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accelerating drug development. exactly.

EMA – Have Our Prayers Been Answered!

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Ema (絵馬) are small wooden plaques on which Shinto worshippers write their prayers or wishes.

Global Harmonisation

- Sites in Edinburgh, Montreal and Nevada
- Harmonisation of practices between all sites for BioA work
- Introduction of the EMA guidelines also has to be fitted into the global harmonisation

EMA Guidelines for Bioanalytical Method Validation – Specifics for Implementation

Legal Basis – Validations performed to the principles of the appropriate requirements. GCP or GLP.

Rejection of the LLOQ or ULOQ during validation leads to rejected batch but not during sample analysis – Section 4.1.4 and Section 5.2

Stability – analyse samples immediately after preparation and after storage

EMA Guidelines for Bioanalytical Method Validation – Specifics for Implementation

Section 4.1.4 – If the next validation batch also fails, then the method should be revised before restarting validation.

Section 5.2 – The overall (mean) accuracy and precision of the QC samples of all accepted runs should be calculated at each concentration level and reported in the analytical report. In case the overall mean accuracy and precision exceeds 15%, this should lead to additional investigations and justifying this deviation.

EMA Guidelines for Bioanalytical Method Validation – Preclinical Specific Problems

Section 4.1 – Generally a full validation should be performed for each species and matrix concerned.

Section 4.2 – Changes for which a partial validation may be needed include…..another matrix or species.

Matrix Effects – Hyperlipidaemic plasma.

Are we really adding value to preclinical by adding more and more cost to the validation of methods for preclinical studies!

Matrix Effects – Haemolysed Plasma

Section 4.1.8 – In addition to the normal matrix it is recommended to investigate matrix effects on other samples e.g. haemolysed and hyperlipidaemic plasma samples.

Our approach

Six independent sources of matrix must be checked for matrix effects, if plasma then one source must be investigated also once the sample have been haemolysed (blood should be frozen before centrifugation to mimic a worst case scenario), exceptions for a difficult or rare matrix are allowed.

Blood Stability

Section 4.1.9 – Sufficient attention should be paid to the stability of the analyte in the sampled matrix directly after the blood sampling of subjects and further preparation before storage, to ensure that the obtained concentrations by the analytical method reflect the concentrations of the analyte in the subject at the moment of sampling. A demonstration of this stability may be needed on a case-by-case basis, depending on the structure of the analyte.

Our approach

Comparative analysis of blood spiked and stored and spiked and analysed. n=6 at LQC and HQC concentrations are assuming 50% plasma yield. Acceptance 15% of the difference between the means of the CV's of each set.

Stability

Stability assessments are done at LQC, HQC and DIQC

This gives us coverage for samples analysed with dilution which during preclinical and early clinical can be significant.

ISR

Section 6 – However as a guide 10% of the samples should be reanalysed in the case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples.

This seems sensible but if you have 1001 samples you would run 50 ISR samples!

Suggestion – 10% for less than 1000 samples,

5% if more than 2000 samples,

100 ISR samples if between 1000 and 2000 samples

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Yes – In many ways the EMA document is more specific and gives guidance based on the most current thinking in bioanalysis.

FDA document is appearing over the horizon!

Acknowledgements

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Thank you for listening.
Any Questions?