

# Current Developments in Guidance for Regulatory Bioanalysis

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# Content

- Regulatory Bioanalysis – some definitions
- Development and History of Guidance for Regulatory Bioanalysis
- Present Status of Guidance Documents
- Future Developments for Guidance

# Regulatory Bioanalysis

## Definition:

Determination of Drug(s) and/or metabolites in biological samples from clinical trials as part of a drug development package.

## Samples:

- Plasma
- Serum
- Urine
- Tissues

# Regulatory Bioanalysis

Methodologies have evolved over the years:

- HPLC – UV, Fluorescence, Electrochemical Detection
- GC – FID, NPD, MS
- LC-MS, LC-MS/MS
- Ligand Binding assays – RIA, ELISA

Common Theme – Determination of unknown trace levels of analytes in complex matrices.

# Regulatory Bioanalysis

Methods must be:

- Accurate
- Precise
- Sensitive
- Specific
- Practicable
- Transferable

These aspects of a method should be demonstrable to give confidence in results generated from application of the method

# Regulatory Bioanalysis

Defining method performance parameters before application of a method to sample analysis = Method Validation

But...

Also need to show that in practice the method remains under control and performs as expected on every occasion it is applied to sample analysis

# Guidance Pre 1990...

# First Steps

1990 Dec 3-5: 1<sup>st</sup> AAPS/FDA Workshop on Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetic Studies

1992 Workshop Report: Shah, V.P. et al., Pharm Res, 1992; 9:588-592



# Experiences of the 1992 Workshop Report

Useful in terms of defining:

- what parameters should be included in a basic Bioanalytical Method Validation
- Target Acceptance/Rejection Criteria associated with Key Validation Parameters

Flexible in terms of how Validation parameters should be defined

# Evolution of Formal Guidance

Based on the 1992 Workshop report, almost every company involved in Drug Development had its own particular approach.

Industry viewed some degree of harmonisation as beneficial, even though this would mean some loss of flexibility.

New technologies (particularly LC-MS/MS) created the need for additional validation parameters.

Increased awareness of the need to develop and refine the 1992 'Guidance' to ensure Quality of Data through uniform interpretation.

# Developments

January 1999: Draft Guidance on Bioanalytical Methods Validation was issued by FDA

January 12-14 2000: 2<sup>nd</sup> AAPS/FDA Workshop on Bioanalytical Methods Validation • A Revisit With a Decade of Progress. Summarised in the 2000 Workshop Report: Shah, V.P. et al., *Pharm Res*, 2000; 17:, 1551-1557

2001 Guidance on Bioanalytical Methods Validation issued by FDA  
([www.fda.gov/cder/guidance/4252fnl.pdf](http://www.fda.gov/cder/guidance/4252fnl.pdf))

# Experiences with 2001 Guidance

Written for Bioequivalence and Bioavailability Studies, but used for all types of clinical trials

More defined framework of definitions and instructions for:

- Method Development
- Method Validation
- Method Application

Final Destination?

# Further Developments

Rapid expansion of LC-MS/MS technologies

Increased use of Ligand Binding Assays

High Profile Problems

...Further Guidance needed.

# Next Steps..

May 1-3 2006: 3<sup>rd</sup> AAPS/FDA Bioanalytical Workshop, on Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays

2007 Workshop Report, Viswanathan, C. T. et al, AAPS Journal, 2007, 9, E30-42 Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays ([www.aapsj.org/articles/aapsj0901/aapsj0901004/aapsj0901004.pdf](http://www.aapsj.org/articles/aapsj0901/aapsj0901004/aapsj0901004.pdf)) *Pharm. Res.* 24(10),1962–1973 (2007)

# Developments from 2006 Workshop

7-8 February 2008: AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples – Implications of Crystal City Recommendations

Fast DM, Kelley M, Viswanathan CT et al. Workshop report and follow-up – AAPS workshop on current topics in GLP bioanalysis: assay reproducibility for incurred samples – implications of Crystal City recommendations. AAPS J.11(2),238–241 (2009).

# 2001-2008

2001 FDA Bioanalytical Guidance in use as a global reference document for Regulatory Bioanalysis.

Areas of changing/developing expectations arising from inspections and concerns highlighted in literature and at meetings were addressed with workshops and reports and changes in practice.



# A Second BMV Guideline!

2008: European Medicines Agency, Committee for Medicinal Products for Human Use. *Concept Paper/Recommendations on the Need for a (CHMP) Guideline on the Validation of Bioanalytical Methods.* European Medicines Agency, London, UK.

Concern: Confusion might be caused with 2 different Bioanalytical Guidelines resulting in divergent or conflicting recommendations in different regions

Solution? Consultation!

# EBF and the EMA Guideline

European Bioanalytical Forum (EBF): Established 2006 by European Pharmaceutical Companies actively engaged in Bioanalysis to discuss best practices and common problems in Bioanalysis.

EBF held closed and open meetings and organised sessions to discuss the EMA concept paper with regulators and the broader bioanalytical community.

# Development of the EMA Guidelines

2009: European Medicines Agency, Committee for Medicinal Products for Human Use. *Draft Guideline on the Validation of Bioanalytical Methods*. European Medicines Agency, London, UK issued for consultation and feedback.

Discussions were held within EBF and AAPS and feedback provided to EMA.

# Implementation of EMA Guideline

The EMA released the final version of its BMV guideline with an overview of the comments received on 21 July 2011 with a date of implementation of 1st February 2012

European Medicines Agency, Committee for Medicinal Products for Human Use. *Guideline on Bioanalytical Method Validation*. European Medicines Agency, London, UK (2011).

## 2 Guidance Documents..

Experiences: there are no significant differences and what differences exist are a consequence of developments in the technology and science being used in Bioanalysis. There is no evidence for divergent thinking between the US and Europe.

Bioanalysis March 2013, Vol. 5, No. 6, Pages 645-659

The European Bioanalysis Forum community's evaluation, interpretation and implementation of the European Medicines Agency guideline on Bioanalytical Method Validation

# What Next?

Global Guidance? – (GBC)

New FDA Guideline

Other Developments

# Birth of Global Bioanalysis Consortium

GBC = Global Bioanalysis Consortium

Conception: 4<sup>th</sup> Calibration and Validation Group Workshop on recent Issues in Regulated Bioanalysis – Montreal, Canada, 22-23 April 2010

281 delegates from 165 companies engaged in Regulatory Bioanalysis in North America, Latin America, Europe, Africa and Asia

Summarised in:

2010 White Paper on Recent Issues in Regulated Bioanalysis & Global Harmonization of Bioanalytical Guidance

Bioanalysis: December 2010, Vol. 2, No. 12, Pages 1945-1960

# GBC

## Objective:

The creation of a group consisting of scientific associations with international profiles (including AAPS, EBF, CVG and APA) to harmonise the current and prospective Guidances to create a single universal set of standards that would be acceptable to regulators in all countries.

## More information:

<http://www.globalbioanalysisconsortium.org/>



# GBC Structure I

## Steering Committee

- 3 Asia Pacific Representatives (China, India, Japan)
- 3 European Representatives
- 3 North American Representatives (USA, Canada)
- 1 Latin American Representative

## Scientific Leadership Team

- Steering Committee plus Harmonisation Team Leaders

# GBC Structure II

## Harmonisation teams

- Topics relevant to All Molecules – 11 'A' Teams
- Topics specific to Large Molecules – 6 'L' Teams
- Topics specific to Small Molecules – 3 'S' Teams

## Team Content

- Team Lead
- 9-11 representatives drawn from each global sector

Teams and Committees include representatives from Pharma companies and CROs

# GPC Teams

## All Molecule Teams

- A1 - Scope & Regulations
- A2 - Tiered approaches for method validation
- A3 - Method transfer, partial/cross validations
- A4 - Reference standards and reagents
- A5 - Sample Management
- A6 - Stability
- A7 - Repeat analysis and ISR
- A8 - Documentation
- A9 - Analytical instrument qualification
- A10 - New Frontiers
- A11 - Biomarkers

## Large Molecule Teams

- L1 - Large molecule specific run acceptance
- L2 - Large molecule specific assay operation
- L3 - Assay formats
- L4 - Reagents and their stability
- L5 - Automation practices in LM bioanalysis
- L6 - Immunogenicity - Effect on PK

## Small Molecule Teams

- S1 - Small molecule specific run acceptance
- S2 - Small molecule specific assay operation
- S3 - Chromatographic run quality assessment

# GBC Outcomes

The conclusions and recommendations from the various sub teams are available on the GBC Website and were published as Global Webinars in May 2013

# FDA New Guideline

April 2009: Brian P Booth (Deputy Director, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US FDA) announced that a draft revision to the 2001 BMV Guidance would be initiated later the same year.

## Objective:

- Better definitions of acceptance criteria for ligand-binding assays.
- Develop better specifications for defining appropriate QC samples
- Address concerns relating to Carryover/contamination and matrix effect
- Define ISR Expectations
- Reporting of rejected runs, QC results and re-assayed samples.
- Make representations on a tiered approach to 'metabolites in safety testing' (MIST)
- Update system suitability specifications to cover the Crystal City III White Paper
- Develop topics with no consensus
  - Different Anticoagulants
  - Analysing samples from animals of different sex on preclinical studies
  - Assays for biomarkers

2009 White Paper on Recent Issues in Regulated Bioanalysis from The 3rd Calibration and Validation Group Workshop Bioanalysis, : January 2010, Vol. 2, No. 1, Pages 53-68

# Publication of Draft FDA Revised Guidance

Released 12 September 2013

<http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>

Note:

Draft – Not for Implementation!

- Contains Nonbinding Recommendations!

# Draft FDA Revised Guidance

## First Impressions:

- Good 'flow' of presentation of information
- Balance of topics relating to Chromatographic and Ligand Binding Procedures with as much common ground as possible
- No conflict with EMA or earlier FDA Guidance
- Less detail than expected in some areas

# Differences in Draft Guidance *cf* 2001 Guidance

- Different Structure
- Inclusion of as much detail on LBA as on chromatographic methods
- Inclusion of ISR recommendations
- Subtle differences in expectations. For example..
  - 2001 ‘...calculations of accuracy and precision excluding values that are determined as outliers can also be reported’
  - 2013 ‘...calculations of accuracy and precision excluding values that are determined as outliers should also be reported’



# Differences in Draft Guidance *cf* 2001 Guidance

- Specific detailed written description of the bioanalytical method to be established *a priori* (Chromatography and LBA)
- Specification of a minimum number of runs for Validation (Chromatography and LBA)
- Recommend Cals and QCs should be prepared from Different Stock solutions – if only 1 used for both, at least 1 Accuracy and Precision data set should be submitted where these were prepared separately (Chromatography and LBA)
- Details about Batch content in relation to plates: each plate should have its own full set of QC samples (Chromatography and LBA)
- If a new QC concentration has to be added (eg to cover samples falling into only part of calibration range) this should be validated before use (Chromatography and LBA)

# Differences in Draft Guidance *cf* 2001 Guidance

- Concentrations below the LLOQ should be reported as zeros
- Monitor IS for drift. To be covered by an SOP.
- Validation Reporting should include:
  - Details of all experiments and whether they passed or failed and reason for failure
  - Data from all stability experiments
- Sample Analysis Reporting should include:
  - All accepted and rejected analytical runs

# Differences in Draft Guidance *cf* 2001 Guidance

- System Suitability
- If a unique or disproportionately high concentration of metabolite discovered in human studies, a fully validated assay may need to be developed for the metabolite.
- Section on Additional Issues:
  - Endogenous compounds
  - Biomarkers
  - Diagnostic Kits
  - New Technologies

# Surprises?

Matrix Effects – Discussed at some length in relation to LC-MS/MS in the White paper, covered in EMA Guidance, but only general references in the draft Guidance:

*‘...ensure the lack of matrix effects throughout application of the method’ and ‘ Matrix effects on ion suppression or enhancement should be addressed’ for chromatography*

*‘The calibration in biological fluids should be compared with calibrators in buffer to detect matrix effects using at least ten sources of blank matrix.’ for LBA*

# Surprises?

- CarryOver – Discussed at some length in the White Paper and EMA Guidance, but only mentioned briefly in draft Guidance
- LBA – No mention of expectations or requirements for duplicate sample analysis other than the use of duplicate non-zero standards for Calibration Curves
- Stability –
  - Amend to relate ‘Measured’ to ‘Nominal’ instead of Day ‘0’ result. No further comment about Day ‘0’
  - No comment about use of data at -20°C in relation to storage at -70°C

# Surprises?

- System Suitability:
  - *'If system suitability is assessed, a specific SOP should be used. Apparatus conditioning and instrument performance should be determined using spiked samples independent of study calibrators, QCs or study samples.'*

# Draft Guidance versus Expectations

## Objective:

- Better definitions of acceptance criteria for ligand-binding assays ✓
- Develop better specifications for defining appropriate QC samples ✓
- Address concerns relating to Carryover/contamination and matrix effect ✗
- Define ISR Expectations ✓
- Reporting of rejected runs, QC results and re-assayed samples. ✓
- Make representations on a tiered approach to 'metabolites in safety testing' (MIST)
- Update system suitability specifications to cover the Crystal City III White Paper
- Develop topics with no consensus
  - Different Anticoagulants ✗
  - Analysing samples from animals of different sex on preclinical studies ✗
  - Assays for biomarkers ✓

# Next Step

Before issue of Final Revised FDA Guidance there will be a consultation period of 90 days.

- By 12 Dec 2013 there will be an FDA/AAPS meeting to discuss the draft Guideline (CC-V)
- In advance of CC-V, the GBC will meet to discuss the draft Guidance
- Either Draft Guidance or outcome of CC-V will be discussed at EBF Open Meeting Barcelona, 20-22 Nov 2013



# Other Developments

## Japan

2009-2011 Discussions leading to the establishment of the Japanese Bioanalytical Forum (JBF) in August 2011 and issue of draft BMV Guidelines for small molecules in March 2012 which was updated in April 2013. The draft guidelines do not conflict with EMA Guidance.

[http://www.nihs.go.jp/drug/BMV/BMV\\_draft\\_130415\\_E.pdf](http://www.nihs.go.jp/drug/BMV/BMV_draft_130415_E.pdf)

Regulated bioanalysis in Japan: where do we come from and where are we going? Noriko Katori, *Bioanalysis*, June 2013, Vol. 5, No. 11, Pp 1321-1323

## China

Identified the need for Harmonised Regulations in 2010 and is working to develop a Chinese Specific Guideline that will be in Harmony with existing and projected international guidelines through the Chinese Bioanalysis Forum (CBF)

Society Spotlight: China Bioanalysis Forum. Daniel Tang *et al*, *Bioanalysis*, March 2013, Vol. 5, No. 6, Pages 641-643

## Brazil

Created a working group in November 2010 and issued a Draft Guidance on BMV in June 2011, with ANVISA Bioanalytical Guidance RDC27/2012 issued in May 2012 and in effect from December 2012. Broadly compatible with the EMA Guidance and sets out minimum criteria for approval in Brazil.

<http://www.in.gov.br/visualiza/index.jsp?data=22/05/2012&jornal=1&pagina=93&totalArquivos=192?>

# Prognosis?

With 2 Major Guidelines in force, there has been no evident conflict, largely due to a healthy dialogue between AAPS/EBF and Regulators.

Can this continue with a revision of the FDA Guidance and a further 3 Guidelines coming into play?

Based on the Draft FDA Guidance of Sept 2013, there is no reason to expect an upset with the new FDA Guidance once finalised.

# The Future

Formal Global Guidance from GBC?

Thank you for your Attention

# Questions?

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