ICH Q2(R1)

Terminology on method validation

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What is a "good" test procedure?

Adequate for the intended purpose!!!

- Reproducibility
- Sensitivity
- Robustness
- Reliable
- Easy, fast

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Courtesy of Stefan Christians, PEI, Germany
Method validation: *fit for purpose*

- Good enough to do the job it is designed to do
- Test the performance under conditions of routine use
- Test leads to results that *allow a decision*, e.g. on the conformity of the tested product
ICH Official Website

Welcome to the ICH Official Website

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Since its announcement of organisational changes in October 2015, ICH has grown as an organisation and now includes 16 Members and 32 Observers.

ICH Assembly Chair and Vice Chair

Ms. Lenita Lindstrom-Somers (EC, Europe) and Dr. Gail Laurence (Health Canada, Canada) were re-elected by the Assembly as its Chair and Vice Chair respectively to serve a two-year term.

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ICH products 2020

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities.

Upcoming Events

ICH Guideline Database

Help to Shape the ICH Guidelines

Recent News

ICH M9 and Q&As reach Step 4 of the ICH Process

ICH Q10 Guideline and Q&As on Biopharmaceutics Classification System (BCS) based products reached Step 4 of the ICH Process.

ICH Q10 and Annexes reach Step 4 of the ICH Process


ICH Q10 Addendum reaches Step 4 of the ICH Process

ICH EMA Addendum to Defining the Appropriate Estimation for a Clinical Pharmacokinetic Population

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Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

**Q1A - Q1F Stability**

**Q2 Analytical Validation**

*Validation of Analytical Procedures: Text and Methodology*

The ICH Harmonised Guideline on Test (previously coded Q2A) was finalised under Step 4 in October 1994. This identifies the validation parameters needed for a variety of analytical methods. It also discusses the characteristics that must be considered during the validation of the analytical procedures which are included as part of registration applications.

The ICH Harmonised Guideline on Methodology (previously coded Q2B) was finalised under Step 4 in November 1996. It extends the Guideline Q2A to include the actual experimental data required, along with the statistical interpretation, for the validation of analytical procedures. The Guideline on Methodology has been incorporated into the Guideline on Test in November 2005 and then renamed Q2(R1), without any changes in the contents of the two Guidelines.

*Date of Step 4: 1 November 2005*

*Status: Step 5*

**Implementation status:**

- **ANVISA, Brazil** - Implemented; Date: 1 July 2017; Reference: RDC 166/2017
- **EC, Europe** - Implemented; Date: 1 December 1996; Reference: CPMP/ICH Q2(R)96
- **FDA, United States** - Implemented; Date: 1 May 1997; Reference: Vol. 62, No. 95, p. 27463-7
- **HSA, Singapore** - Implemented; Date: 31 December 2008; Reference: Analytical Validation guidelines
- **Health Canada, Canada** - Implemented; Date: 5 June 2015; Reference: File #: MPS 6859-601
- **MFD, Republic of Korea** - implemented; Date: 1 November 2004; Reference:
Terminology

- Specificity
- Range
- Linearity
- Accuracy
- Precision
- Limit of Detection
- Limit of Quantitation
- Robustness
Specificity

• **Degree of (absence of) interference**
  • **Identity test:**
    Against all other possible components, incl. all other products in facility
  • **Assay/impurity test:**
    Interference of related impurities, degradants, matrix etc., e.g. by spiking into matrix
Range

• Interval for which a suitable level of precision, accuracy and linearity needs to be demonstrated
• Assay: 80 % – 120 % of test concentration
• Content uniformity: 70 – 130 % of nominal level
• Impurity: reporting level – 120% of specification
Linearity

• The ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample
Accuracy

• Closeness of agreement between the found value (measurement) and the true value

Accurate

Inaccurate
Precision

• Closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample

• Repeatability
  • Precision under the same operating conditions over a short interval of time; intra-assay precision

• Intermediate precision
  • Within-laboratories variations

• Reproducibility
  • Precision between laboratories (collaborative studies, usually applied to standardization of methodology)
Accuracy and precision

Accurate
Precise

Inaccurate
Precise

Accurate
Imprecise

Inaccurate
Imprecise
Detection and quantitation limit

• **LOD**
  • Lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value

• **LOQ**
  • The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy
Robustness

• Capacity to remain unaffected by small, deliberate variations in method parameters; indication of reliability during normal usage

• NB: part of method development
Method validation in a changing world

- The ICH Q2 *Analytical Validation* guidelines were developed in the 1990s
- Our view on methods and MD/MV has changed
- ICH Q2 is under revision and a new guideline, ICH Q14 *Analytical Procedure Development* is under development