The EMA Bioanalytical Method Validation Guideline: process, history, discussions and evaluation of its content.

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on behalf of EBF

Presented at:

5th EBF Open Symposium

16 November 2012

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1: EMA processes

EMA BMV Guideline: Dates & Places

- **18-Dec-2008**
  Concept paper/recommendations on the need for a (CHMP) guideline on the validation of bioanalytical methods
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002964.pdf

- **19-Nov-2009**
  Draft. Guideline on the validation of bioanalytical methods
  http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500018062.pdf

- **21-Jul-2011**
  Guideline on the validation of bioanalytical methods
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

- **21-Jul-2011**
  Overview of comments received on 'Guideline on the validation of bioanalytical methods'
  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/08/WC500109687.pdf

EMA BMV Guideline: who, why & how

- Rapporteur: Netherlands
  Co-Rapporteur: France
  Inspectors
- EMA: no bioanalytical guideline available
- New BE guideline with a section on bioanalytical methods
- ICH/FDA/current scientific knowledge

European Medicines Agency (EMA)

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 18 December 2008
Doc. Ref. EMEA/CHMP/EWP/531305/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER/RECOMMENDATIONS ON THE NEED FOR A (CHMP) GUIDELINE ON THE VALIDATION OF BIOANALYTICAL METHODS

AGREED BY EFFICACY WORKING PARTY	October 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 December 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2009

Concept paper/recommendations on the need for a (CHMP) guideline on the validation of bioanalytical methods

PROBLEM STATEMENT

- The CHMP does not have a Note for Guidance on validation of bio-analytical methods, although analytical methods and validations are included in most application dossiers.
- The new guideline will provide recommendations for the validation of a bioanalytical method. Next to that, specific topics should be addressed with regard to the bioanalytical method, i.e. the actual analysis of study samples.
- Furthermore it is not the purpose of the new guideline to introduce fully new criteria, but it should be in line with current scientific knowledge on this topic.

European Medicines Agency

London, 19 November 2009
Doc. Ref: EMEA/CHMP/EWP/192217/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON VALIDATION OF BIOANALYTICAL METHODS

DRAFT AGREED BY THE EFFICACY WORKING PARTY	September 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 November 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2010

Draft - Guideline on validation of bioanalytical methods

SCOPE

- This guideline provides requirements for the validation of bioanalytical methods.
- In addition, specific aspects of the bioanalytical method itself will be addressed, e.g. the actual analysis of samples from toxicokinetic studies and clinical trials.
- Furthermore, this guideline will describe when partial validation or cross validation may represent an appropriate alternative approach to the complete validation of an analytical method.
- Some special techniques such as radio-labeled analysis methods using ^{14}C labeled drugs, are not covered here, but even in such cases efforts should be made to apply to the principles of this guideline.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMEA/CHMP/EWP/192217/2009
Committee for Medicinal Products for Human Use (CHMP)

Guideline on bioanalytical method validation

Draft agreed by the Efficacy Working Party	September 2009
Adoption by CHMP for release for consultation	19 November 2009
End of consultation (deadline for comments)	31 May 2010
Agreed by Pharmacokinetics Working Party (PKWP)	June 2011
Adoption by CHMP	21 July 2011
Date for coming into effect	1 February 2012

EBF

Guideline on bioanalytical method validation

Scope

- This guideline provides recommendations for the validation of bioanalytical methods applied to measure drug concentrations in biological matrices obtained in animal toxicokinetic studies and all phases of clinical trials. As ligand binding assays differ substantially from chromatographic analytical methods, separate validation recommendations for ligand binding assays are provided.
- In addition, specific aspects for the analysis of study samples will be addressed.
- Furthermore, this guideline will describe when partial validation or cross validation should be carried out in addition to the full validation of an analytical method.
- Methods used for determining quantitative concentrations of biomarkers used in assessing pharmacodynamic endpoints are out of the scope of this guideline.

2: EBF interactions

EBF activities

- Concept paper (Dec 2008)
  - Jan 2009 discussions during closed meeting
  - Jan-Feb 2009 collect comments from members
  - Mar 2009 provide EBF comments to EMA
  - Dec 2009 session during 2nd EBF open symposium
- Draft guideline (Dec 2009)
  - Jan-Feb 2010 collect comment from members
  - Apr 2010 EBF/EUFEPS workshop
  - May 2010 symposium at NBC 2010
  - May 2010 provide EBF comments to EMA
  - Dec 2010 'GBC session' at 3rd EBF open symposium
- Final guideline (Jul 2011)
  - Aug-Oct 2011 collect comments from members
  - Nov 2011 session at 4th EBF open symposium
  - Mar 2012 discussion on implementation at EBF closed workshop 2012

EBF workshop on implementation of EMA BMV guideline

- Divided the guideline in 10 parts
  - All molecules: Summary – 3, 5, 6 and 8 - definitions
  - Small: 4 - 4.1.3, 4.1.4 - 4.1.7 and 4.1.8 - 4.4
  - Large: 7 - 7.1.1.6, 7.1.1.7 - 7.1.1.13 and 7.2 - 7.3.3
- Groups of ± 6 members preparing a part
- Excel and powerpoint templates for group presentations
- Workshop 15-16 March 2012

EBF workshop on implementation of EMA BMV guideline

Evaluate guideline focusing on:

- Challenges on implementation:
  - Common understandings
  - Ambiguities
  - Technical or operational challenges
  - Issues
- Differences to FDA 2001 guidance and subsequent Crystal City white papers [16-18)

- Outcome and recommendations are planned to be published in Bioanalysis Q1 2013

3: Final EMA BMV guideline

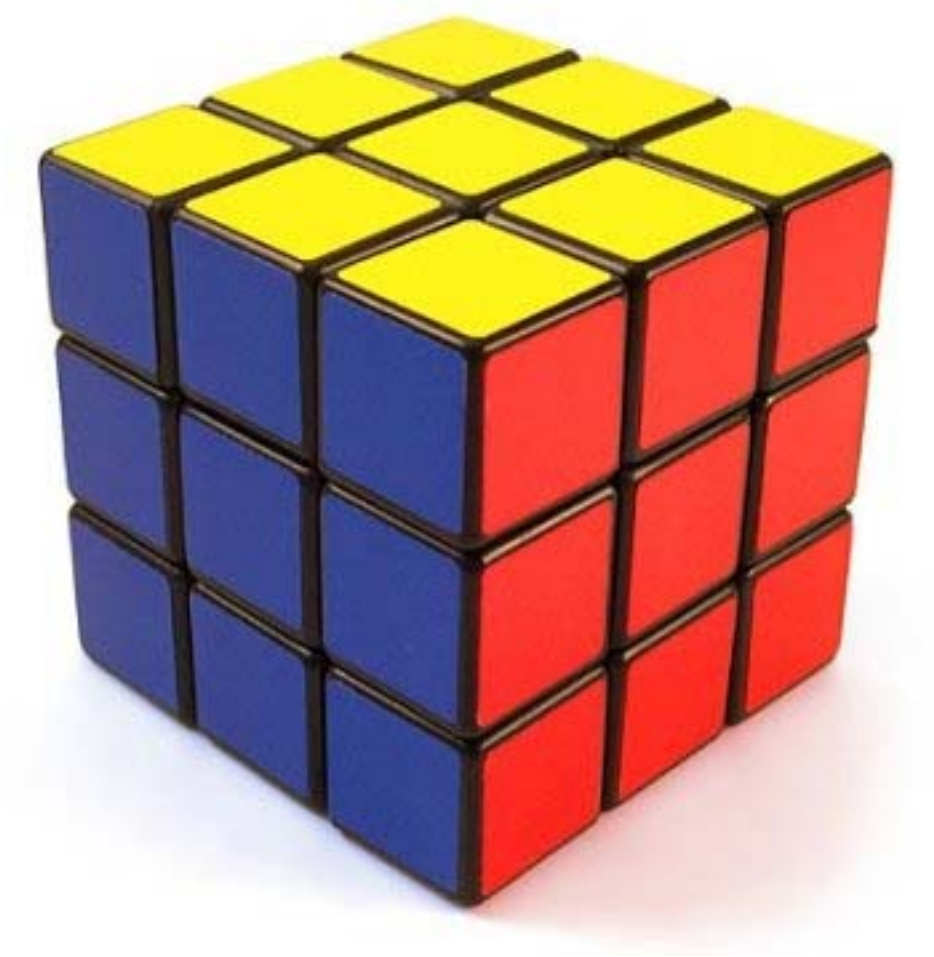

Table of contents

Table of contents (continued)

Some reflections

- Well written
- Clear structure
- Clear distinction between method validation and sample analysis
- First BMV guideline addressing the specifics for LBA/macromolecules
- Defines applicable quality systems: GLP (pre-clinical) and GCP (clinical)
- Good match with current thinking in BA community
- Good fit with EMA Bioequivalence guideline*)
- Fits with developing concepts within EMA on GCP for bioanalytical laboratories

- *) BUT: Clinical studies under GLP

Part 4: Points of attention

Points of Attention

- 3. Legal basis
  - Clinical: validation and sample analysis according to GCP
    - Reference to: “Reflection Paper for Laboratories that perform the analysis or evaluation of clinical trial samples”
  - Pre-clinical: GLP validation for GLP studies
    - ‘Non-GLP pre-clinical: fit for purpose

- 4.1 Full validation of an analytical method
  - Generally a full validation should be performed for each species
    - Note: Partial validation for species or matrix change (4.2 Partial validation)
  - Reference standards: CoA of IS is not mandatory
  - Recommended to use stable isotope labeled IS for MS based assays

Points of Attention (continued)

- 4.1.1 Selectivity
  - Special attention to metabolites and their stability
  - Test on co-medication normally used in the subject population
- 4.1.4 Calibration curve
  - 75% with a minimum of 6 must be within ± 15% (20% lloq)
  - Two consecutive failed batches: revise method before restarting validation
- 4.1.5 Accuracy and 4.1.6 Precison
  - QC levels: Lo 3x LLOQ, Me at 50% of cal curve range, Hi at 75%
  - Statistics: between-run accuracy = overall accuracy
  - Statistics: between-run precision = overall precision

Points of Attention (continued)

- 4.1.7 Dilution integrity
  - Dilution integrity should cover the dilution applied to the study samples
- 4.1.8 Matrix effect
  - 6 individual samples, two concentrations, haemolysed and hyperlipidaemic
- 4.1.9 Stability
  - Stability during sampling/before storage (blood)
  - Multi analytes: stability in matrix containing all analytes
  - LTS results must be available before issuing the study report
- 4.2 Partial validation
  - Changes for which a partial validation may be needed … another matrix or species
    - Note: Generally a full validation should be performed for each species (4.1 Full validation)

Points of Attention (continued)

- 4.3 Cross validation
  - Different methods. How different can different be before it is different?
- 5.2 Acceptance criteria for the analytical run
  - Runs ≠ batches
  - Multiple analytes: one curve for each analyte. If one fails, others can still be reported.
  - If overall mean precision and accuracy exceeds 15% an investigation must be started. In BE studies: “may result in rejection of the data”
- 5.4 Reanalysis of study samples
  - Deviating IS response: sample reanalysis
- 6. Incurred sample reanalysis
  - 10% for first 1000, 5% of the rest
  - Follows principles of EBF recommendation paper

Points of Attention (continued)

- 7. Ligand binding assays
  - First guideline specifically addressing LBA
  - No (major) deviations from the current practices
  - Follows general principles as for small molecules/chromatographic assays
- 8 Reporting
  - 20% Chromatograms in BE studies, representative in other cases.
  - Report overall statistics of QCs

- General
  - Recovery: not requested by EMA (but in FDA 2001)
  - Runs ≠ batches

Part 5. References

References - Papers

- **European Bioanalysis Forum and the way forward towards harmonized regulations**
  Berthold Lausecker, Peter van Amsterdam, Margarete Brudny-Kloeppel, *et.al.*
  Bioanalysis, Aug 2009, Vol. 1, No. 5, Pages 873-875

- **Incurred sample reproducibility: views and recommendations by the European Bioanalysis Forum**
  Philip Timmerman, Silke Luedtke, Peter van Amsterdam, *et.al.*
  Bioanalysis 1(6), 1049-1056 (2009)

- **Towards harmonized regulations for bioanalysis: moving forward!**
  Peter van Amsterdam, Berthold Lausecker, Silke Luedtke, *et.al.*
  Bioanalysis, Apr 2010, Vol. 2, No. 4, Pages 689-691

- **SQA opinion paper on global harmonization of the bioanalytical method validation guidances**
  Christopher Tudan, Stephen Rogenthien, Anthony Jones
  Bioanalysis, Dec 2010, Vol. 2, No. 12, Pages 1921-1925.

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- **Bioanalytical method validation: notable points in the 2009 draft EMA Guideline and differences with the 2001 FDA Guidance**
  Graeme Smith
  Bioanalysis (2010) 2(5), 929–935

- **Workshop/Conference Report on EMA Draft Guideline on Validation of Bioanalytical Methods**
  Henning Blume, Erich Brendel, Margarete Brudny-Klöppel, *et.al.*
  European Journal of Pharmaceutical Sciences 42 (2011) 300–305

- **Building the Global Bioanalysis Consortium – working towards a functional globally acceptable and harmonized guideline on bioanalytical method validation**
  Peter van Amsterdam, Mark Arnold, Surendra Bansal, *et.al.*
  Bioanalysis, Nov 2010, Vol. 2, No. 11, Pages 1801-1803.

- **Conference Report: US FDA/EMA harmonization of their bioanalytical guidance/guideline and activities of the Global Bioanalytical Consortium**
  Fabio Garofolo, Josée Michon, Virginie Leclaire, *et.al.*
  Bioanalysis, Feb 2012, Vol. 4, No. 3, Pages 231-236.

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  Peter van Amsterdam, Arjen Companjen, Margarete Brudny-Kloeppel, *et.al.*
  Bioanalysis, 2013

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- **European Medicines Agency draft guideline on validation of bioanalytical methods.**
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- **Guideline on the validation of bioanalytical methods**
  EMEA/CHMP/EWP/192217/2009
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

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- **Guideline on the investigation of Bioequivalence**
  CPMP/EWP/QWP/1401/98
  http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

- **Reflection Paper for Laboratories that perform the analysis or evaluation of clinical trial samples**
  EMA/INS/GCP/532137/2010
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/09/WC500096987.pdf

- **Overview of comments received on 'Guideline on the validation of bioanalytical methods'**
  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/08/WC500109687.pdf

- **Overview of comments received on 'Reflection paper on Guidance for laboratories that perform the analysis or evaluation of clinical samples**
  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500122956.pdf

Acknowledgements

- Jan Welink (MEB) and Olivier Le Blaye (affsaps) for allowing me to use a number of their slides
- EBF members for participating in surveys, evaluating the concept, draft and final guideline and co-authoring, reviewing and editing EBF presentations and papers
- EBF SC for reviewing the slide deck
- The EMA for stimulating us to continuously improve our work
- JBF for giving me the opportunity to present at their 2nd Japan Bioanalysis Forum meeting.
- Acbio for giving me the opportunity to present at their 1st Latin American Meeting on Bioanalysis