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Bioanalytical Method Validation – FDA & EMA perspectives.

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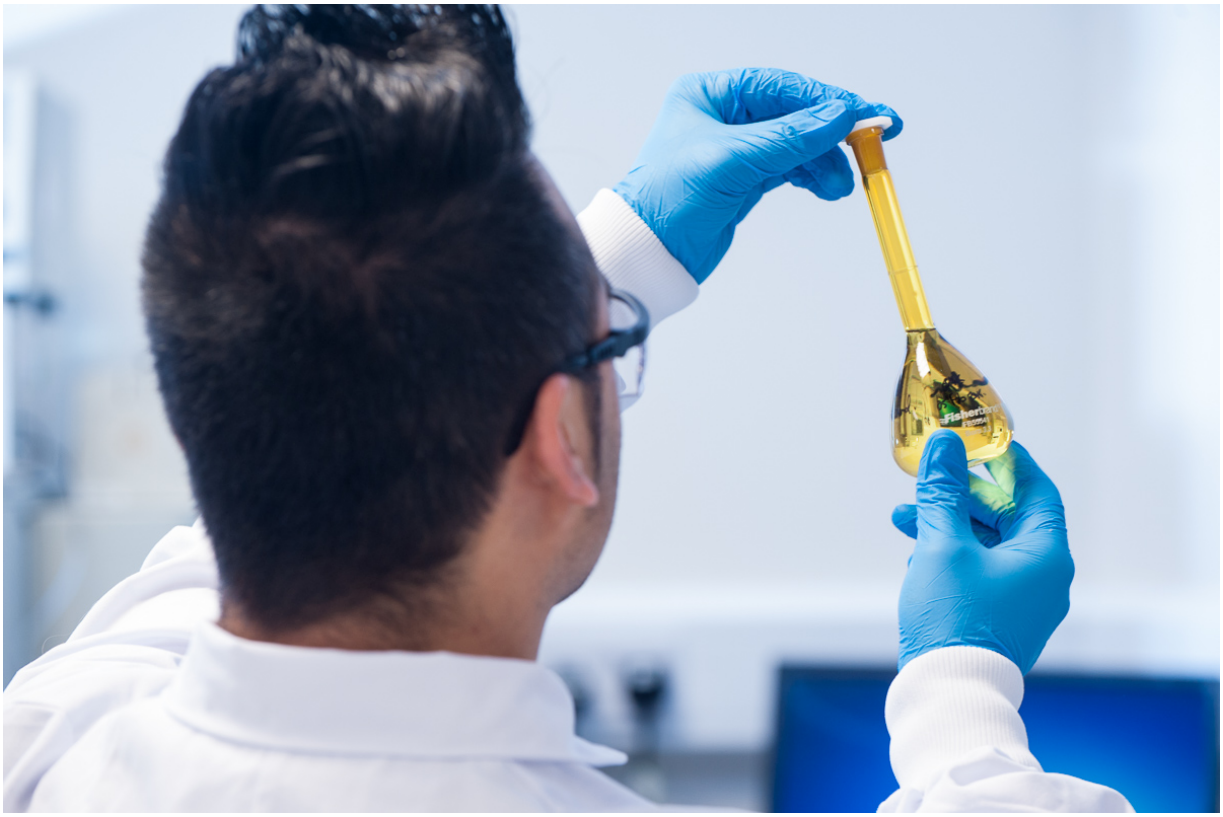

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ICH M10 is a very welcome, comprehensive document and provides much clarity in the area of bioanalytical validation. An overview of comments has recently been published and the industry are awaiting notification of next steps.

Our bioanalytical team within Almac are fully aware of this guidance and are dedicated to providing top quality, specialist bioanalysis and pharmacokinetic analysis services at every stage of your product development cycle from discovery to pivotal clinical studies. We have the ability to provide both bioanalysis and PK data on an interim basis facilitating our clients to make decisions on a continuous basis. This is particularly useful at the Proof of Concept phase or Dose Escalation studies where the pharmacokinetic data is often crucial to making important safety decisions regarding dosing.

Our team is committed to working with our clients to fully understand their projects and ultimate objective. We are equally committed to small standalone bioanalysis projects as well as large projects, where we coordinate all activities from protocol development, CRO selection, in house bioanalysis, PK to integrated ICH report.

Our department combines a depth of experience and expertise with a unique and flexible approach, treating each project separately and providing solutions that are appropriate to the stage of the project and to the client's specific needs. We have 4 study directors at Almac each with >20 years' experience in the field.

Validation is an essential requirement to ensure the reliability of data from preclinical and clinical studies from which key decisions and conclusions are drawn regarding the safety and efficacy of new and existing medicinal products (both human and veterinary). It is critical that the methods used are well characterised and appropriately validated and documented to ensure that reliable data supports key regulatory decisions.

The European Medicines Agency (EMA) issued draft guidance in February 2019 in the form of ICH M10 to provide recommendations for the validation of bioanalytical assays for chemical and biological drug quantification and their application in the analysis of study samples. Notable differences between these guidelines are summarised broadly by the following areas:

- **Terminology:** the FDA references bench-top stability vs EMA's short term stability.
- **Validation parameters and experiments:** one example is where the FDA guidance assumes long term stability at -20 covering lower temperatures, whereas the EMA requires a bracketing approach.

Typically, bioanalytical method validation covers toxicokinetic properties in preclinical studies, PK analysis in clinical studies (Phases I – IV) and BA / BE comparative studies. Whilst the EMA issued guidance in 2011 with the FDA following with guidance for ligand binding assays in 2014, and bioanalytical validation in 2018, there were still many "greys" areas. ICH M10 has consolidated the best practise from these references into one harmonised document and clarified any areas of uncertainty. Additionally, the information in the new guideline applies to the quantitative analysis by ligand binding assays (LBAs) and chromatographic methods such as liquid chromatography (LC) or gas chromatography (GC), which are typically used in combination with mass spectrometry (MS) detection and occasionally with other detectors.

Beginning with method development, the below bioanalytical parameters should be considered to ensure that the method is suitable for validation:

- Reference standard
- Calibration curve
- Quality control samples
- Intra-assay precision
- Carry-over
- Recovery
- Intra-assay accuracy & precision
- Selectivity & specificity
- Matrix effects
- Parallelism (LBA's only)
- Stability (matrix, extract, stock & reference standard/IS)
- Dilution integrity

Whilst extensive record keeping is not required, any changes to procedures should be recorded, as well as any issues with resolutions, to provide a rationale for any changes made to validated methods immediately prior to or in the course of analysing study samples required for further studies.

Within ICH M10 the objective for method validation is to define each parameter and its acceptance criteria, define where each partial or cross validation occurs, and establish the requirements for reference standards and critical reagents. For study sample analysis, the criteria for validity of each analytical run should be considered and noted, as well as the conditions on which reanalysis can be performed. Incurred sample reanalysis should also be considered.

ICH M10 also provides clear guidance on the following areas:

- Partial validation: this means evaluating modifications to fully validated methods. These can range from one within-run accuracy and precision, to nearly full validation. If stability is established in one facility it does not necessarily have to be repeated. Examples where partial validation are appropriate include site change, calibration range and a change in anticoagulant.
- Cross validation: this is performed in advance and only considered appropriate under the following circumstances:
    - Different methods within a study
    - Different methods across studies
    - Using the same method but within a different laboratory
- Cross validation is assessed by measuring the same set of Quality Control documents in triplicate and study samples (>30 if available) with both assays in both laboratories (where applicable).
- Incurred sample reanalysis: this only needs to be performed:
    - For main toxicokinetic studies (once per species)
    - All pivotal bioanalytical (BA) / bioequivalence (BE) studies
    - Pivotal patient trial – once per population
    - Pivotal trial in patients with impaired hepatic / renal function

In terms of quantity of samples required, 10% up to 1000 samples, plus 5% of number of samples exceeding 1000.

Recommended specification limits:

- Chromatographic methods: <20% for 2/3 of repeats
- LBA methods: <30% for 2/3 of repeats

In terms of documentation clarification, ICH M10 requires a detailed table of contents for both validation and bioanalytical reports. It also outlines information to be included in any Common Technical Document generated (section 2.6.4 / 2.7.1):

- Summary of assay methods used for each study
- Summary table of all relevant validation reports including partial and cross validation reports
- Discussion of any method changes (evolution of methods, reasons, unique aspects)
- For comparative BA / BE studies, a list of regulatory site inspections and outcomes.

Other "grey" areas clarified by ICH M10 include:

- Endogenous compounds: the guideline provides detail on 4 acceptable approaches plus standard addition, backward subtraction, surrogate matrix and surrogate analyte
- Commercial kits: it is noted that the kit method must be validated to the standard outlined in ICH Q10
- Dried matrix methods

We would be delighted to hear from you and help with your testing requirements, please contact: almacanalytical@almacgroup.com

References

1. EMA ICH M10 on bioanalytical method validation https://www.ema.europa.eu/en/ich-m10-bioanalytical-method-validation
2. BIOANALYTICAL METHOD VALIDATION20M10212223 Draft version https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-m10-bioanalytical-method-validation-step-2b_en.pdf

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