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
2. EBF interactions
3. Content guideline
4. Points of attention
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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
  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

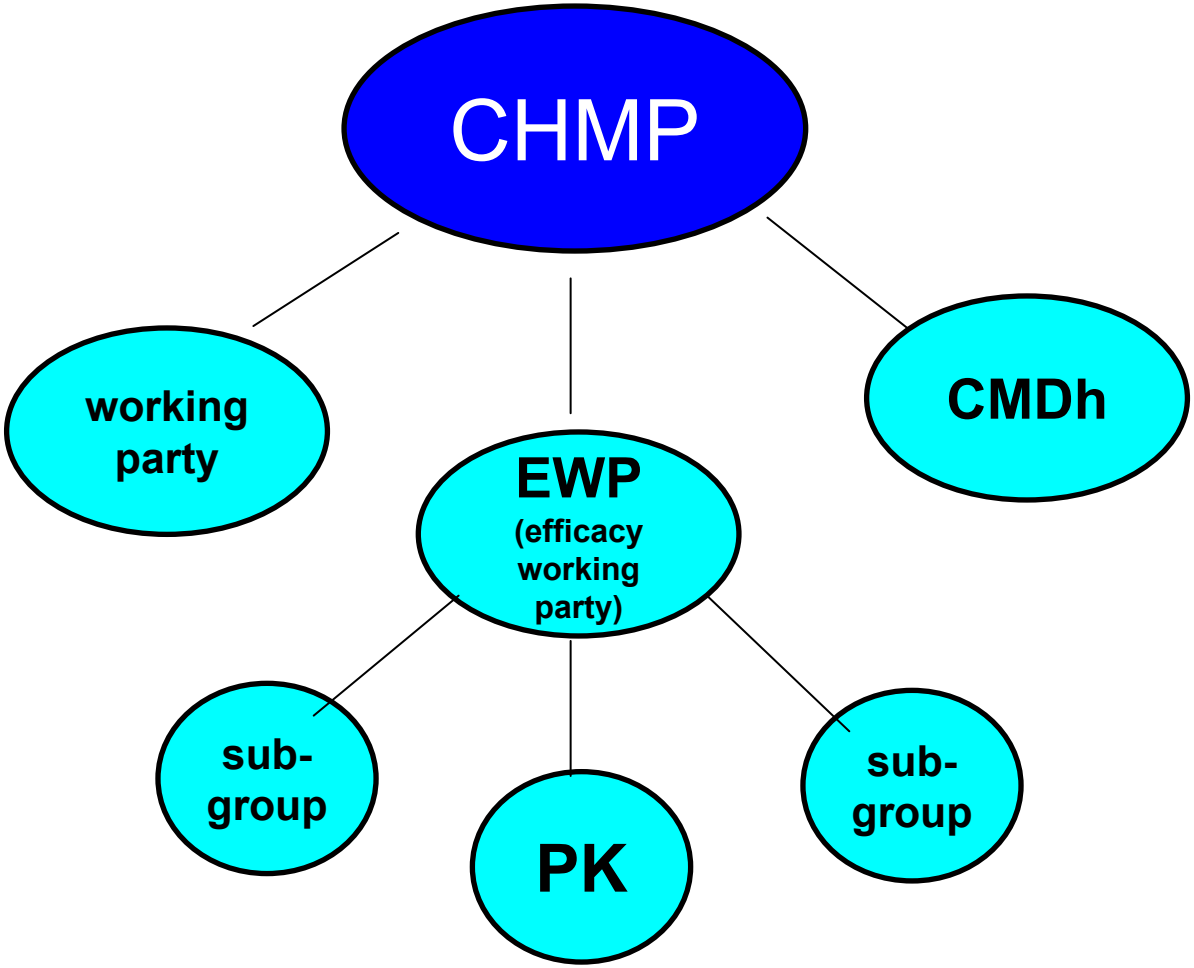
European Medicines Agency (EMA)

EMA - European Medicines Agency

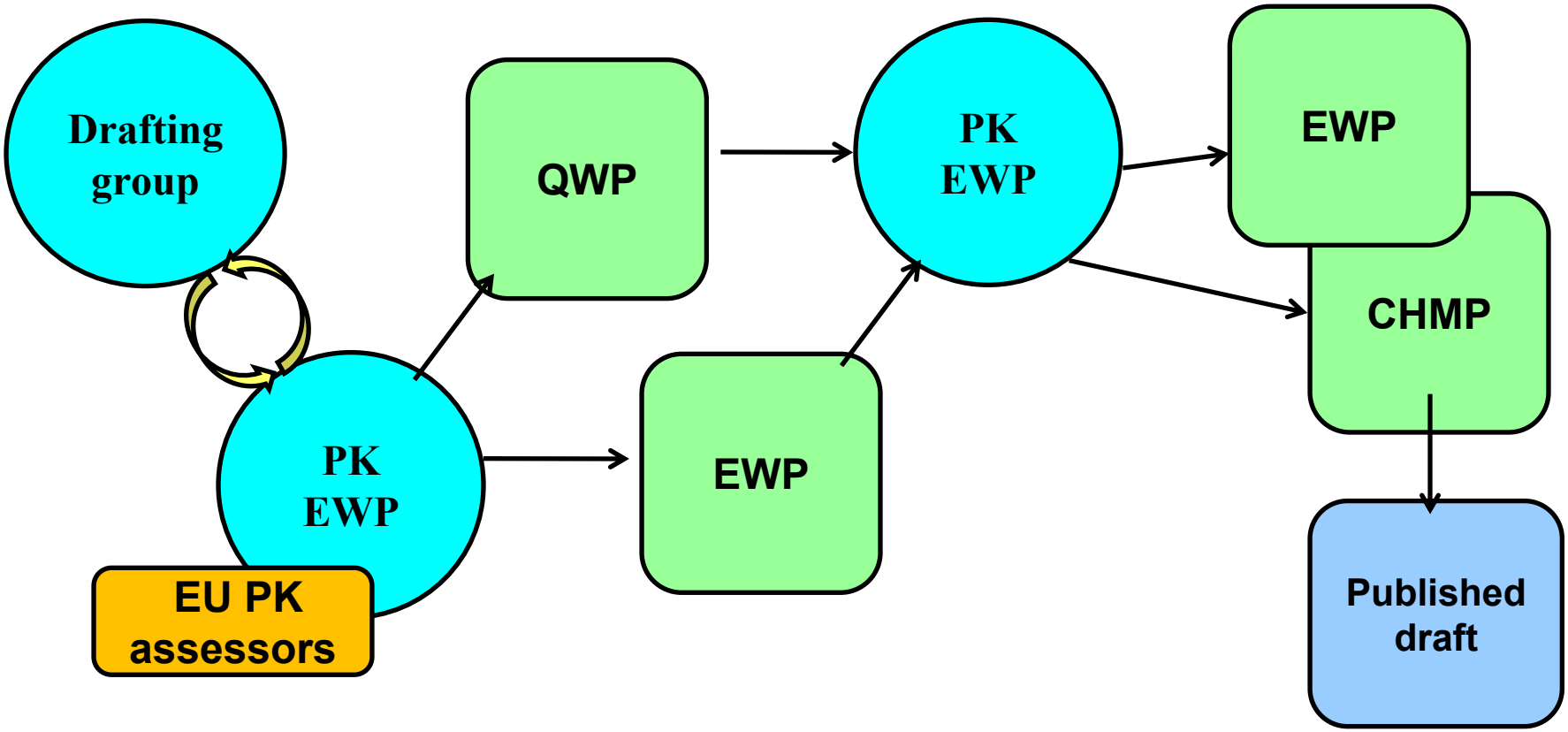
CHMP – Committee for Human Medicinal Products

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

Committee for Human Medicinal Products



Drafting the Bioanalytical Guideline



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

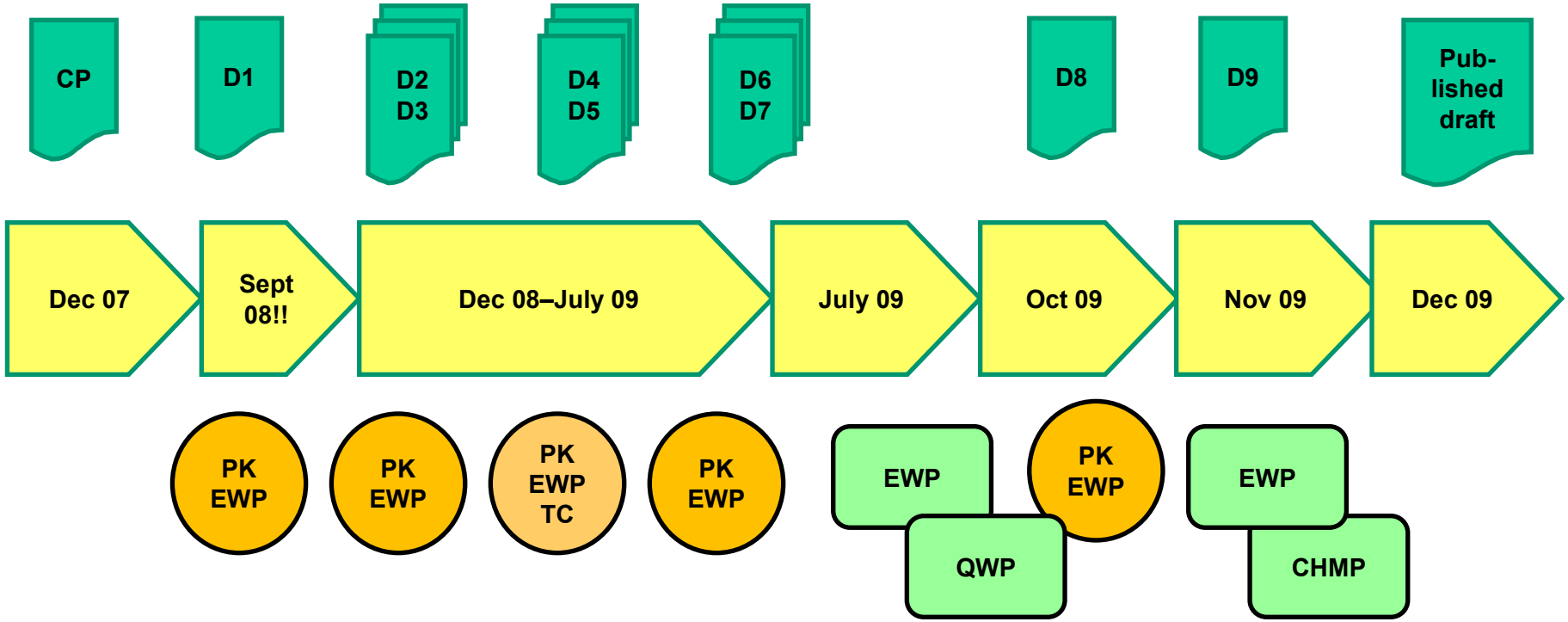
AGREED BY EFFICACY WORKING PARTY	October 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 December 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2009

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



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

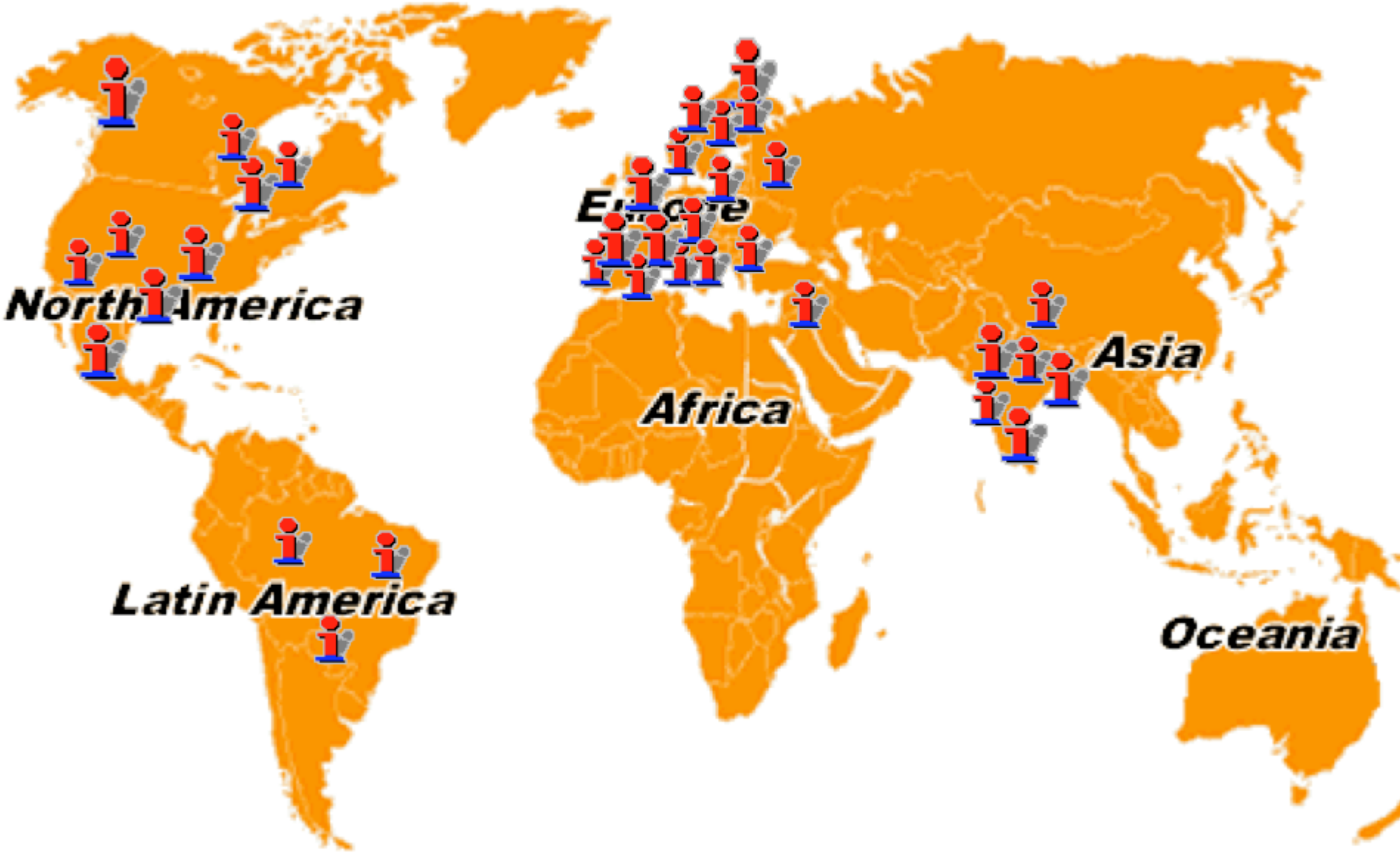
SCOPE

- 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-labelled analysis methods using ^{14}C 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



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

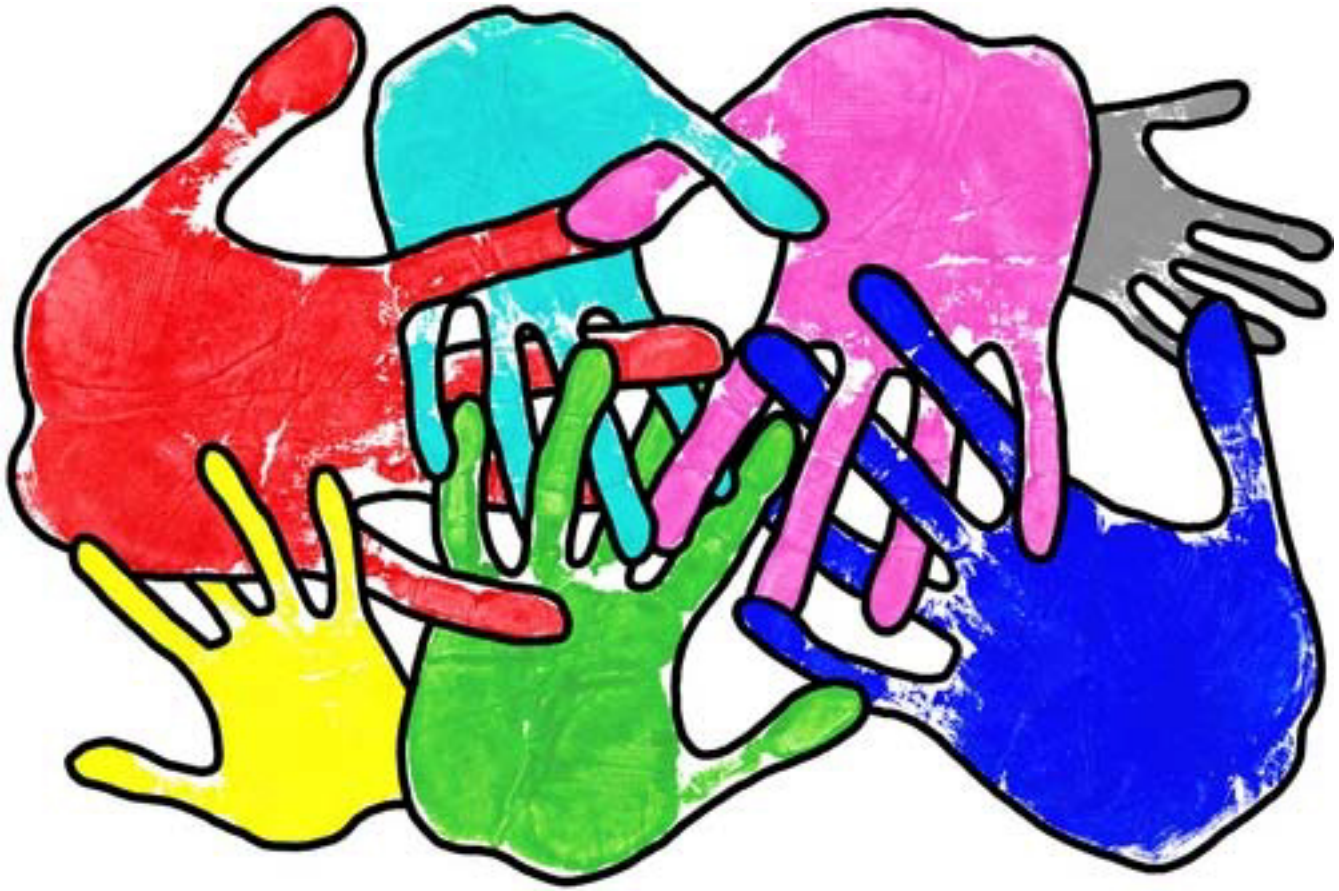
EBF

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.

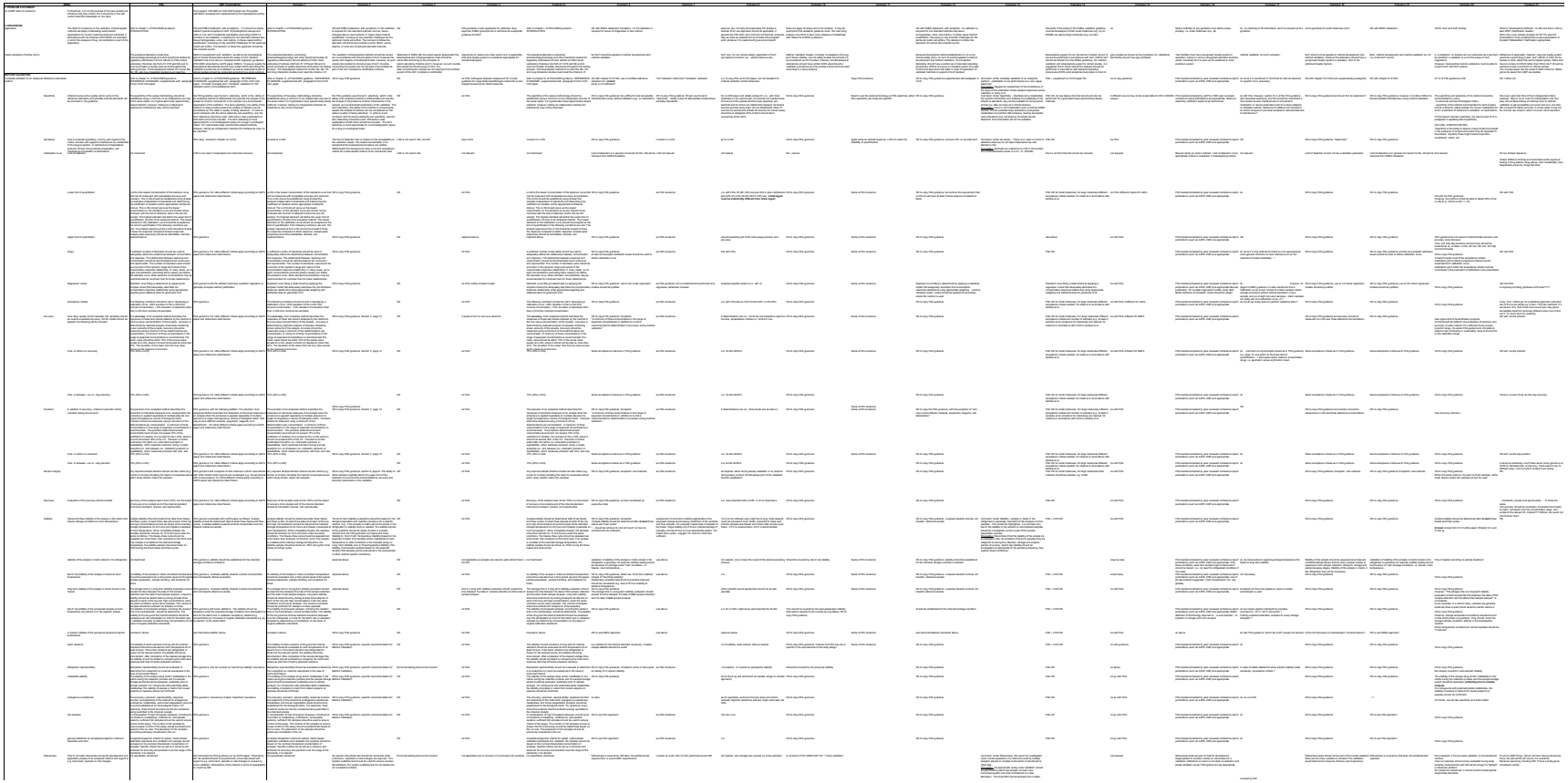
Part 2: EBF interactions



EBF activities

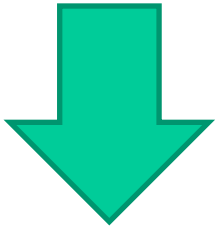
- Concept paper (Dec 2008)
  - Jan 2009 discussions during closed meeting
  - Jan-Feb 2009 collect comments from members
  - Mar 2009 provide EBF comments to EMA
  - Dec 2009 session during 2nd EBF open symposium
- Draft guideline (Dec 2009)
  - Jan-Feb 2010 collect comment from members
  - Apr 2010 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 → do a survey



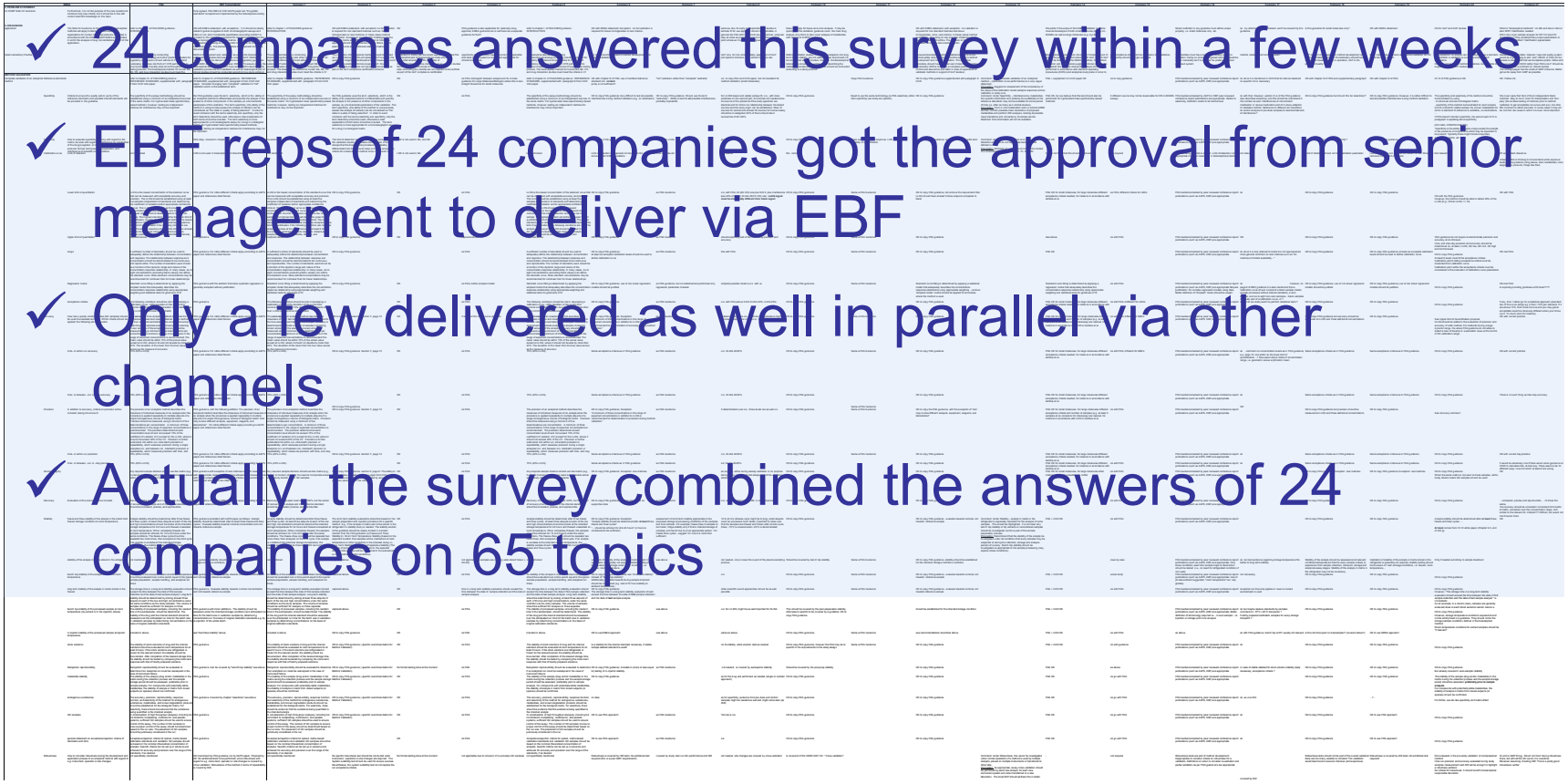
EMA concept paper
The survey: some facts

- 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



- ✓ 24 companies answered this survey within a few weeks
- ✓ EBF reps of 24 companies got the approval from senior management to deliver via EBF
- ✓ Only a few delivered as well in parallel via other channels
- ✓ Actually, the survey combined the answers of 24 companies on 65 topics

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:

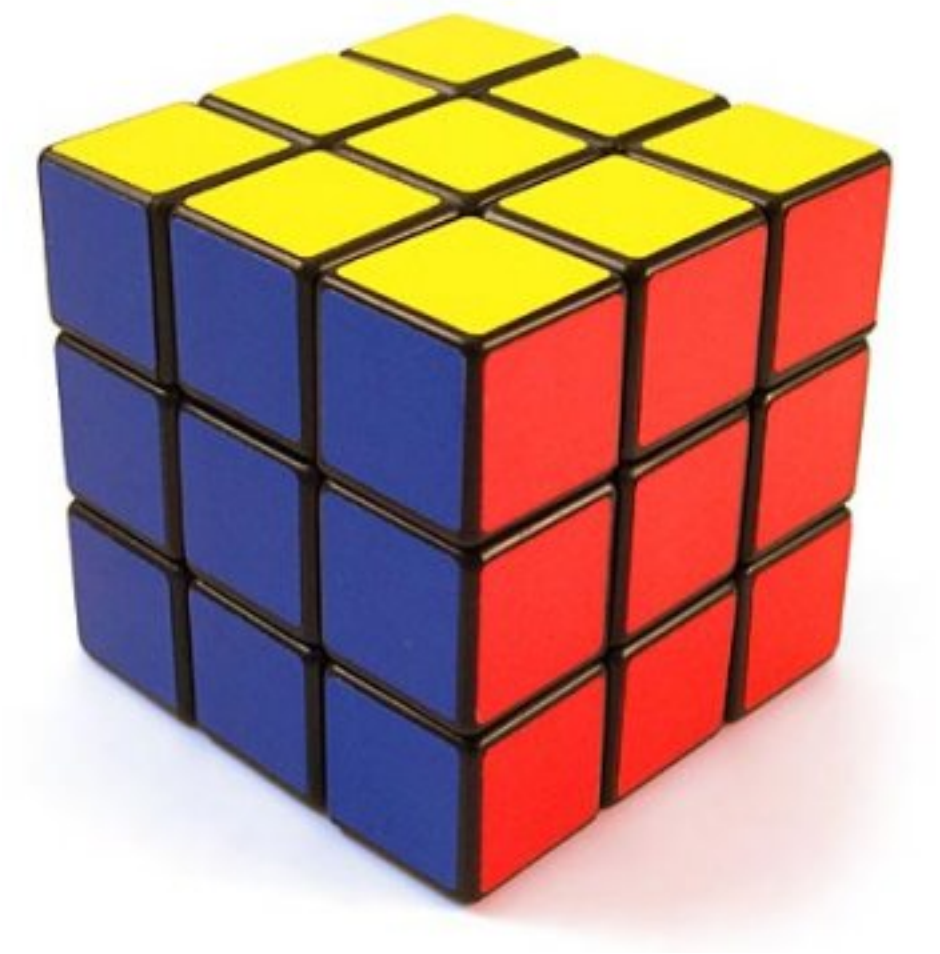
- Introduction
- Problem Statement
  - Application of guideline
  - GLP
- Complete Validation
- Reference standard
- Specificity
- Sensitivity
- Limit Of Detection LOD
- LLOQ - ULOQ
- Range of Calibration Curve
- Accuracy - Precision
- Dilution Integrity, Parallelism
- Stability
- Robustness
- Matrix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

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4.1.4 Calibration curve 4.1.5 Accuracy 4.1.6 Precision 4.1.7 Dilution integrity	7.1.1.7 Calibration curve 7.1.1.8 Precision and accuracy 7.1.1.9 Dilutional liniarity
4.1.8 Matrix effect 4.1.9 Stability 4.2 Partial validation 4.3 Cross validation	7.1.1.5 Matrix selection 7.1.1.6 Minimum required dilution 7.1.1.11 Stability of the samples 7.2 Partial validation and cross validation
5 Analysis of study samples	7.3.1 Analytical run 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
    - 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, Silke Luedtke, Philip Timmerman
  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, Margarete Brudny-Kloeppel, Berthold Lausecker
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  Peter van Amsterdam, Berthold Lausecker, Silke Luedtke, Philip Timmerman, Margarete Brudny-Kloeppel
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- **SQA opinion paper on global harmonization of the bioanalytical method validation guidances**
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  Bioanalysis, Dec 2010, Vol. 2, No. 12, Pages 1921-1925.

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  Greame 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-Klo¨ppel, Sylvia Grebe, Berthold Lausecker, Gabriele Rohde, Christoph Siethoff
  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, Douglas Fast, Fabio Garofolo, Steve Lowes, Philip Timmerman, Eric Woolf
  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**
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  Bioanalysis, Feb 2012, Vol. 4, No. 3, Pages 231-236.

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

- **European Medicines Agency draft guideline on validation of bioanalytical methods.**
  EMA/CHMP/EWP/192217/2009
  www.ema.europa.eu/pdfs/human/ ewp/19221709en.pdf

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  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

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  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500122956.pdf

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- 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 symposium.

EBF Brussels 2012 Conference 'Hatching' - European Bioanalysis Forum

http://bru2012.europeanbioanalysisforum.eu/

references

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