m = 1$, the precision of the reportable result equals the intermediate precision. The two-term equation with the repeatability variance is used when no repeated analysis of the same sample solution is possible (e.g., titration of solids).

$$s_{RR}^2 = \frac{s_b^2}{k} + \frac{s_p^2}{k*n} + \frac{s_{sys}^2}{k*n*m} = \frac{s_b^2}{k} + \frac{s_r^2}{k*n} \quad [1]$$

s^2 = variance between series (b), of repeatability (r), of sample preparation (p), and of system (sys)
k = number of runs using independent reference standard analysis (calibration)
n = number of sample preparations
m = number of injections/analysis of the same solution

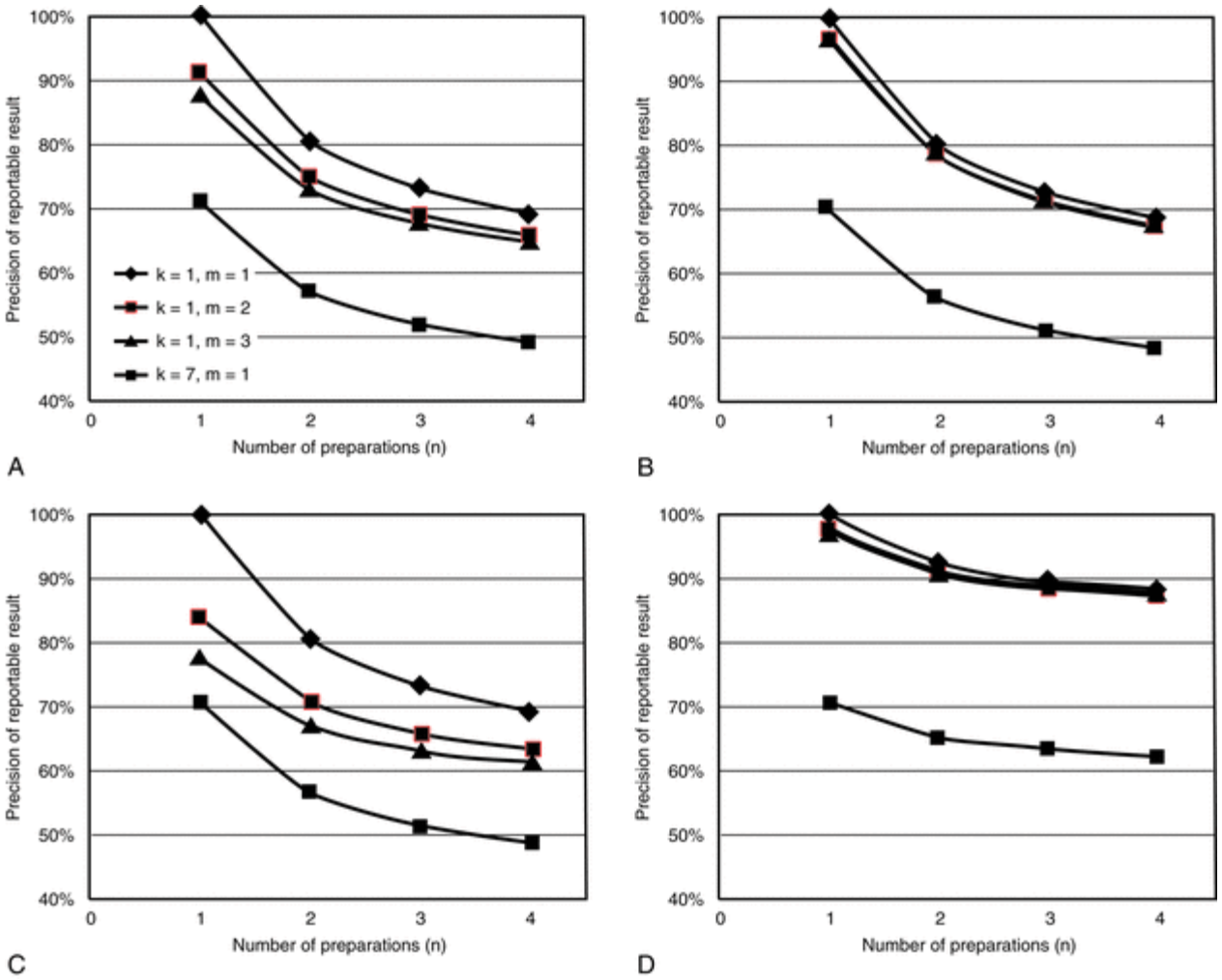


Figure 1. Precision of the reportable result for various formats, dependent on the relative variance contributions. Injection variance: sample preparation variance: between-run variance = 35%:35%:30% (A); 10%:60%:30% (B); 60%:10%:30% (C); and 10%:20%:70% (D).

Using *Equation 1*, it is possible to make a scientifically based decision on the required or necessary number of determinations, depending on the corresponding weight of the variance contributions (see *Figure 1*). If the variance contribution of injection is small, increasing the number of injections will have a negligible impact on the precision of the reportable result, and hence a single injection is sufficient (*Figure 1A*). In the case of a considerable fraction of the injection variance, as is typical for impurity determinations and often for drug substance assays, the precision can be increased by repeated injections (*Figure 1B*), maintaining a single sample preparation for the format of the reportable result.

A large between-series variance can only be offset by increasing the number of series for each reportable result, which is often done in biological assays, but not in chemical analysis. Because the improvement of precision is only proportional to the square root of the replicate number, the "gain" will get smaller. Therefore, a balance between effort and gain should be sought, with the primary evaluation based on the precision required from the application, as established in the ATP. An appropriately justified reportable result will achieve a better estimate of the true value, and thus guarantee a more reliable decision. This should by no means be confused with hiding variability. Of course, it has to be verified that the actual routine variability is as expected.

However, the format of the reportable result is just one aspect of the ACS. Even with a single sample preparation as the reportable result, one may decide to analyze more samples, for example, as a precaution to identify special-cause errors. Besides this "statistical" optimization of the precision, the knowledge of the variance contributions can also be used as a starting point to achieve method optimization. For example, a large variance of sample preparation differing between series may be caused by different operators and could be reduced by providing better instructions and/or controls. Further sub-analysis of between-run variation factors, such as analyst, equipment, reagents, etc., may also be used to limit variability by using more detailed instructions or restrictions as part of the ACS, if needed.

OPTIMIZATION OF THE CALIBRATION FORMAT

In the case of external calibration, the variability of the reference standard analysis is one of the factors (besides instrument, operator, reagents, etc.) that affects the between-series variance contribution at the intermediate precision/reproducibility level. Therefore, the precision of the reportable result is only valid for the very calibration format used in the precision study. Of course, repeating the whole precision study with various calibration formats would be very time consuming. Instead, the number of reference standard replicates can be optimized using a statistical approach also based on variance contributions, which can largely be obtained from the original precision study (see *Equation 2*) [for details, see Ermer and Agut (*26*)]. Note that the uncertainty of the declared reference standard content cannot be influenced by the number of determinations. If relevant, it has to be considered as an additional, fixed variance term in *Equation 2*.

$$CV^2_{RR^*} = CV^2_{RR} - CV^2_{RP} \cdot \left(\frac{1}{n_{RS}} - \frac{1}{n_{RS^*}} \right) - CV^2_{I} \cdot \left(\frac{1}{n_{RS} * m_{RS}} - \frac{1}{n_{RS^*} * m_{RS^*}} \right) \quad [$$

CV^2_{RP} and CV^2_{I} = squares of reference standard preparation coefficient of variation (relative standard deviation) and injection/system CV, respectively
n_{RS}, m_{RS} = number of injections and preparations (i.e., format) of reference standard analyses used for the precision study to obtain intermediate precision
n_{RS^*}, m_{RS^*} = number of preparations of reference standard analyses for an alternative format

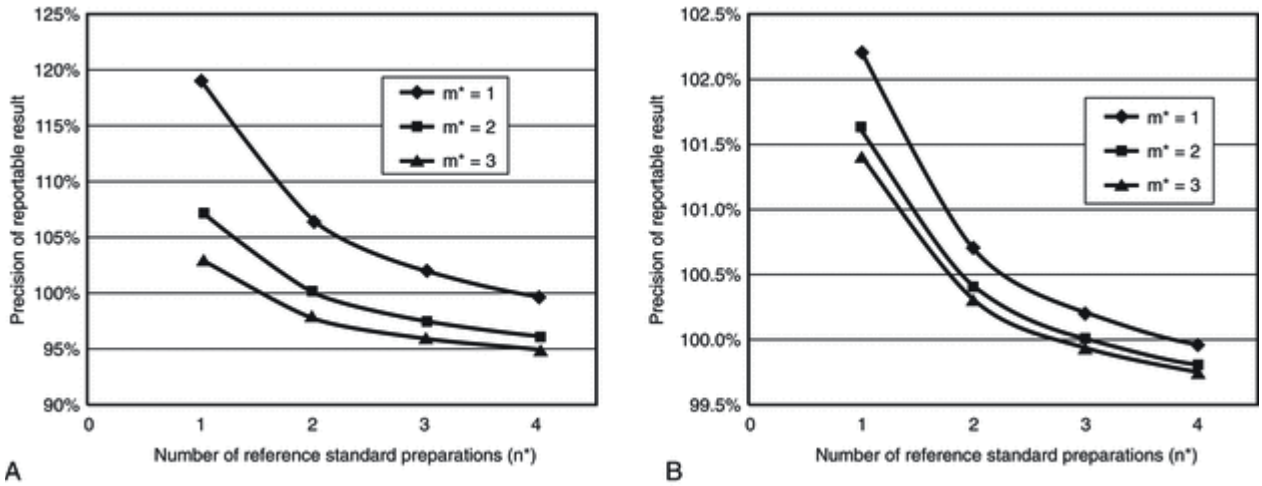


Figure 2. Dependence of intermediate precision on the format of calibration. The calculated precisions for alternative calibration formats are normalized with respect to the intermediate precision obtained in the precision study. The following relative standard deviations for the reference standard were used: API, example A: CV_{RR} = 0.76%, CV_{RP} = 0.14%, CV_I = 0.58%; Tablet, example B: CV_{RR} = 1.42%, CV_{RP} = 0.35%, CV_I = 0.22%.

In the case of a larger number for the new calibration format, the original relative standard deviation of the reportable result will decrease according to the weight of the reference standard variances. For a smaller number, the difference of the reciprocal numbers becomes negative, and hence the original relative standard deviation would increase. The impact of the format of the calibration depends on the contribution of the reference standard variances to the overall variability. The larger this contribution, the larger is the sensitivity to format variations (*Figure 2A*). On the other hand, in the case of a small contribution, the number of reference standard analyses can be minimized without much impact on the reportable result precision. For the example shown in *Figure 2B*, a single reference standard preparation and injection would not affect the precision of the reportable result significantly. In the case of impurity determinations also, the concentration dependence of the precision should be considered, defining a sufficiently large reference standard concentration to ensure an optimized precision (*19,22–27*).

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Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle

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ABSTRACT In this *Stimuli* article, the USP Validation and Verification Expert Panel discusses how the development of an analytical target profile (ATP) can be achieved and how the ATP is used in relation to the analytical procedure in the three stages of the lifecycle. The importance of the ATP was briefly discussed in a previous *Stimuli* article, *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification* (*PF* 39(5) [Sept.–Oct. 2013]). The 2013 *Stimuli* article described how the ATP captures the quality attributes of the reportable value, which reflects the fitness for purpose of the analytical procedure and connects all stages of the procedure lifecycle. Examples of ATPs for assays and an impurity testing were provided for illustrative purposes. The ATP is discussed further in this article, including its development, the linkage between the ATP and analytical control strategy, and application to each of the three analytical procedure lifecycle stages: design, qualification, and performance verification. This article is intended to be a companion to a separate *Stimuli* article that discusses application of analytical procedures and establishes a control strategy for analytical procedures (see *Analytical Control Strategy* in this issue of *PF*). Although the focus is on compendial procedures, some concepts may also be applied to other types of procedures as appropriate.

This article will consider the following questions related to the ATP:

- What is an ATP, and why is it useful?
- How can the ATP criteria (data quality attributes) be established?
- How can an ATP be applied during the three stages of the procedure lifecycle?

This article discusses an approach that may be used to determine an ATP, which leads to a better understanding of total analytical error associated with the result produced by the procedure. Holding the reportable value produced by the analytical procedure accountable to the ATP can promote development of a more in-depth control strategy through better control of risks, allowing procedures to perform more consistently throughout the lifecycle, particularly when used in new environments or as technologies advance. Specific examples of an ATP for the assay of a solid dosage form (tablet) are included.

Comments are requested, including suggestions for alternative ATP approaches.

INTRODUCTION

The current approach to development, validation, verification, and transfer of analytical procedures has served the industry well. The lifecycle approach—comprised of the development (stage 1), qualification (stage 2), and monitoring of the performance of analytical procedures (stage 3)—is an extension of the current guidance, taking advantage of our learnings from quality by design (QbD).

Application of lifecycle concepts to analytical procedures is optional; however, it does provide a framework for enhanced understanding and control of the variability associated with the results generated by the analytical procedure.

This article discusses the ATP concept in greater detail and presents two options for an ATP statement, as well as discussing how such statements may be assessed. It is important to note that the approach provided here is intended as an example and is not meant to suggest a single approach or suggest that current approaches are in need of complete reform. Other approaches that have more or less rigor may also be appropriate. The main point of this article is to illustrate the benefits of applying the ATP concept to better understand and control measurement uncertainty.

What Is the ATP and Why Is It Useful?

The ultimate purpose of an analytical procedure is to generate a test result, and based on this result, to make a decision about the parent body, sample, batch, or in-process intermediate from which the laboratory sample is obtained. The proposed lifecycle approach includes consideration of the target measurement uncertainty (TMU) (*1*) and the bias simultaneously. TMU is a more comprehensive term than the traditional term "precision" to represent random errors, and bias is a term traditionally used to represent systematic errors or accuracy. These terms (uncertainty and bias), when examined holistically, can be considered to represent the TMU associated with the reportable value generated by the procedure.

A fundamental component of the lifecycle approach is establishing a predefined objective that stipulates the performance requirements for the analytical procedure. This is captured in the ATP.

The ATP states the required quality of the results produced by a procedure in terms of the acceptable error in the measurement; in other words, it states the allowable TMU associated with the reportable value.

Because the ATP describes the quality attributes of the reportable value, it is applied during the procedure lifecycle and connects all of its stages.

As described in a recent *Stimuli* article [see *Fitness for Use: Decision Rules and Target Measurement Uncertainty* in *PF* 42(2)] (*2*), the criteria captured in the ATP should reference the product or output of the procedure, i.e., the results, rather than performance characteristics of the analytical procedure. The term performance characteristics refers to the performance aspects of the procedure itself (rather than the output); performance characteristics are described in the FDA pharmaceutical validation guidelines; *Validation of Compendial Procedures* ⟨1225⟩; and International Council for Harmonisation (ICH) Q2(R1). Validation practices are frequently treated as a check-box exercise in which analysts compare the validation results to validation criteria—often these are default criteria—to satisfy compliance objectives. Less consideration may

be given to understanding total measurement error and how it will influence the decisions to be made, for example the decision to accept or reject a batch.

Currently, the pharmaceutical industry develops and validates procedures in alignment with ICH and USP guidance. The guidance recommends setting criteria and separately assessing performance characteristics that are good indicators of the performance of an analytical procedure: accuracy, precision, linearity, specificity, sensitivity, and robustness. Although these indicators are important to understand during development, they do not provide a direct measure of the quality, or the error associated with the results generated by the procedure (*3*). It is common practice to establish default criteria for these validation elements, although the rationale for these criteria is not always transparent. These default validation criteria are often established based on several considerations including product specifications, typical variability of methodology used to characterize drug substances and products, and regulatory feedback. However, they often lose their connection to the ultimate purpose of an analytical procedure, which is generating results upon which decisions are based. Identifying the required output in terms of the final result of the analytical procedure in an ATP statement provides a target for development and helps to ensure that the procedure is developed toward predetermined requirements that are directly linked to the intended use of the procedure and the specifications. Hence, results will be generated during routine testing with an understanding of the TMU associated with them, as well as the effect on decisions made with those results.

All procedure performance characteristics, including the validation elements discussed above, will ultimately be consolidated in the attributes of the final result as illustrated in *Figure 1*.

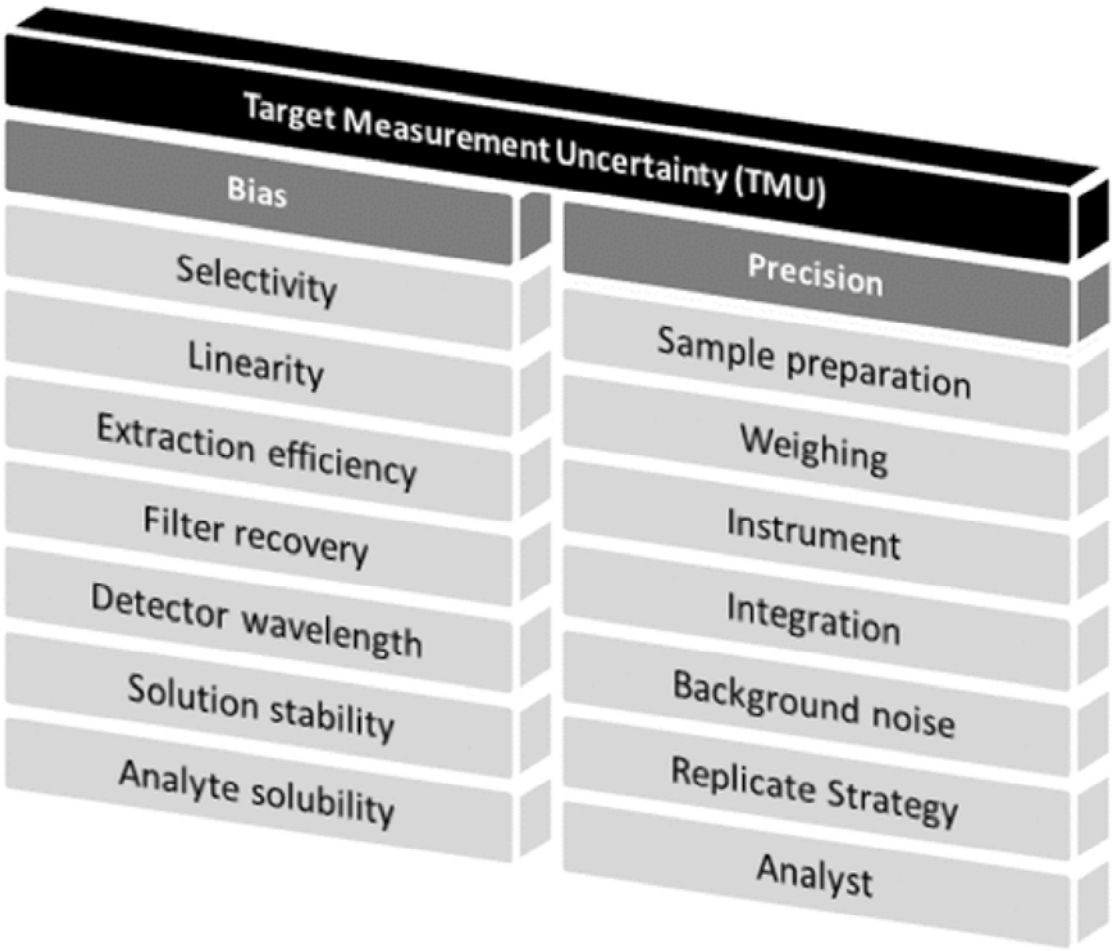

Figure 1. Consolidation of attributes contributing to TMU through bias and precision.

Before considering the determination of the ATP, it is important to discuss the concept of a true value versus a measured value. Each result has a corresponding actual value, called a true value. The true value cannot be known unless a sample was measured an infinite number of times, which is not practical. In practice, the true value is estimated by obtaining a measurement; this is called the measured value. It is the measured value that is used for the final result. Therefore, the acceptable measurement error, which describes the difference between the true value and the measured value, is considered in the TMU.

How Can the ATP Criteria Be Established?

The ATP should establish criteria for the TMU of the test results that are used to make a decision about a batch (reportable value). As a first step in determining ATP criteria, the product specification or target (draft or final) should be identified. For these examples, we will assume our tablet drug product has an assay specification of 95.0%–105.0%, which is common for solid oral dosage forms.

There are several ways to structure an ATP, and two examples are provided here. The first example (ATP #1) is aligned with current USP and ICH guidances, with the important improvement that the performance requirements are linked to the reportable value. The second example (ATP #2) is based on the ATP that appeared in the initial *Stimuli* article [see *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance*

Qualification, and Procedure Performance Verification in *PF* 39(5)] and references a more rigorous statistical approach compared to our current industry guidance. Either of these example ATPs may be appropriate, depending on the circumstances in which it is applied and how the criteria are established and justified.

When determining an ATP, the following should be considered:

- Sample to be tested
- Matrix in which the analyte will be present
- Range of analyte content (or concentration if appropriate). Ideally, this should reference the content in the product (e.g., drug substance, drug product, or excipient), not the amount of analyte in the sample solution subjected to the analytical measurement)
- Allowable error for the measurement as assessed through bias and precision
- Allowable risk of the criteria not being met (proportion of results that are expected to be within the acceptance criteria)
- Confidence that the measurement uncertainty and risk criteria are met

The ATP considers the acceptable level of risk of making an incorrect decision with the reportable values. Setting decision rules (*1*) may assist in this area, but is not always necessary. As a first consideration, the acceptable level of risk should be linked to patient safety and product efficacy, as well as the risk of erroneously accepting a batch that does not meet specifications. Manufacturer risk, i.e., the risk of erroneously rejecting a lot that meets specifications [a false out-of-specification (OOS) result] can also be considered when criteria for risk are established. In many cases, pharmaceutical specifications are established based on a quality rationale related to the capability of processes and analytical procedures, rather than clinical relevance. In these cases, manufacturer risk may be the main consideration when establishing an acceptable level of risk. When considered in this way, the ATP is independent of the technique and can be used to guide technique selection and procedure development in the design and understanding stage.

Because the ATP describes the quality of the reportable value, the current ICH and USP validation guidance can be incorporated into an ATP as shown below for a drug product assay in *Example 1*.

EXAMPLE 1: ATP #1

The procedure must be able to accurately quantify [drug] in the [description of test article] in the presence of [*x, y, z*] with the following requirements for the reportable values: Accuracy = 100% ± *D*% and Precision ≤ *E*%.

Note that [*x, y, z*] are the specified impurities and excipients.

Advantages of this approach to an ATP are:

- The ATP is easy to understand, the calculations are relatively straightforward, and the data are easy to assess for ATP conformance by nonstatisticians.
- The ATP includes criteria for accuracy and precision of the reportable value and is therefore linked to the quality of the reportable values. In current approaches, criteria for accuracy and precision are often established based on generally accepted industry practices using default criteria. However, in a QbD approach, these criteria should be aligned with the specification and the product and process needs.

- The QbD approach encourages understanding and control of sources of variability (defined control strategy).

Limitations of this approach include:

- Accuracy and precision are assessed separately so that TMU of the results is not explicitly defined.
- This approach does not quantify the risk of making a wrong decision by including probability and confidence criteria. However, although the level of risk is not transparent, risk can be controlled through alignment of specifications and accuracy/precision criteria such that reportable values that are within specification have a low probability of being on an edge of failure with respect to clinical relevance.

EXAMPLE 2: ATP #2

A simplified version of the ATP that was described in the initial *Stimuli* article of *PF* 39(5) is shown below as ATP #2. This example contains criteria for TMU (±*C%*) and is directly linked to the results generated by the procedure.

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [*x*, *y*, *z*] so that the reportable values fall within a TMU of ± *C%*.

The ATP inputs for [analyte], [description of test article], and [*x, y, z*] can be specified.

C describes the acceptable TMU. It considers the acceptable difference between the measured value and the target value and can be established based on a fraction of the specification range.

Assessment of Different ATP Scenarios

There are several ways to assess TMU, and one example is shown here. In this example, a two-sided beta-content tolerance interval (TI) approach is used to model ATP criteria to understand the effect of the various inputs on measurement uncertainty and its consequences for the design of the qualification study in stage 2. It should be noted that this is simply one way to assess measurement uncertainty. Other approaches, including other statistical approaches (*4*) and different criteria and supporting rationales, may also be acceptable (*5*,*6*).

The TI is a statistical concept that describes the proportion or fraction of future results that will fall within a given range with defined level of confidence. The TI concept can be used to assess TMU, which can be compared to ATP criteria. To establish TMU for the ATP, ideally the TMU should be a fraction of the specification range. In this case, 60% of the specification range (95% –105%) is chosen so that TMU is ±3.0%. This is acceptable because the specifications for pharmaceutical product assays are often based on method and manufacturing capabilities, and in this case the drug product assay specification is well within clinically relevant requirements. In this example, we expect batches to be manufactured to a nominal target value of 100% of label claim. Therefore, the main risk is to the manufacturer in that the procedure may generate OOS results that may lead to rejection of a batch that is actually acceptable. Associating a TMU with the reportable value will help with making the correct decision and aid in the assessment of OOS results.

The above values are inserted into the ATP statement, which becomes:

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

Once the ATP criteria have been determined, the next step is to model the ATP to determine its feasibility in terms of the selected technology and intended use of the procedure. The modelling step provides the chemist with an idea of how accurate and precise the procedure needs to be, hence it provides an orientation guide to develop the procedure and associated control strategy. In this example, the ATP is modelled using a two-sided beta-content tolerance interval approach calculator available at http://statpages.info/tolintvl.html.

Using a TI approach and based on the ATP statement, one can explore different scenarios that consider the proportion of results that lie within a given range of the true value, the associated confidence, the magnitude of procedure bias, and the maximum allowed precision. In this example, the proportion is set at 90% because it is desirable for a high proportion of results to meet the TMU requirement. Note that the TI calculator above can only determine TIs for a single series. In this case, a series is a single run with a given analyst and instrument on a given day. Therefore, the maximum allowed precision calculated in this way corresponds to repeatability. This target can be used to assess the general feasibility, and as a guide for the development phase. The repeatability target chosen from the scenarios given in *Table 1* is based on six determinations. This approach is loosely aligned with ICH recommendations and leaves sufficient flexibility for the intermediate precision factors, which are considered in the final qualification study in stage 2 of the lifecycle approach.

Because we are dealing with drug product for which we cannot know the true value of the active content due to variability in the production process, for the purposes of the ATP we assume our true value is the target value of 100% label claim.

The following scenarios are evaluated using the TI calculator:

- Confidence scenarios: 90% vs. 50%
- Bias scenarios: 0% vs. 1%
- Number of determinations (repeatability): 6 vs. 12 replicates

Table 1 shows the outcome of modeling these scenarios. With the exception of *Scenario 4*, all of these examples have TIs within the range of −3.0 to +3.0, which means they are potentially capable of meeting the TMU criteria defined in the ATP of ±3.0%. The precision values shown in *Table 1* are intended as estimates to guide method design and optimization of the control strategy during stage 1 and are not intended as requirements for subsequent intermediate precision studies that will be used for qualification (this will be discussed later in stage 2.)

Note—It is a useful exercise to use the website tool to create various scenarios and explore the relationships between precision, bias, proportion, and confidence. In this example, six determinations are chosen because this aligns with common industry practice.

Table 1. ATP Scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Proportion	90%	90%	90%	90%
Confidence	50%	50%	90%	50%
Bias[a]	1.0%	0%	0%	3.0%
Determinations	6	6	6	6
Estimated maximum %RSD (repeatability)	1.1%	1.6%	1.0%	2.0%
Tolerance interval	−1.0 to +3.0	±3.0	−1.0 to +3.0	−1.8 to +6.8

[a] For the purpose of the web link, insert the bias (difference from the target value) in the box for the mean value.

In *Table 1*, *Scenarios 1* and *2* are identical except for the 1% bias in *Scenario 1* while *Scenario 2* has 0% bias. The presence of 1.0% procedure bias in *Scenario 1* results in a decrease in the estimate of the maximum relative standard deviation (%RSD) from 1.6% (*Scenario 2*) to 1.1% (*Scenario 1*) for six determinations to maintain the same level of measurement uncertainty. These scenarios highlight the relationship between bias and precision, i.e., if bias exists, the maximum allowable %RSD will decrease to account for the increase in bias.

Scenario 3 shows an example having a high degree of confidence (90%) and proportion (90%). In this scenario, the corresponding maximum allowable %RSD is 1.0% as demonstrated with six determinations when there is 0% procedure bias. This level of combined precision and bias may be challenging to achieve during routine use of drug product assays.

To put this into perspective, the current approach, as described in ICH Q2, has separate requirements for accuracy and precision leading to wider criteria for total variability than may be apparent. An example would be an assay with acceptance criteria of 3.0% accuracy and 2.0% RSD (commonly applied default criteria for accuracy and repeatability studies) (*2,3*). These individual acceptance criteria could be considered acceptable using the current approach.

As shown in *Scenario 4*, this would produce a TI of −0.8% to 6.8% at 50% confidence with 90% proportion based on six determinations. This corresponds to a maximum TMU of 6.8%. Although this example is oversimplified from a statistical perspective, it illustrates how the proposed ATP approach can be used to control the measurement uncertainty to a defined maximum level, with bias and precision evaluated holistically.

In this example, *Scenario 2* in *Table 1* is chosen as a guide for procedure design, targeting: a) <1.6% RSD for repeatability, and b) zero or negligible bias (ideally, any bias due to systematic errors will be resolved during method development, therefore the target bias for the procedure is selected as 0%). An RSD of 1.6% is reasonable and generally achievable for a drug product tablet procedure. Note that this is a precision estimate to use as a guide during development of the procedure and control strategy. The final tolerance interval will be calculated from the results of the intermediate precision study during the qualification stage 2.

Proportion is set at 90% to reflect the desire for a high proportion of results to fall within the TMU. A value of 50% confidence is chosen as it aligns with typical industry practices.

Advantages of the approach described by ATP #2 include:

- It is consistent with the spirit of ICH and USP guidance and the metrological approach.
- It increases the chemist's awareness of the relationships between precision, bias, proportion, confidence, and number of determinations.
- Accuracy and uncertainty are assessed holistically so that TMU is explicitly constrained.
- It considers the risk of making a wrong decision by including criteria for the proportion of the results that should meet ATP criteria with a level of confidence.
- Established approaches described in Eurachem (*1*) and ISO (*7*) guidances can be applied to determine TMU.

Challenges and limitations of this approach are:

- This is a different way of thinking for analytical chemists. It requires the use of statistical tools/software, and statisticians may be needed to support analytical chemists and/or to perform these assessments, particularly for design of the qualification study in stage 2.
- More samples than is the current practice may be needed to demonstrate adherence.
- This approach may be challenging to implement with some of the tighter industry specifications (for example, the API assay) without decreasing the probability and confidence requirements to a level that some may find undesirable. Note that this is not an indication that current procedures are unsuitable to ensure patient safety but is instead the result of specifications that are established based on quality arguments related to process and procedure capability.

There are situations when an analyst may not have enough information to finalize the ATP criteria, such as when specifications have not yet been finalized. In these cases, an ATP can be established based on target specifications, prior knowledge, or the intended use of the procedure. Any changes to the ATP should trigger an assessment of the appropriateness of the analytical procedure. The ATP should not be changed based solely on procedure capability.

How Can an ATP Be Applied During the Three Stages of the Procedure Lifecycle?

STAGE 1: PROCEDURE DESIGN, DEVELOPMENT, AND UNDERSTANDING

ATP criteria should be established before starting procedure design activities. Note that ATP criteria are independent of the technique, allowing an analyst to select any technique that is capable of providing the performance needed to meet the ATP criteria.

When the need for a monograph procedure is identified, relevant information should be gathered before conducting laboratory studies. This information may include known chemical structures, solubility, reactivity, and stability of the molecules of interest. A literature search may also be useful to find out how the procedure has been applied or modified by others. The intended purpose of the procedure for routine use must always be considered. Any relevant information identified during the knowledge-gathering stage, such as criteria for run time, equipment type, and others, are also considered during the design and development stage. However, this information is not captured in the ATP.

By following the current approach as outlined in ICH and USP guidance documents, it is relatively straightforward to translate validation criteria into procedure performance characteristics (e.g., specificity, sensitivity, and others) to guide procedure development

activities. For example, validation characteristics such as specificity, linear range, and sensitivity are evaluated as part of the development activities, often by using default validation criteria as a reference. Thus, there is a clear and direct connection between validation guidance and procedure development activities when following the current approach.

In the lifecycle approach, relevant performance characteristics should be assessed as described in ICH Q2(R1) and ⟨1225⟩ during stage 1. The connection between the analytical performance characteristics described by ICH Q2(R1) and ⟨1225⟩ and the criteria for TMU captured in the ATP may not be apparent because some of the analytical performance characteristics are not cited directly in the ATP. ICH and USP analytical performance characteristics are important and necessary to meet the level of quality of the data stipulated in the ATP. In other words, if the procedure does not have a suitable calibration model, appropriate specificity, sensitivity, and others, the ATP (which describes the allowable TMU) will not be met. Targets for these performance characteristics can be established based on ATP criteria to support procedure design activities and can be included in the control strategy.

It is important to consider all steps in the analytical procedure during the procedure design stage, including the preparation conditions for standards and test samples. Sample preparation conditions are frequently a source of procedure variability and/or bias and should be confirmed through systematic extraction studies to ensure robust, rugged, and complete extraction (*8*).

During stage 1, system suitability and other method controls in the monograph (if available) are assessed. A preliminary assessment of the ability of the procedure to yield results with the required TMU as stated in the ATP is performed using real and/or spiked samples. On the basis of these studies, additional or different procedure controls can be proposed as needed.

Additional controls based on risk assessments and multifactor studies may also be added at this stage to ensure that the operation of the procedure is adequate for its intended use. It is important to investigate sources of variability and systematic bias during stage 1 so they may be eliminated or controlled during routine use of the procedure. This is discussed in more detail in the companion *Stimuli* article, *Analytical Control Strategy* (*9*).

If the results generated during subsequent studies fail to meet the ATP criteria, the design stage can be revisited, targets for performance characteristics can be refined, and design activities can be continued based on the refined targets. Note that returning to the design stage after failure to meet ATP criteria is one of several options; another option is to refine the control strategy, e.g., the routine replication strategy (*10*).

In this example, a tolerance interval approach is used. Before beginning a qualification study, recovery data collected during stage 1 can be assessed using a tolerance interval approach. This assessment is usually done with spiked samples. A method precision study—using the proposed routine procedure with its controls to test the finished product—may also be performed. These studies are intended to provide supporting evidence for the absence of significant bias and a confirmation that the precision is at an appropriate level before qualification of the procedure. Although bias and precision estimates at this stage do not guarantee that a qualification study will be successful, they can flag a potentially problematic procedure.

EXAMPLE USING DATA FROM A RECOVERY STUDY AND A METHOD PRECISION STUDY

Scenario 2 in *Table 1* is used as a guide. The ATP is as follows:

ATP: The procedure must be able to quantify [analyte] in the [describe test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

The simulated data in *Table 2a* were obtained for the following recovery design:

- Six determinations at 80%
- Six determinations at 120%
- Six determinations at nominal concentration

Simulated data for a method precision study to include six sample preparations of the finished product using the proposed routine procedure and its control strategy thus far are listed in *Table 2b.*

Table 2a. Simulated Data Generated for a Recovery Study

Level	Determinations (%)						Average	%RSD
	1	2	3	4	5	6		
80%	101.4	98.7	100.0	99.7	101.8	100.4	100.3	1.15%
100%	100.3	99.8	98.7	101.6	99.5	99.4	99.9	0.99%
120%	99.3	100.6	101.5	101.3	100.2	98.4	100.2	1.20%

Table 2b. Simulated Data Generated from a Method Precision Study

Sample	Percent of Label Claim (%)						Average	%RSD
	1	2	3	4	5	6		
	101.3	98.9	98.4	101.1	99.7	101.2	100.1	1.27

The average values in *Table 2a* and *Table 2b* indicate that there is negligible systematic error (bias) at all concentrations. Studies performed during stage 1 should support this. The small difference between the target values and 100% is assumed to be due to random error and reflect the real variance in the procedure (this will be investigated further during the qualification study in stage 2). Therefore the bias (systematic error) is considered to be zero. The tolerance intervals can be calculated by entering the following into the tolerance interval calculator at http://statpages.info/tolintvl.html:

- Precision estimates in *Table 2a* and *Table 2b*
- Average: 100.0% (bias is zero)
- Proportion: 90%
- Desired confidence: 50%
- Number of replicates: 6

The TMU of ±3.0% described in the ATP is used as target criteria for the following tolerance intervals shown in *Table 3*:

Table 3. Calculated Tolerance Intervals for Qualification Study Using a TI Calculator

Level	Calculated Tolerance Interval	Meets Target Criteria of ±3%

Level	Calculated Tolerance Interval	Meets Target Criteria of ±3%
80%	−2.2 to +2.2	Yes
100%	−1.9 to +1.9	Yes
120%	−2.3 to +2.3	Yes
Method precision study	−2.42 to +2.42	Yes

The calculated TIs at each concentration of the recovery study and the method precision study meet the target criteria of ±3.0% with a 90% proportion and 50% confidence. This indicates that the procedure, when run with its control strategy, is capable of generating results that will meet the requirements of the ATP. At the conclusion of the design stage, a control strategy is proposed and is included with the procedure conditions. The procedure is ready to be qualified.

STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION

Once an ATP has been established, design activities are complete, knowledge is compiled and documented, and a procedure control strategy has been proposed and shown to pass a recovery study, the performance of the procedure is ready to be qualified. The purpose of qualification is to confirm that the procedure meets the ATP criteria and remains appropriate for the testing of the product and the environment in which it is to be used routinely. Qualification consists of a study in which the precision of the reportable value is assessed. The laboratory that will be using the procedure to generate results should perform the qualification study. It is envisioned that this may also replace the current method transfer approach and will include the implementation of compendial procedures. A protocol is drafted and the qualification study is executed by following the procedure as written and with the appropriate controls. Note that the ATP does not specify the details of the experimental protocol to be used to qualify the analytical procedure, although it does provide the primary acceptance criteria for the study.

The qualification experiments are performed according to a protocol and compared against the predetermined acceptance criteria described in the ATP. The protocol should include, but is not limited to, the following: the ATP criteria, proportion, and confidence values for the qualification study (if appropriate to the specific ATP approach); a description of or reference to the procedure including its control strategy; a description of the experiments including the number of standards, test sample, and series analysis that will be performed; and the statistical approach to be used to analyze the data. The system suitability described in a compendial procedure should be considered as a minimum control strategy during the qualification stage. Ideally, the control strategy has been optimized prior to entering the qualification stage. Any additions to the control strategy should be included in the analytical procedure attached to the qualification protocol. Some examples of these additions may be clarification of laboratory sample preparation instructions, composite strategy (*11*), routine replication strategy (*8*), and addition of environmental controls.

Qualification strategies will depend on the criteria described in the ATP and on the intended use of the procedure. An example of a qualification strategy is provided in this article; however, other approaches and designs are acceptable. Note that some qualification strategies may require consultation with a statistician.

EXAMPLE QUALIFICATION STRATEGY

The ATP used in this example is as follows:

ATP: The procedure must be able to quantify [analyte] in the [describe test article] in the presence of specified impurities and excipients so that the reportable values fall within a TMU of ±3.0%.

This particular qualification design consists of four series with six determinations for each series, where a series is a single run by a given analyst on a single instrument on a given day. This example is based on simulated data considered to be representative of a typical tablet formulation. The data were simulated with the following inputs: True batch mean = 100.0%; within series %RSD = 1.0%; between series standard deviation = 1.0%.

When using a TI approach, the proportion and level of confidence are captured in the protocol prior to starting the qualification study. This example used a proportion of 90% and a confidence of 50%. Note that the design of the qualification study, i.e., the number of series and determinations, has an impact on the reliability of the estimated precision. Consultation with a statistician can be helpful in developing an appropriate design. In this example, a 4 × 6 design is applied.

Table 4. Simulated Data Used to Demonstrate an ATP Qualification Study

Series	Determinations						Average	SD	% RS
1	100.3	99.9	98.8	101.5	100.1	100.2	100.1	0.8790	0.8
2	99.2	100.2	100.1	100.7	100.9	101.3	100.4	0.7284	0.7
3	101.9	99.5	98.6	101.0	98.6	99.8	99.9	1.3178	1.3
4	101.8	100.6	101.7	102.1	101.3	101.1	101.4	0.5554	0.5
Calculated TI[a]								−1.9 to +2.	
Average (n = 24)								100.47	

[a] Calculated TI is discussed in Hoffman and Kringle (*12*).

The total variance of an analytical procedure often is partitioned into components attributable to the different sources of variability. The first source is the observed variation when an analytical procedure is used repeatedly to assess the same sample over a short period of time by a single analyst using the same equipment (where each replication involves the entire process including the sample preparation). This is referred to as the repeatability component.

The second source is variation that occurs when an analytical procedure is used in the same laboratory under random conditions such as different analysts, equipment, or days. The sum of these two components is called intermediate precision (or ruggedness). For the design in *Table 4*, the intermediate precision and TI can be calculated as shown in the *Appendix*. The TI tool used in stage 1 is not appropriate for this type of design because it does not correctly consider the degrees of freedom and sources of error for multiple series.

As shown in *Table 4* the TI calculated for this example is −1.9 to +2.8 (98.1–102.8), which is within the ATP criteria of ±3.0%. The ATP criteria have been met, and the procedure is considered to be qualified for routine use.

At the conclusion of the qualification stage, the study results are documented in comparison to the ATP requirements, and a conclusion is written as to whether the procedure has been shown to meet ATP criteria. If the outcome of the qualification process is satisfactory, the laboratory is considered to be qualified to run the procedure in routine applications.

The calculated TI is for a single reportable value. If the TI for these single reportable values falls outside the established ATP criteria, the procedure can be re-evaluated, including consideration of the following steps:

1. Confirm that the control strategy is optimized for the test environment.
2. Examine the routine replication strategy used to calculate a reportable result, i.e., increase the number of replicates (*9*).
3. Redevelop the procedure (stage 1).
4. Consider implementation of alternative analytical technology (stage 1).
5. Confirm that the probability and confidence values that were selected are appropriate for the intended use of the procedure.

STAGE 3: PROCEDURE PERFORMANCE VERIFICATION

Stage 3 of the procedure lifecycle ensures that the analytical procedure remains in control and continues to meet the ATP criteria. Therefore, the ATP is used as a reference point from which to monitor the performance of the procedure during stage 3 of the lifecycle of the analytical procedure.

The performance of the procedure and its ability to generate results that meet the ATP criteria should be monitored throughout the lifecycle. Routine use of analytical procedures in the testing lab provides the opportunity to trend performance. This is discussed in more detail in the control strategy article (*8*). Note that it may not be practical to trend the TMU described in the ATP. This is because the error is a combination of both the systematic (bias) component and the random (precision) component, and it is difficult to monitor the systematic component under our current industry paradigm. Therefore it is acceptable to trend the precision of the results as well other events, such as system suitability failures and confirmed OOS results.

In some cases it may be necessary to revise the ATP criteria. Changes to the ATP can be triggered by updates to specifications as a result of monograph updates. Changes and the associated rationale should be captured. Any changes to ATP criteria should trigger reassessment of the analytical procedure against the revised ATP criteria.

CONCLUSIONS

This article discusses in greater detail the ATP concept that was discussed in the *Stimuli* article published in 2013, *Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification* (*13*). It provides a simple example showing how to establish criteria that can be used to assess the quality of final test results that are used to make decisions about pharmaceutical products. Elements of accuracy and precision from ICH Q2 and ⟨1225⟩ are assessed holistically to show how they contribute to TMU. Although the example shown here focuses on a tablet drug product assay test, the concepts may also be applicable to other types of tests. In addition, statistical approaches other than TIs may be applied as appropriate. The main objective of this article is to

provide a simple example showing how sources of variability described in ICH Q2 and ⟨1225⟩ can be considered together to provide a better link between the performance of a procedure and the decisions made with reportable values generated in pharmaceutical analytical laboratories. An additional advantage of using an ATP is that it can drive the development of a robust control strategy, resulting in better, more consistent performance of an analytical procedure throughout its lifecycle.

APPENDIX

Calculation of Intermediate Precision and B-Content TIs for the Qualification Study in Table 4

In *PF* 40(5), the In-Process Revision of *Statistical Tools for Procedure Validation* ⟨1210⟩ gives the following formulas for calculating the mean ($\overline{Y}$) and intermediate precision: $(\hat{\sigma}^2_{IP})$. The mean is calculated by summing (Σ) all determinations across all series and dividing by the total number of determinations:

$$\overline{Y} = \frac{\sum_{i=1}^{r}\sum_{j=1}^{c} Y_{ij}}{cr}$$

The intermediate precision is a function of two variance components, S_1^2 and S_2^2, where $\overline{Y}$ is the mean of the i^{th} series and Y_{ij} is the j^{th} determination in the i^{th} series:

$$S_1^2 = \frac{r\sum_{i=1}^{c}\left(\overline{Y}_i - \overline{Y}\right)^2}{c-1}$$

$$S_2^2 = \frac{\sum_{i=1}^{c}\sum_{j=1}^{r}\left(Y_{ij} - \overline{Y}_i\right)^2}{c(r-1)}$$

$$\overline{Y} = 100.47$$

$$S_1^2 = 2.742$$

$$S_2^2 = 0.834$$

$$\hat{\sigma}^2_{IP} = \left(\frac{1}{r}\right)S_1^2 + \left(1-\frac{1}{r}\right)S_2^2$$

$$\hat{\sigma}^2_{IP} = \left(\frac{1}{6}\right) * 2.742 + \left(1-\frac{1}{6}\right) * 0.834 = 1.15$$

An upper 100(1−α)% confidence bound U_{GW} for $\hat{\sigma}^2_{IP}$ is based on a method from Graybill and Wang (*14*). This method is called the modified large-sample confidence interval and has been

recommended for biopharmaceutical applications by Nijhuis and van den Heuvel (*15*). This formula is:

$$U_{GW} = \hat{\sigma}_{IP}^2 + \sqrt{H_1^2\left(\frac{1}{r}\right)^2 (S_1^2)^2 + H_2^2\left(1-\frac{1}{r}\right)^2 (S_2^2)^2}$$

$$U_{GW} = 1.15 + \sqrt{1.47^2\left(\frac{1}{6}\right)^2 7.52 + 0.29^2\left(1-\frac{1}{6}\right)^2 0.696}$$

$$U_{GW} = 1.86$$

$$H_1 = \frac{c-1}{\chi^2_{\alpha;c-1}} - 1$$

$$H_1 = \frac{4-1}{1.21} - 1 = 1.47$$

$$H_2 = \frac{c(r-1)}{\chi^2_{\alpha;c(r-1)}} - 1$$

$$H_2 = \frac{4(6-1)}{15.45} - 1 = 0.294$$

Hoffman and Kringle (*12*) recommend using the B-content TI to assess accuracy and precision simultaneously.

A two-sided B-content TI is:

$$\bar{Y} \pm Z_{\frac{1+\beta}{2}} \sqrt{\left(1+\frac{S_1^2}{rc\hat{\sigma}_{IP}^2}\right) x U_{GW}}$$

$$100.47 \pm 1.645 \sqrt{\left(1+\frac{2.742}{6x4x1.15}\right) x 1.86}$$

where: $\bar{Y}$ = average of all determinations

c = number of series (n = 4)

r = number of determinations per series (n = 6)

$\hat{\sigma}_{IP}^2$ = intermediate precision

S_1^2 = among-run mean sum of squares

S_2^2 = mean squared error

U_{GW} = upper confidence bound

H_1 = ratio of the degrees of freedom for the chi-square to the critical value from the chi-square distribution

H_2 = ratio of the degrees of freedom for the chi-square to the critical value from the chi-square distribution

$\chi^2_{\alpha;c-1}$= the percentile of a central chi-squared distribution with c= −1 degrees of freedom and area to the left

$Z_{\frac{1+\beta}{2}}$ = represents a standard normal quantile with area $\frac{1+\beta}{2}$ to the left.

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STIMULI TO THE REVISION PROCESS

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Proposed New USP General Chapter: The Analytical Procedure Lifecycle *⟨1220⟩*

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ABSTRACT An analytical procedure must be demonstrated to be fit for its intended purpose. It is useful to consider the entire lifecycle of an analytical procedure, i.e., its design and development, qualification, and continued verification. The current concepts of validation, verification, and transfer of procedures address portions of the lifecycle but do not consider it holistically. The purpose of this proposed new chapter is to more fully address the entire procedure lifecycle and define concepts that may be useful. This approach is consistent with the concept of quality by design (QbD) as described in International Council for Harmonisation (ICH) Q8-R2, Q9, Q10, and Q11. The lifecycle approach can potentially be applied to all procedures, although the level of effort should be consistent with the complexity and criticality of the procedure.

INTRODUCTION

This *Stimuli* article provides the framework for *The Analytical Procedure Lifecycle* ⟨1220⟩. This article describes the current thinking of the USP *Validation and Verification Expert Panel* which advises the *General Chapters—Chemical Analysis Expert Committee* with regard to future trends in analytical procedures development, qualification, and continued monitoring. These concepts are described here for the purpose of offering an alternative approach to the classical analytical validation and subsequent verification and transfer, viewing these activities as a continuum and closely interrelated rather than as discrete actions. This enhanced approach potentially offers several advantages, including:

- Improved understanding of the procedure and control of sources of variability, which are linked to the intended use of the procedure as described in the analytical target profile (ATP)
- Procedures that are more robust, resulting in fewer failures during use and during qualification in a new laboratory
- Reduction of overall resources required for a new or revised procedure. The levels of effort, formality, and documentation should be commensurate with the level of risk
- Identification of adverse trends, allowing proactive measures and facilitation of continued improvements and change control through continued monitoring

The *Validation and Verification Expert Panel* considers this lifecycle approach to still be evolving, as International Council for Harmonisation (ICH) Q8, Q9, and Q10 concepts are being adopted by the analytical community. Therefore, it is advisable to provide guidance on how to incorporate lifecycle management strategies into analytical procedures, which will increase

flexibility in demonstrating the fitness of analytical procedures while leaving the option open to use the classical approach described in *Transfer of Analytical Procedures* ⟨1224⟩, *Validation of Compendial Procedures* ⟨1225⟩, and *Verification of Compendial Procedures* ⟨1226⟩. In addition to offering a preview of the proposed general chapter, the General Chapters—Chemical Analysis Expert Committee and the Validation and Verification Expert Panel are seeking specific input from users in the pharmaceutical industry regarding the following questions:

1. Would a general chapter on the lifecycle approach be valuable?
2. Is the information presented herein sufficient for implementation of an analytical procedure under the quality by design (QbD) approach?
3. Would incorporation of references to statistical tools, either in this chapter or in another chapter, be valuable?
4. Can you provide input or approaches that would improve this proposed general chapter?

The content and scope of the proposed general chapter will be refined on the basis of responses to this *Stimuli* article. Because stakeholders may have differing views, the objective of this *Stimuli* article is to identify and build areas of consensus that may be included in ⟨1220⟩.

THE LIFECYCLE APPROACH

Reportable values generated using qualified analytical procedures provide the basis for key decisions regarding compliance of a test article with regulatory, compendial, and manufacturing limits. These values may be applied against decision rules that provide a prescription for the acceptance or rejection of a drug product or drug substance. This is based on the analytical measurement, the uncertainty of the measurement, and the acceptance criteria, taking into account the acceptable level of risk of making a wrong decision.

Application of lifecycle management concepts to analytical procedures is based on QbD and provides an opportunity to use the knowledge gained from the application of scientific approaches and apply that knowledge to reportable values generated when using the analytical procedure. The concept of QbD is understood as a systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8). The quality risk management (QRM) for an analytical procedure is a systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the analytical procedure lifecycle. It is important to understand and control sources of variability to ensure that measurement uncertainty is aligned with the decisions that will be made using results generated by an analytical procedure.

Lifecycle Stages

In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, one can use a three-stage concept (see *Figure 1*) that is aligned with current process validation terminology:

Stage 1: Procedure Design and Development

Stage 2: Procedure Performance Qualification

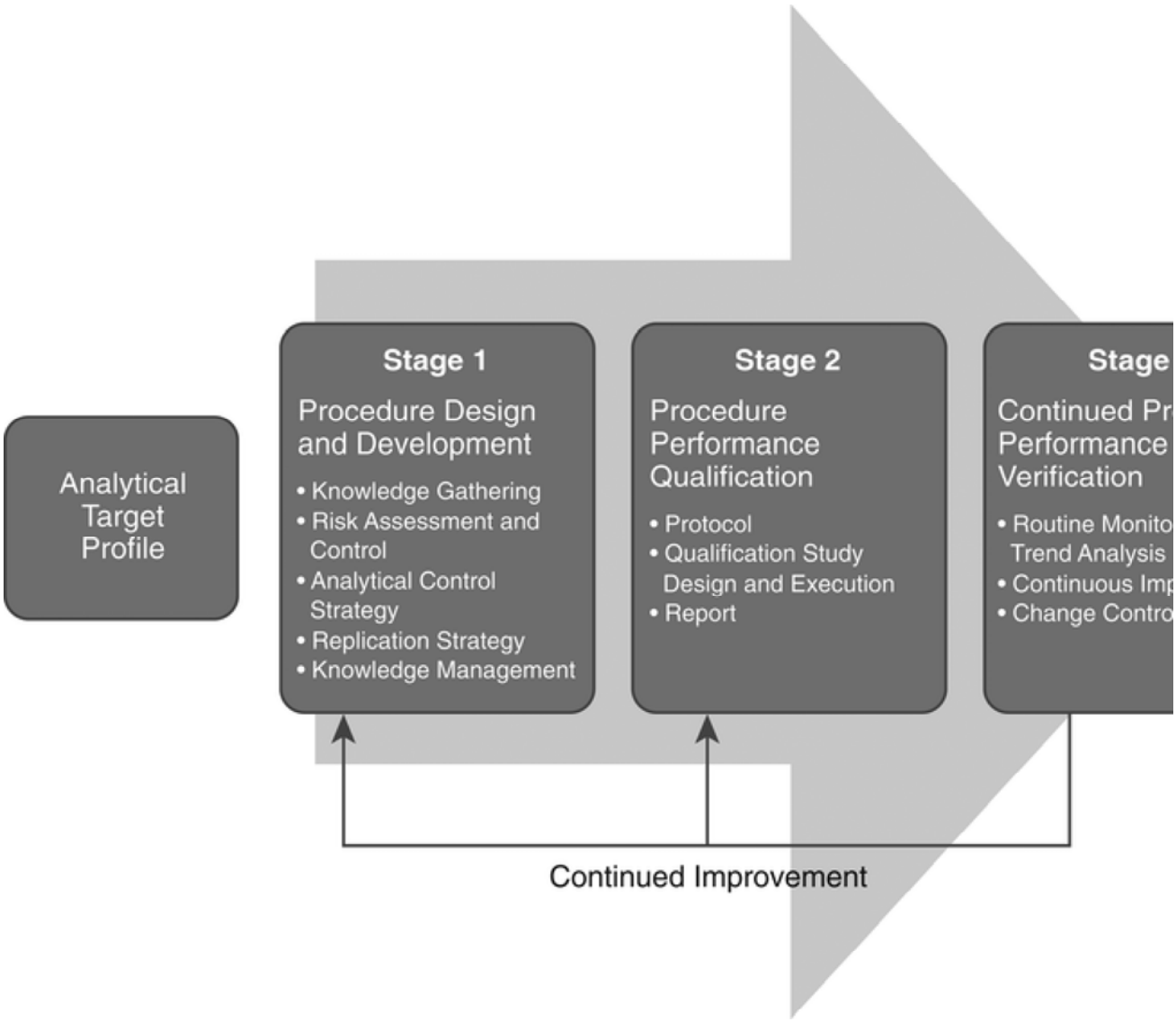

Figure 1. The analytical procedure lifecycle.

Analytical Target Profile

A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective that stipulates the performance requirements for the analytical procedure. These requirements are described in the ATP. The ATP states the required quality of the reportable value produced by an analytical procedure in terms of the target measurement uncertainty (TMU). ATP criteria are derived from external requirements and not only from the performance of the analytical procedure. The acceptable level of risk of making an incorrect decision is considered when establishing an ATP. The reportable value may be the mean of multiple analytical results, if there is a defined replication strategy that is documented in the procedure. TMU is the maximum uncertainty that can be associated with a reportable result while still remaining fit for its intended purpose. TMU is a consolidation of the uncertainty from all sources, as illustrated in *Figure 2*.

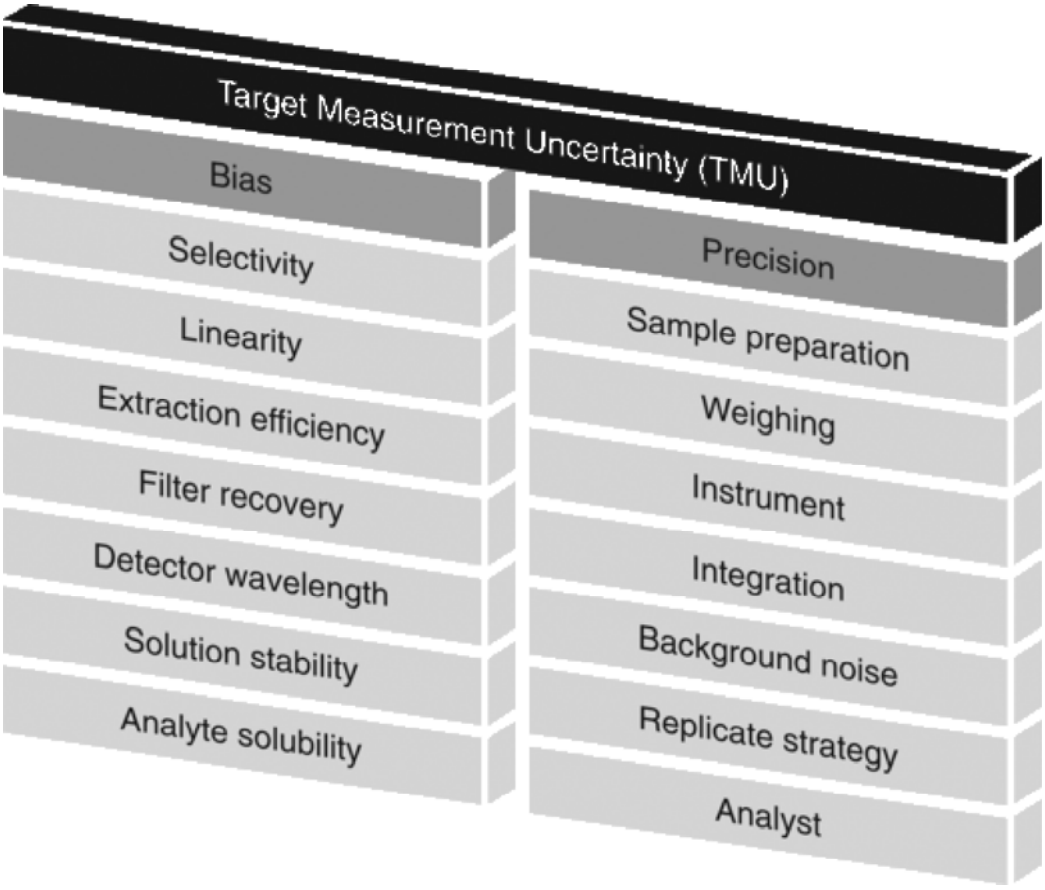

Figure 2. Consolidation of attributes contributing to TMU through accuracy (bias) and precision.

When establishing an ATP, the following should be considered, where relevant:

- Sample to be tested
- Matrix in which the analyte will be present
- Allowable error for the measurement as assessed through accuracy (bias) and precision, both of which make up the TMU
- Allowable risk of the criteria not being met (proportion of results that are expected to be within the acceptance criteria)
- Assurance that the measurement uncertainty and risk criteria are met

The current ICH and USP validation guidance can be incorporated into an ATP, with emphasis on the quality of the reportable value as shown for a drug product assay (*Example 1*).

EXAMPLE 1: ATP #1

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] with the following requirements for the reportable values: Accuracy = 100% ± D% and Precision ≤ E%.

The ATP inputs for [analyte], [description of test article] and [*x, y, z*] (which may be impurities or excipients) can be specified. Values for *D* and *E* should be specified. For example, *D* may be expressed as a percentage of label claim and *E* may be expressed as a percentage of relative standard deviation (%RSD). Alternative units are acceptable as long as they are unambiguous.

Advantages of this approach to an ATP are:

- The ATP is easy to understand, calculations are relatively straightforward, and data are easy to assess for ATP conformance by non-statisticians.
- The ATP includes criteria for accuracy (bias) and precision of the reportable value and is therefore linked to the quality of the reportable values.
- This approach encourages understanding and control of sources of variability (defined control strategy).

Limitations of this approach include:

- Accuracy (bias) and precision are assessed separately so that the TMU of the results is not explicitly defined.
- This approach does not quantify the risk of making a wrong decision by including probability and confidence criteria. However, while the level of risk is not transparent, risk can be controlled through the alignment of specifications and accuracy (bias)/precision criteria such that reportable values that are within specification have a low probability of being on an edge of failure with respect to clinical relevance.

In current approaches, criteria for accuracy (bias) and precision are often established based on generally accepted industry practices using default criteria. However, in a QbD approach, these criteria are aligned with the specification and product and process needs, and the criteria focus on the reportable value.

EXAMPLE 2: ATP #2

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] so that the reportable values fall within a TMU of ±C%.

The ATP inputs for [analyte], [description of test article] and [*x, y, z*] (which may be impurities or excipients) can be specified.

This example contains criteria for the TMU, (±*C*%), which is directly linked to the results generated by the procedure. The TMU considers the acceptable difference between the measured reportable value and the target value and can be established based on a fraction of the specification range.

The ATP serves as a reference point for assessing the fitness of an analytical procedure, not only in the development phase but also during all changes within the analytical lifecycle. Note that the ATP is not linked to a specific analytical procedure. Thus, it is conceivable that more than one analytical procedure could meet the requirement of an ATP, and that an alternate procedure that meets the requirement stated in the ATP would be acceptable.

For procedures that do not already have an ATP, including existing procedures in compendial monographs, one can be constructed. For instance, the ATP may be based on product acceptance criteria and any existing requirements for the analytical procedure as stated in the monograph.

In assessing new or existing procedures for their ability to meet an ATP, analysts may use statistical methods for analyzing prospectively designed studies. In the case of existing procedures for which significant data are available, statistical procedures for retrospective

evaluation of historical data, such as stability data, laboratory investigations, check samples/controls, release data, and others may be used. The level of variability present in the historical data may trigger additional studies that aim to understand and reduce or eliminate sources of variability and also improve the data quality by means of an optimized control strategy to meet the ATP.

STAGE 1: PROCEDURE DESIGN AND DEVELOPMENT

Knowledge Gathering

When the need for a procedure is identified, relevant information should be gathered prior to conducting laboratory studies. Such information may include known chemical structures, solubility, reactivity, and stability of the molecules of interest. A literature search may also be useful to understand how the procedure has been applied or modified by others. The intended purpose and fitness for routine use must always be considered. Any relevant information identified during the knowledge-gathering stage—such as the range over which the procedure will be used, criteria for run time, equipment type, and other information—is also considered during the design and development stage. However, this information is not captured in the ATP.

Once the knowledge-gathering phase is complete, the information is used to select an appropriate technology and procedure likely to meet the requirements defined in the ATP.

Risk Assessment Evaluation and Control

The objective of a risk assessment is to develop understanding of procedure variables and their impact on the reportable value, which will assist in the development of a control strategy.

For example, tools such as process maps and Ishikawa diagrams (fishbone diagrams) may be used, in addition to prior knowledge, to provide structure to a brainstorming and information-gathering exercise to identify variables. The attributes shown in *Figure 2* may serve as a useful starting point. It is important to consider all steps in the analytical procedure, including development of standard and test sample preparation. It is important to ensure that the sample preparation step does not cause the analyte to undergo any significant (uncontrolled or unintended) changes in its relevant properties from the moment of sampling to the time when the actual analysis is carried out. Sample preparation conditions are frequently a source of procedure variability and/or bias and its influence in the performance of the procedure should be investigated. In the case of sample preparation that involves dissolving a sample prior to analysis, systematic extraction studies should be performed to ensure robust, rugged, and complete extraction/dissolution. It is also important to investigate sources of variability and systematic bias during Stage 1 so that they may be eliminated or controlled during routine use of the procedure.

Besides accuracy (bias) and precision, which are defined in the ATP, experiments may include other method-specific performance attributes known as traditional validation characteristics (see *Figure 2*). However, these characteristics are eventually consolidated into the ATP attributes.

Risk-assessment tools may be used to prioritize which variables should be studied to evaluate their impact on the reportable results. Results from experiments investigating variables can be used to develop and justify the control strategy.

Design of experiments (DOE) is a fundamental methodology for the QRM process. It is a systematic method to determine the relationships between variables affecting a process, and it is used to find cause-and-effect relationships. This information is needed to manage process inputs in order to optimize the output of the procedure. Multi-factor studies are a powerful way to develop understanding, although single-factor studies are also appropriate in some cases. DOE also utilizes statistical data treatment, which allows clear determinations regarding the significance of a variable and/or its interactions towards the output.

Analytical Control Strategy

The analytical control strategy is a planned set of controls, which is the output of the QRM process. It is derived from an understanding of both the requirements for the reportable value established in the ATP and the understanding of the analytical procedure as a process.

The variables that need to be controlled and their acceptable ranges (from the risk assessment and subsequent experiments) should be explicitly specified in the procedure. Typical controls may include limits for variability of calibration and between replicates; instructions for environmental controls (light, temperature, and humidity); sample solution stability; and, for chromatographic methods, system suitability requirements such as sensitivity, resolution, etc. In addition, the controls may include variables and aspects related to the sample, sample preparation, standards, reagents, the facility, equipment operating conditions, the format of the reportable value (i.e., number of replicates), and the frequency of monitoring and control.

A replication strategy may be applied to reduce the random variability of the mean (reportable value). It should be noted that increasing the number of replicates will only reduce the random variability corresponding to the step that is replicated. For example, increasing the number of injections will reduce the injection variance, whereas increasing the number of sample preparations will reduce the variance associated with sample preparation.

The analytical control strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle. Different control strategies may be required in different labs or when using different equipment.

Knowledge Management

Knowledge management for analytical procedures is a systematic approach to acquiring, analyzing, storing, and disseminating information, and is an important factor in ensuring the ongoing effectiveness of the control strategy. Knowledge management should include, but should not be limited to, development activities, technology transfer activities to internal sites and contract laboratories, qualification and monitoring studies over the lifecycle of the analytical procedure, and change management activities. The knowledge gathered to develop the procedure understanding should be collected in a repository and shared as needed to support implementation of the control strategy across sites that use the analytical procedure. Changes and improvements to a qualified analytical procedure should be made through the change control system.

Preparing for Qualification

Before beginning a qualification study, data collected during Stage 1 can be assessed to provide supporting evidence for the absence of significant bias and a confirmation that the

precision is at an appropriate level, as well as other pertinent analytical characteristics. Although bias and precision estimates at this stage do not guarantee that a qualification study will be successful, they can flag a potentially problematic procedure.

As an integral part of preparation for laboratory qualification to execute a compendial procedure or a procedure from another site, the process of QRM should be carried out, and the control strategy of the procedure should be verified or expanded to ensure that the requirements of the ATP are met.

STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION

Once an ATP has been established and design activities are completed with appropriate minimization of bias and uncertainty, knowledge is compiled and documented. A procedure control strategy is proposed and the performance of the procedure is ready to be qualified. The purpose of qualification is to confirm that the procedure generates reportable values that meet the ATP criteria and remain appropriate for the testing of the product in the environment where it will be used. The laboratory that will be using the procedure to generate results should perform the qualification study.

The protocol for the qualification study should be documented and should include (but is not limited to) the ATP; method-specific performance attributes and acceptance criteria; a description of or reference to the procedure including its control strategy; a description of the experiments including the number of standards, test sample, and series analysis that will be performed; and the statistical approach to be used to analyze the data.

The analytical control strategy may be refined and updated as a consequence of any learning from the qualification study. For example, further controls may be added to reduce sources of variability that are identified in the routine operating environment in an analytical laboratory, or replication levels (multiple preparations, multiple injections, etc.) may be modified based on the uncertainty in the reportable value.

Qualification strategies will depend on the criteria described in the ATP and on the intended use of the procedure.

STAGE 3: CONTINUED PROCEDURE PERFORMANCE VERIFICATION

Stage 3 of the procedure lifecycle ensures that the analytical procedure remains in control, i.e., this stage maintains the established performance level and thus continues to meet ATP criteria. Therefore, the ATP is used as a reference point for the performance of the procedure during Stage 3 of the lifecycle of the analytical procedure.

This stage includes both routine monitoring and evaluation of the analytical procedure's performance after changes to determine if the analytical procedure continues to be fit for purpose.

Routine Monitoring

Effective monitoring of an analytical procedure provides confidence that the reportable value generated is fit for purpose.

This stage should include an ongoing program to collect and analyze data that relate to analytical procedure performance. Monitoring may include tracking analytical results, system suitability failures, out-of-specification or out-of-trend investigations, stability trends, or other parameters as appropriate. If the monitoring data indicate that the procedure is not in control, an investigation should be performed with a goal of identifying the root cause. Corrective and preventive action should be taken to ensure that the analytical control strategy is updated in the analytical procedure.

A routine monitoring program therefore needs to be designed to:

- Ensure that the performance of the procedure or of appropriate steps (for example, injection and sample preparation variability) maintains an acceptable level over the procedure lifetime. (This is done to conclude that the reportable values produced by the procedure continue to meet the ATP requirement.)
- Provide an early indication of potential procedure performance issues or adverse trends.
- Identify any changes required to the analytical procedure.

Changes to an Analytical Procedure

During the lifecycle of a pharmaceutical product, both the manufacturing process and the analytical procedure are likely to experience a number of changes because of continued improvement activities or the need to operate the method and/or process in a different environment (method transfer).

Depending on the degree of change, the actions required to qualify the change will be different. Some examples are given below:

- A change to a procedure variable to a value within the range that was previously qualified would not require additional experimentation to qualify the change.
- A change to a procedure variable to a value outside the range that was previously qualified to produce fit-for-purpose data would require performance of a risk assessment. The risk assessment should consider which procedure performance characteristics may be impacted by the change and should then perform an appropriate procedure performance qualification study to confirm that the change does not impact the method's ability to meet the ATP.
- A change to a new laboratory would require review of the risk assessment and an appropriate qualification study (which might include comparability testing or a reduced or full requalification).
- A change to a new procedure/technique would require performance of appropriate development and qualification activities (Stages 1 and 2) to demonstrate conformance of the new procedure to the ATP.
- A change impacting the ATP, e.g., a specification limit change or a need to apply the procedure to measure levels of analytes not considered in the original ATP, would require an update to the ATP and a review of the existing procedure design and qualification data (Stages 1 and 2) to determine whether the procedure will still meet the requirements of the new ATP.

The level of activities required to confirm that a changed analytical procedure is producing fit-for-purpose data will depend on an assessment of 1) the risk associated with the change, 2) the

knowledge available about the procedure, and 3) the effectiveness of the control strategy. It is recommended that for all changes, a risk assessment should be carried out to determine the appropriate level of activities required. The aim of the exercise is to provide confidence that the modified method will produce results that meet the criteria defined in the ATP. This may be assessed by considering the risk that the change in the method will have on the accuracy (bias) and precision of the reportable value. Risk assessment tools can be used to provide guidance on what actions are appropriate to verify that the method is performing as required.

Applying a lifecycle approach to analytical procedures should ensure that quality objectives for the reportable values are met on a consistent basis.

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