



05 December 2017
EMA/750178/2017

Essential considerations for successful qualification of novel methodologies

The European Medicines Agency (EMA) qualification of novel methodologies (e.g. biomarkers, clinical outcome assessments, imaging methods, new animal models, statistical methods, innovative trial methodologies, big data approaches) is a voluntary scientific pathway to establish the regulatory acceptability of a specific use of a methodology for the development of medicinal products.

The purpose of this document is to highlight important points to consider that have been identified as common major challenges and limitations which compromise successful qualification of innovative methods.

The following checklist does not provide comprehensive guidance. There is a wide variety of potential specific scientific and regulatory considerations which may best be addressed by requesting qualification advice offered by the EMA¹.

1. Definition of the Context(s) of Use (CoU)

- Full, clear and concise description of the way a novel methodology is to be used and the medicine development related purpose of the use. The Context of Use is the critical reference point for the regulatory assessment of any qualification application.

2. Selection of Endpoint(s)

- Diagnostic and prognostic performance (sensitivity and specificity) should be demonstrated².
- Predictive values for medicine response and likelihood ratio (LR) are to be addressed². Levels of positive or negative predictive value are to be characterised².
- Sensitivity to detect change reflecting the clinical status of patients should be demonstrated.

3. Statistical Analysis Plan (SAP)

- The study design and data analysis must support the intended context of use (CoU).

¹ [EMA/CHMP/SAWP/72894/2008](#)

² [CPMP/EWP/1119/98/Rev. 1](#)



- The statistical planning of the qualification approach must be appropriate and follow a pre-specified statistical analysis plan (SAP)³.
- Exploratory studies and approaches can be included as appropriate.
- Generally, confirmatory studies and data sets are required to achieve the qualification of a method. It will have to be justified whether the qualification objective can be supported appropriately by retrospective studies, or whether prospective studies are required.
- Cross-validation approaches (e.g. due to limitations to obtain appropriately sized exploratory and confirmatory data sets in rare disease scenarios) should apply appropriate methodology and should be pre-specified, not envisaged *post hoc*.

4. Demonstration of clinical utility

- The impact on diagnostic thinking, patient management and clinical outcome must be specified and justified.

5. Standard of truth / surrogate standard of truth

- In case an assessment of the standard of truth (true status of the patient or the value of the measurement) is not possible or unethical (e.g. a required measure is too invasive), a surrogate standard of truth must be established and justified.

6. Appropriateness of the analytical platform

- Technical and performance characteristics must be specified and justified with respect to the Context of Use (CoU).
- Robustness 'fit for purpose' must be demonstrated.
- The analytical platform, as intended for use, must be validated⁴.

7. Other considerations with available regulatory guidance

- Format and data structure: ICH E16⁵ (focus on Pharmacogenomic biomarkers).
- Sampling and data management: ICH E18⁶ (focus on Pharmacogenomic biomarkers).
- Biological matrix sampling, storage and transportation: Reflection paper on pharmacogenomic samples, testing and data handling⁷.

³ [ICH Topic E9, Statistical Principles for Clinical Trials](#)

⁴ [EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**](#)

⁵ [ICH E16, Genomic Biomarkers Related to Drug Response](#)

⁶ [ICH E18, Guideline on genomic sampling and management of genomic data](#)

⁷ [EMA/CHMP/PGxWP/201914/2006](#)