# Evolution of Analytical Procedure Validation Concepts: Part II– Incorporation of Science and Risk-based Principles in ICH Q14 and Q2(R2) Guidelines

Published on: December 20, 2022

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*This article focuses on drawing parallels between ICH Q14/Q2(R2), United States Pharmacopeia (USP) <1220>, and International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025:2017.*

In parallel to the evolution of compendial and regulatory approaches addressing new quality paradigms for analytical procedure validation (discussed in Part I of this article), fundamentals of the quality by design (QbD) concept have been incorporated into the new International Council for Harmonisation (ICH) Q14 and ICH Q2(R2), which were recently released for public consultation. This article focuses on drawing parallels between ICH Q14/Q2(R2), *United States Pharmacopeia* (*USP*) <1220>, and International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025:2017.

## ICH Q14 Draft Guideline: Analytical Procedure Development

In March 2022, the ICH Q14 draft guideline was published for public consultation aiming to describe science- and risk-based approaches for developing and maintaining analytical procedure suitable for assessing the quality of chemical and biological/biotechnological drug substances and drug products (1). ICH Q14 considers the application of QbD principles to the development and analytical procedure life cycle (APLC) management based on the systematic approach suggested in ICH Q8, together with principles described in ICH Q9.

One of the most significant sections for industry is chapter 7, "*Lifecycle Management and Post-Approval Changes of Analytical Procedures*", which mentions several elements for APLC management, in line with Q12. Examples are established conditions (EC), post-approval change management protocols (PACMPs), product life cycle change management (PLCM), and pharmaceutical quality system (PQS).

In addition, Q14 introduces the elements method operable design region (MODR) and analytical target profile (ATP), which support the industry in applying the enhanced approach and may facilitate regulatory communication of post-approval changes and allow for regulatory flexibility, possibly reducing the burden on industry. Q14 mentions that ATP could also form the basis of a PACMP, which would allow changes between technologies to be reported at a lower reporting category, provided that the previously established performance requirements for a change are met (1). Although Q14 does not clearly emphasize the role of the MODR in the PACMPs, this element could build the basis for allowing suitable risk management, enabling comprehensive analytical changes management within the qualified operating ranges while identifying which conditions meet ATP

## Implications of Q14 and Q2(R2) draft guidelines

**USP <1220>, Q14 and Q2(R2)**

- No additional expectations or mandated requirements are expected in Q14, Q2(R2) and USP <1220>. The minimal approach can still be used.
- Q14 and Q2(R2) are consistent with the principles described in USP <1220>, but not in full agreement.
- Although Q14/Q2(R2) represent great progress towards implementation of sound science and QRM, their publication as separate documents still leaves some gaps since a comprehensive and continuous APLC is not presented.

**ICH Q14**

- Presents strategies that allow for a more comprehensive AP change management and risk assessment (e.g., MODR, ATP, and ACS can be the basis for PACMPs and can be included in the regulatory dossiers).
- Provides flexibility for post-approval changes and potential reduction of burden in the industry.
- Presents the enhanced approach with a focus on fitness for use

**ICH Q2(R2)**

requirements without running additional experimentation or validation. From a compendial perspective, the inclusion of validated MODR in compendial monographs can provide a certain degree of flexibility for risk management to ensure fitness for use ("operating range procedure" instead of "traditional fixed-point procedure"). Other analytical QbD (AQbD) elements may be potentially incorporated into monographs, such as the ATP, replication strategy (e.g., number of injections; sample and standard preparation) and analytical control strategy (ACS [e.g., system suitability and any relevant attribute/requirement]). The ATP and AQbD principles were introduced by joint working groups of the European Federation of the Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2010 (2,3), and later in a few *USP* stimuli articles (4–9) and *USP* <1220> (10). The MODR was introduced by several authors in 2010 (11,12), in *USP* <1220> (10) and in ICH Q14(1). The first official mention of MODR by health authorities was in the European Medicines Agency (EMA)–FDA pilot program report (13).

Key aspects in Q14 include the following:

- Minimal (traditional) or enhanced approaches to analytical procedure development can be applied.



- More connectivity with other stages of the APLC.
- Use of prior knowledge to design a more suitable validation protocol and implementation of risk-based approaches.
- Provides support for validation of multivariate procedures such as PATs using other techniques rather than just chromatographic procedures or offline procedures.
- No changes are required in terms of assessing specificity/selectivity, working range, accuracy and precision.
- An alternative approach for combined accuracy and precision may be used and may help to ensure fitness for use.

**Compendial Activities**

- <1225>, <1226>, and <1224> may be revised since they lack the connectivity to other APLC stages.
- <1039> may be revised to provide guidance on the development of multivariate procedures and complement the principles described in USP <1225> providing support for development of RTRT and PATs.
- <1220> and <1225> may be revised to be harmonized with Q14/Q2(R2).
- AQbD elements may be incorporated into compendial monographs. The enhanced approach may change how compendial monographs are written in the future, providing a certain degree of flexibility.

## Evolution of Analytical Procedure Validation Concepts: Part I – Analytical Procedure Life Cycle and Compendial Approaches

To read Part 1 of this article, click here.

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- The enhanced approach offers a systematic way of developing analytical procedure and managing knowledge. This approach is similar to stage 1 described in *USP* <1220>.
- Knowledge and quality risk management (QRM) are presented as key enablers of the enhanced approach as well as the definition of ATP.
- Other elements included in the enhanced approach are the use of multivariate experiments, establishment of an analytical procedure control strategy, and definition of reporting categories of

ECs, proven acceptable ranges (PARs), or MODR. All this information can be used to build the lifecycle change management plan and can be shared in the regulatory dossiers.

- Q14 highlights the important role of robustness assessment during procedure development.
- Q14 emphasizes the importance of establishing analytical procedure control strategy and recommends ongoing monitoring of selected analytical procedure outputs to look for any trends considering the analytical procedure control strategy as major enabler. However, little guidance is given on how to conduct ongoing monitoring.
- Q14 brings a section dedicated to development of multivariate analytical procedure and real-time release testing (RTRT), building off existing guidance (e.g., Q2(R2) and Q13). It presents the multivariate model lifecycle and provides support for the use of multivariate prediction models for risk assessment.
- A section on submission of analytical procedure–related information has also been included to facilitate harmonization of the level of details submitted by applicants.

As discussed in Part I of this article, the ICH Expert Working Group (EWG) decided to split the APLC stages into Q14 and Q2(R2) guidelines, attempting to not significantly change the structure of Q2(R2) from its previous version (14). Although both guidelines present some level of interconnectivity, stronger connectivity could have been built to facilitate the knowledge management. QRM should be emphasized, because this is what connects all stages. **Tables I and II** show a comparison of terminology and elements between Q14 and *USP* <1220>.

**Table I.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14 and United States Pharmacopeia (USP) General Chapter <1220>–ATP and Stage 1. [Click to enlarge]

| Stages of APLC (<1220>) | APLC Elements | ICH Q14 | USP GC <1220> |
|---|---|---|---|
| ATP | ATP | **Concept:** "It consists of a description of the intended purpose, appropriate details on the product attributes to be measured and relevant performance characteristics with associated performance criteria."<br>"The ATP includes the performance requirements for a single attribute or a set of quality attributes."<br>**Note:** It does not mention the role of measurement uncertainty (MU) and total analytical error (TAE) except in Annex A where TAE is included in the example of ATP. | **Same concept:**<br>"The ATP is a prospective description of the desired performance of an analytical procedure that is used to measure a quality attribute, and it defines the required quality of the reportable value produced by the procedure, aligned with the quality target product profile (QTPP)."<br>It emphasizes the importance of establishing suitable performance requirements (e.g., maximum MU and maximum acceptable total error for quantitative procedures). |
| Stage 1 | Proven Acceptable Ranges (PAR) | "A characterized range of an analytical procedure parameter for which operation within this range, while keeping other parameters constant, will result in an analytical measurement meeting relevant performance criteria. Univariate examination of a single parameter can establish PARs for the analytical procedure." | Concept is not described. |
| Stage 1 | MODR | **Concept:** "It consists of combined ranges for two or more variables within which the analytical procedure is shown to be fit for the intended use."<br>**Movements within range:** "Moving within an established parameter (e.g., PAR or MODR) range does not require regulatory notification."<br>"If appropriately justified and validated a PAR or MODR allows flexibility within the approved range(s) to be managed within a company's PQS. Changes outside of the approved ranges or expansion of said ranges require regulatory reporting."<br>"For practical reasons and following a risk-based approach, it may not be necessary or feasible to validate the entirety of a MODR. The part of a PAR or a MODR intended for routine use in the 210 analytical procedure must be covered by validation data."<br>**Note:** It shows two options for MODR validation, but it does not emphasize the importance of robustness study to generate the MODR. It does not cover a comprehensive validation protocol for MODR. | **Same concept:**<br>**Concept:** "The MODR is the multivariate space of analytical procedure parameters that ensures the ATP is fulfilled and therefore provide assurance of the quality of the measured value. The MODR should ideally be obtained through well-designed experiments that consider multivariate interactions."<br>Knowledge about robustness "also enables the determination of robust operation regions for procedure parameters and, if desired, a method operable design region (MODR)."<br>**Movements within the range:** "An adjustment to a procedure parameter to a value within the range that was previously qualified (e.g., a change within the MODR) may not require additional experimentation before implementation."<br>However, any changes to the routine operating conditions within the MODR should be risk assessed against the ability to meet the ATP criteria and further studies performed as needed prior to implementation of the new operating conditions."<br>**Note:** It does not provide guidance on how to validate the MODR. |
| Stage 1 | Replication Strategy | Mentioned only in Annex A. It does not provide comprehensive guidance. | Replication Strategy is considered as one of the elements of stage 1. |
| Stage 1 | Analytical Control Strategy | "Analytical Procedure Control Strategy (APCS): should ensure that the analytical procedure performs as expected during routine use throughout its lifecycle and consists of a set of controls, derived from current understanding of the analytical procedure including development data, risk assessment and robustness."<br>"It should be defined before validation (ICH Q2) and should be confirmed after validation has been finalized." | **Different term: Analytical Control Strategy (ACS)**<br>**Same concept:** "The ACS is a set of controls needed to ensure the procedure performs as expected and plays a key role in ensuring that the ATP is realized throughout the life cycle. The preliminary ACS is identified during the procedure development process in Stage 1 and includes System Suitability and other environmental or procedure controls needed for the procedure to meet the ATP." |
| Stage 1 | Established Conditions (EC) | "ECs could consist of performance criteria and the analytical procedure principle (i.e., the physicochemical basis or specific technology), and set points and/or ranges for one or more parameters (in line with ICH Q12). ECs can be identified using risk assessment tools prior knowledge, and learnings from uni- and/or multi-variate experimentation." | The term EC is not considered in GC 1220, where the final conditions and the validated operating ranges (portions of the MODR) along with risk criteria and the set of controls can be considered equivalent to EC. |

**Table II.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14 and United States Pharmacopeia (USP) General Chapter <1220> – Stages 2 and 3. APLC is analytical procedure life cycle. [Click to enlarge]

| Stages of APLC (<1220>) | APLC Elements | ICH Q14 | USP GC <1220> |
|---|---|---|---|
| Stage 2: Analytical Procedure Performance Qualification | Procedure Validation | This stage is not covered in Q14. For procedure validation, refer to ICH Q2(R2). | In USP <1220>, the framework proposed to manage procedure life cycle encompasses stage 2 Analytical Procedure Performance Qualification. This may include procedure validation, transfer, and verification. In USP <1220>, "procedure validation" has a broader meaning than in Q2(R2), since it encompasses all activities that take place to ensure that the procedure is fit for use throughout the procedure life cycle. |
| Stage 3: Ongoing Procedure Performance Verification | Ongoing Procedure Performance Verification | "Ongoing monitoring of selected analytical procedure outputs is recommended to look for any trends. Review of analytical procedure outputs facilitates the procedure lifecycle management and enables proactive intervention to avoid failures."<br>Little guidance is provided on stage 3, which is an essential piece of the analytical procedure life cycle. | Stage 3: Ongoing Procedure Performance Verification<br>"ensures that the analytical procedure remains in control during routine use and thus continues to meet the ATP criteria. This stage includes both routine monitoring of data linked to the performance of the analytical procedure and evaluation of the procedure's performance after changes to determine if the analytical procedure continues to be fit for purpose." |
| Life Cycle Management | — | "Changes to analytical procedures can occur throughout the product lifecycle and could involve modification of existing procedures or a complete replacement including introduction of a new technology. The tools and enablers discussed in ICH Q12 are applicable to analytical procedures." | "Changes to analytical procedures may be needed over the life cycle and can be prompted by several events including needed changes identified through a routine monitoring program, the adoption of new technology, or changes to the ATP. Such changes should be risk assessed for their impact to determine the appropriate activities required. In addition, appropriate change management approaches and documentation should be used when making changes to a procedure." |
| Lifecycle Management | Post-Approval Changes of Analytical Procedures | "The use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes." | This is not described. However, <1220> discusses quality risk management as a comprehensive process to allow for managing procedure life cycle and analytical condition changes. |
| All Stages | Development of Multivariate Analytical Procedures | Section 8. Development of Multivariate Analytical Procedures | Not described in <1220>. Few elements are described in USP <1039>, which requires review to become better connected to USP <1220> and provide more guidance on development and validation of multivariate procedures and the multivariate model life cycle. |
| All Stages | Development of Real Time Release (RTR) Testing | Section 9. Development of Analytical Procedures for Real-Time Release Testing. Special Considerations | Not described in <1220>. Few elements are described in USP <1039>, which should be revised to provide guidance for RTRT and process control strategies using process analytical technologies (PATs). These should all be connected to USP <1220> at some point. |

## Q2(R2) Draft Guideline: Validation of Analytical Procedures

ICH Q2(R2) applies to new or revised AP used for release and stability testing of commercial drug substances and products (chemical and biological/biotechnological). However, it can be applied to support clinical studies development, as well as other types of products, with appropriate regulatory authority consultation as needed (15). Q2(R2) can also be applied to other analytical procedure used as part of the control strategy (Q8–Q10) following a risk-based approach (15), enlarging its scope to validate procedures to be used for manufacturing process monitoring and other stages involved in the pharmaceutical product life cycle. Q2(R2) can be seen (in part) as similar to stage 2 described in *USP* <1220>; however, the two documents have the following significant differences:

- Q2(R2) does not include guidance for procedure transfer and verification, which are part of stage 2 in *USP* <1220>.
- The concept of "analytical procedure validation" differs between Q2(R2) and *USP* <1220>.

1. As per *USP* <1220>, "Analytical procedure performance qualification" (APPQ) refers to all activities performed in APLC stage 2, conducted to confirm that the procedure is fit for its intended purpose, and may include "traditional" procedure validation, transfer, and verification (10,16). APPQ is inspired by the term "process performance qualification" included in FDA's guidance on process validation (17), referring to activities that confirm that the commercial manufacturing process design and performance are as expected.
2. As per *USP* <1220>, "AP validation" refers to a broader concept that encompasses all activities that confirm that a procedure is suitable for use and that take place over the entire APLC, not just activities restricted to stage 2 and "traditional validation". Q2(R2) still describes the "traditional" procedure validation concept only. The more holistic concept of validation introduced in *USP* <1220> expands the well-known activities to integrate them into the procedure life cycle and include them in a process that incorporates the ATP. Q2(R2) does not mention ATP and does not emphasize: the link between the ATP performance characteristics and the intended purpose of the reportable value; and the probability assessment of making a wrong decision.

A high-level summary of new principles included in Q2(R2) is provided in the following sections.

**Knowledge management versus checkbox exercise: incorporation of risk-based approach principles**. ICH Q2(R2) emphasizes the importance of using prior knowledge to design the validation protocol and illustrates the interdependencies of APLC stages covered in Q14. The ATP is an element considered as a guide to ensure fitness for use along the entire APLC in *USP* <1220>. However, the ATP was not mentioned in Q2(R2), which still leaves some gaps in ensuring fitness for use and representing the APLC holistically. A new section entitled

"Validation during the lifecycle of an AP" was included to emphasize the importance of APLC management. Q2(R2) mentions that changes may be required during the product life cycle and that science- and risk-based principles can be used to justify whether or not a given performance characteristic needs revalidation. This provides connectivity to Q14 (section 7), which is in line with Q12, and provides a certain flexibility for submission of post-approval changes by the industry.

**Amplify spectrum of analytical techniques and support validation of RTRT**. While ICH Q2(R1) places a greater focus on chromatographic procedures and is not sufficient to establish the suitability of multivariate procedures, Q2(R2) amplifies the spectrum of analytical procedure that it can be applied to, such as UV (entire spectrum), infrared spectroscopy (IR), near-infrared spectroscopy (NIR), nuclear magnetic resonance (NMR), mass spectrometry (MS), liquid chromatography-mass spectrometry (LC-MS), etc. The new section, 3.4, in Q2(R2) provides considerations for validation of multivariate analytical procedure. This supports development of process analytical technologies (PATs), which usually apply multivariate data and require the use of machine learning methodologies for large data set processing and analysis. Q2(R2) builds off existing principles described in Q13 (continuous manufacturing) (18) and supports the development and validation of not just offline procedures but also in-line/online/at-line procedures that can be used for process monitoring/control and RTRT. *USP* <1039> Chemometrics provides general guidance on the application of machine learning algorithms in the development of multivariate procedures; however, it does not provide connectivity to the APLC described in *USP* <1220> and may be revised in the near future to provide best practices for development of PATs and to cover a wider spectrum of analytical techniques. *USP* <1039> may also be used as a risk-based approach for development of different compendial standards, along with *USP* <1220>.

**Performance characteristics at a glance.** In ICH Q2(R2), the language around a few performance characteristics was changed to accommodate suitable considerations for the validation of uni- and multi-variate procedures. **Table III** provides a summary of these changes.

**Table III.** Comparison of performance characteristics described in International Council for Harmonisation (ICH) Q2(R1) and Q2(R2) and how they relate to *United States Pharmacopeia* (*USP*) chapters and ICH Q14.

| Typical Performance Characteristics in Q2(R2) | Comments | Drawing a parallel to existing USP chapters | Connectivity with Q14 |
|---|---|---|---|
| **Specificity/Selectivity** | Q2(R1) mentions only specificity. Q2(R2) mentions both specificity and selectivity, enlarging the applicability of Q2(R2) to other techniques since multivariate techniques usually provide complex data sets containing signals related to several variables. Q2(R2) emphasizes that specificity/selectivity should be demonstrated to fulfill the accuracy requirements by showing unbiased measurement of target compounds individually and/or from other components in the sample matrix. | This may trigger the review of *USP* <1225>. | |
| **Working Range: Linearity, Range, Quantitation Limit, and Detection Limit in Q2(R1)** | In Q2(R2), "Linearity" has been removed and became a broader concept called "Working Range", including:<br>- Suitability of Calibration Model (Linear Response, Non-Linear Response, and Multivariate Calibration)<br>- Lower Range Limit Verification, including Quantitation Limit (QL) and Detection Limit (DL) | This may trigger the review of *USP* <1225> and development of stimuli articles. | |
| **Accuracy and Precision** | Q2(R2) presents a combined approach that can be used as an alternative to evaluating accuracy and precision separately, while Q1(R1) presents only individual assessment of accuracy and precision. | Combined approach is consistent with *USP* <1210> Statistical Tool for Procedure Validation (published in 2018). <1210> Section 3.2 provides examples of combined validation of accuracy and precision using prediction and tolerance intervals. | This provides connectivity to the term included in Q14, "Total Analytical Error (TAE)," since prediction and tolerance intervals are a few approaches that can be used to estimate TAE. In Q14, TAE is considered an alternative approach that may be used to establish performance requirement to be included in the ATP. |

**Table III.** Comparison of performance characteristics described in International Council for Harmonisation (ICH) Q2(R1) and Q2(R2) and how they relate to United States Pharmacopeia (USP) chapters and ICH Q14. [Click to enlarge]

**Table IV.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14, Q2(R2), *United States Pharmacopeia* (*USP*) <1220>, and *International Organization for Standardization/International Electrotechnical Commission (ISO/IEC)* 17025–Part I. GUM is *Guide to the Expression of Uncertainty in Measurement*.

| Concept | ISO | ISO/IEC 17025 | ICH Q14&Q2(R2) | USP <1220> |
|---|---|---|---|---|
| **Fit for purpose** | ISO focuses on the needs of the customer. For analytical chemistry, this includes the client's use of the reportable value.<br>The GUM in its definition of true value states that it must have an uncertainty appropriate for a given purpose.<br>ISO 9001 is based on seven quality management principles (QMP), of which the first is Customer Focus. | "7.2.2.3 The performance characteristics of validated methods, as assessed for the intended use, shall be relevant to the customers' needs and consistent with specified requirements." | "fit for its intended purpose: to measure an attribute or attributes of the analyzed material with the needed specificity/selectivity, accuracy and/or precision over the reportable range."(Q14) | Demonstration of meeting the intended use as specified in the analytical target profile (ATP) through the analytical procedure life cycle (APLC). |
| **Risk** | ISO has many standards dealing with risk, including the ISO 31000 family of standards relating to risk management. | The risk-based thinking has enabled some reduction in prescriptive requirements and their replacement by performance-based requirements. | Q9/Q14 addresses risk extensively. | Addresses risk extensively. |
| **Decision Rules** | Included in many ISO standards (e.g., ISO 14253-1:2017). | Decision rules are included, and their use is required by ISO/IEC 17025:2017,7.8.6. | Decision rules are not mentioned explicitly in Q2 or Q14 but can be used to achieve requirements. | Decision rules are included. |
| **Probability** | For example, ISO 3534-1:2006 | Probability is part of decision rules. | Probability is mentioned under risk. | *USP* <1210> addresses probability. |
| **ATP** | Not included. ISO does require clear, concise, specific understanding of the customer's needs. The ATP is one mechanism to achieve this. | Although the components of an ATP are included (e.g., target MU, probability) the concept of ATP is not included. | Included in Q14, but not in Q2(R2). | Included. Focus on the fit for purpose of the reportable value. |

**Table IV.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14, Q2(R2), United States Pharmacopeia (USP) <1220>, and International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025–Part I. GUM is Guide to the Expression of Uncertainty in Measurement. [Click to enlarge]

## Drawing parallels between ISO standards, ICH Q14/Q2(R2), and *USP* <1220>

The evolution of validation concept principles to a APLC risk-based approach is also occurring in other industries, standard-setting bodies, and regulations. Consequently, they are incorporating similar tools and approaches, often taking these from metrology. In this section, the approaches of the ISO standards, especially ISO/IEC 17025:2017; the ICH Q14/Q2(R2); and *USP* <1220> are presented and compared (**Tables IV and V**). They may use different terms or emphasize various related concepts differently, but they all have this same focus: "ensure that a procedure is fit for use".

Another similarity between these guidelines is the importance of assessing risk. Risk is based on fit for purpose, because risk is assessed by its impact on the analytical procedure's fitness for purpose. In addition, probability is part of risk, where the probability of being wrong (or the probability of a reportable value not being fit for its purpose) is used to assess the risk of making the wrong decision about product compliance/quality. The acceptable probability of being wrong; the clear, concise definition of what is being measured; and the acceptable range of results can be determined using the decision rule, measurand, and target measurement uncertainty and then can be included in the ATP. These items then guide the ongoing analytical procedure performance verification during routine use and also when changes are made. These relationships are shown in **Figure 1**.

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**Table V.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14, Q2(R2), *United States Pharmacopeia (USP)* <1220>, and *International Organization for Standardization/International Electrotechnical Commission (ISO/IEC)* 17025 – Part II.

| Concept | ISO | ISO/IEC 17025 | ICH Q14&Q2(R2) | USP <1220> |
|---|---|---|---|---|
| **Measurand** | Included, see the International Vocabulary of Metrology (VIM) (19) [19]. | Included | The term measurand is not used. ICH does require a complete understanding of the analyte and matrix. | Measurand term is used in conjunction with MU. |
| **Measurement Uncertainty (MU)** | The GUM is the definitive metrological guide dealing with MU. | Section 7.6 deals with MU. MU is used extensively. | ICH mentions uncertainty in regard to the reference AP. | *USP* <1220> and *USP* stimuli article (5) [5] include MU. |
| **Total Error** | The metrological MU (see GUM) is used extensively, while total analytical error (TAE) is not used. Uncertainty includes both systematic and random error. | Uses MU. | Uses TAE. | TAE and MU are treated interchangeably. |
| **Quality by Design** | QMP is included. | QbD is part of method validation. | Driven by AQbD principles | Driven by AQbD principles |
| **AP Qualification/ Method Validation** | Validation is a QMP. | Section 7.2.2 | Integral to Q14. | Stage 2 in Life Cycle. |
| **Ongoing AP Verification** | Ensuring that the results meet customer requirements is a Quality Management Principle. | Section 7.7, Ensuring the Validity of Results | Included under AP Control Strategy. | Stage 3 in Life Cycle. |
| **Statistical Process Control (SPC)** | SPC is part of the Quality Management Principles. | Part of section 7.7 | ICH Q14 does not address SPC specifically, e.g., it does not include control chart use. | Part of stage 3. |
| **Regulations** | May or may not be required by relevant regulations. | Voluntary standard | ICH documents are guides, not standards, in the pharmaceutical industry. They may or may not be referenced by regulations. | USP <1220> is an informational chapter. |

**Table V.** Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14, Q2(R2), United States Pharmacopeia (USP) <1220>, and International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025 – Part II. [Click to enlarge]

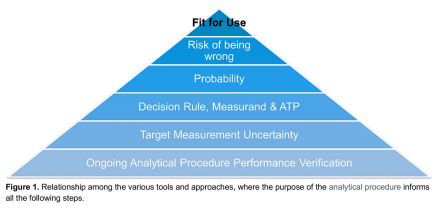


**Figure 1.** Relationship among the various tools and approaches, where the purpose of the analytical procedure informs all the following steps. [Figure courtesy of the authors. Click to enlarge]


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# Write it Down, Investigate, and Control

Published on: January 3, 2023
Susan Haigney

*FDA sent a variety of warning letters to drug manufacturers at the end of 2022 highlighting myriad CGMP and quality control violations.*