

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

Peter van Amsterdam on behalf of EBF

Presented at:

2nd JBF meeting

9 March 2012, Tokyo

Contents

- 1. EMA processes
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- 5. References

Part 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 <u>http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002964.</u> <u>pdf</u>

> 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

<u>http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500018062</u> .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)





EMA - European Medicines Agency

CHMP - Committee for Human Medicinal Products

Member/Member State (n=27)
 Alternate/MS
 Member from Iceland & Norway
 Co-opted members







Drafting the Bioanalytical Guideline



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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.

Draft Bioanalytical guideline: timeline







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



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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-labelled analysis methods using ¹⁴C labelled drugs, are not covered here, but even in such cases efforts should be made to apply to the

principles of this guideline.



From draft to final: Consultation period

Comments received from > 50 sources

Informal and formal contacts with FDA, under confidentiality agreements

Discussions at workshops, meetings...

- EBF 2nd open symposium: Barcelona, Dec 2009
- EBF/EUFEPS workshop: Brussels, April 2010
- CVG 4th WRIB: Montreal, Apr 2010
- EBF symposium @NBC: San Francisco, May 2010
- BFG Symposium @AAPS: New Orleans, Nov 2010
- EBF 3rd open symposium: Barcelona, Dec 2010



Consultation period: received comments





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				



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.



Part 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 problem solving \rightarrow do a survey

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EMA concept paper The survey: some facts

Date Survey (sent out) : 27th Jan 2009
 Date Survey (data received): 15th Mar 2009
 Survey data consolidation: 10 days
 Survey outcome approval time: 4 days



Consolidated results



EBF problem solving → do a survey outcome





Consolidated EBF Feedback to EMA - considerations

Covers all aspects of EMA concept paper

Covers all aspects of FDA/CDER 2001 Guidance

 Guidance for Industry Bioanalytical Method Validation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001



Consolidated EBF Feedback to EMA – considerations – continued

Covers 2006 Crystal City III recommendations

 Workshop/Conference Report — Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays. C. T. Viswanathan et al. The AAPS Journal 2007 9 (1)

Considers other related regulations/guidance

- OECD: e.g. OECD GLP 1-15
- ICH: e.g. ICH S3A, ICH E6, ICH Q2
- FDA: e.g. 21CFR 320.29, 21CFR part 58, 21CFR part 11
- EMA: e.g. CPMP/EWP/QWP/1401/98
- MHRA: e.g. Lab GCP guidance 07/2009



EBF provided general comments

EBF supports the EMA guideline as a step towards further harmonization in bioanalysis: as a consequence, the guideline shouldn't have different recommendations from FDA as outlined in [1-3] and associated conference reports and white papers, and it should stimulate towards an ICH guideline in the near future. Contradictions in various guidances could lead to non-resolvable uncertainties in the bioanalytical community and/or undue duplication of work

EBF would also appreciate a guidance on biomarkers

However, due to the broad array of BM assays and technologies used we do not suggest to include it in this guidance as it would increase the complexity



EBF provided general comments – cont.

EBF's comments refer to chromatographic assays, LBAs, cell based and all other type of assays used for quantitation for non-clinical and clinical PK purposes.

therefore

- The guideline should clearly outline the different recommendations and acceptance criteria for LC-MS/MS assays and LBAs
- The chapter "reanalysis of subject samples" should differentiate between reanalysis due to technical and human error (e.g. instrument failure, mistake during manual pipetting), obviously implausible PK results (e.g. outliers on PK profile, control sample contamination) and incurred sample reproducibility (ISR).



Detailed feedback to EMA on all topics touched by the concept paper:

- Introduction
- Problem Statement
 - Application of guideline
 - GLP
- Complete Validation
- Reference standard
- Specificity
- Sensitivity
- Limit Of Detection LOD
- LLOQ ULOQ
- Range of Calibration Curve
- Accuracy Precision
- Dilution Integrity, Parallelism

- Stability
- Robustness
- Matrix effects
- Partial and Cross Validations
- Bioanalytical Method: analysis of (study) samples
- Reanalysis of subject samples
- Re-integration of chromatograms
- Incurred Sample Reanalysis (ISR)
- Rare Matrices
- Carry over
- Determination of metabolites during development



EBF workshop on implementation of EMA BMV guideline

Divided the guideline in 10 parts

- All molecules: Summary 1 2 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 \pm 6 members preparing a part
- Excel and powerpoint templates for group presentations
- Workshop 15-16 March 2012

Outcome and recommendations are planned to be published in Bioanalysis Q2/Q3 2012



Part 3: Final EMA BMV guideline





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 (preclinical) 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



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 - 7.1. Method validation
 - o 7.1.1. Full validation (multiple subchapters)
 - 7.2. Partial validation and cross-validation
 - 7.3. Analysis of study samples
 - o 7.3.1. Analytical run
 - o 7.3.2. Acceptance criteria for study sample analysis
 - o 7.3.3. Incurred samples reanalysis

8. Reports

- 8.1. Validation report
- 8.2. Analytical report
- Definitions



SMALL/CHROMATOGRAPHY	LARGE/LIGAND BINDING						
1 Intro	oduction						
2 S	Scope						
3 Leg	al basis						
4.1.1 Selectivity	7.1.1.3 Selectivity 7.1.1.2 Specificity						
4.1.2 Carry-over	7.1.1.4 Carry-over effect						
4.1.3 LLOQ							
4.1.4 Calibration curve	7.1.1.7 Calibration curve						
4.1.5 Accuracy 4.1.6 Precision	7.1.1.8 Precision and accuracy						
4.1.7 Dilution integrity	7.1.1.9 Dilutional liniarity						
4.1.8 Matrix effect	7.1.1.5 Matrix selection 7.1.1.6 Minimum required dilution						
4.1.9 Stability	7.1.1.11 Stability of the samples						
4.2 Partial validation4.3 Cross validation	7.2 Partial validation and cross validation						
	7.3.1 Analytical run						
5 Analysis of study samples	7.3.2 Acceptance criteria						
	7.1.1.1 Reference standards						
6 ISR	7.3.3 ISR						
	7.1.1.10 Parallelism						
	7.1.1.12 Reagents						
	7.1.1.13 Commercial kits						
8 Reports							



Part 4: Points of attention





Points of Attention

- ➤ 3. Legal basis
 - Clinical: validation and sample analysis according to GCP
 - o Reference to: "Reflection Paper for Laboratories that perform the analysis or evaluation of clinical trial samples"
 - Pre-clinical: GLP validation for GLP studies
 - o '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
 - o 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



- ➤ 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 \pm 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, <u>Me at 50% of cal curve range</u>, Hi at 75%
 - Statistics: between-run accuracy = overall accuracy
 - Statistics: between-run precision = overall precision



- ➤ 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
 - o Note: Generally a full validation should be performed for each species (4.1 Full validation)



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- ➤ 4.3 Cross validation
 - Different methods. How different can different be before it is different?
- ➢ 5.2 Acceptance criteria for the analytical run
 - Runs \neq 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



- 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 \neq batches

Part 5. References





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