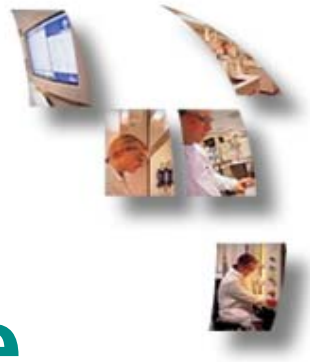


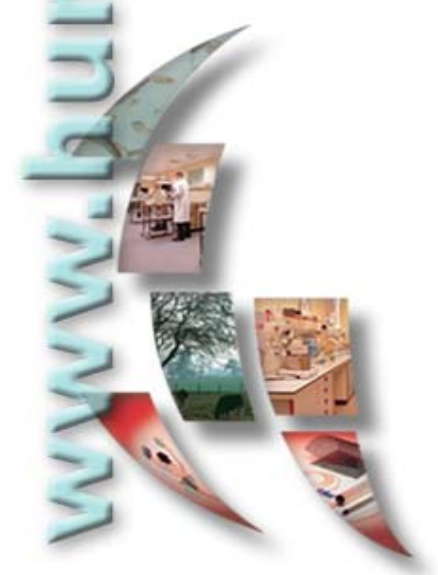
Method validation status versus regulatory compliance status

John Smeraglia

Associate Director
Bioanalytical Sciences

Huntingdon Life Sciences

EBF Open Symposium, Barcelona,
14-16 November 2012



Overview

- Method validation status versus regulatory compliance status – what's the problem?
- What are the bioanalytical guidelines for?
- What are the various GxPs for?
- How do we bring science and regulatory compliance together?

What's problem?

- Confused relationship between the bioanalytical guidance documents and regulatory compliance
- Widespread misapprehension that GLP/GCP compliance means that PK and biomarker methods need to be validated to the full weight of the FDA/EMA BMV guidelines

Bioanalytical guidance documents

- 2001 FDA Guidance for industry, 2007 White Paper and 2009 ISR workshop report
- 2012 EMA Guideline on bioanalytical method validation
- FDA Guidance – “This guidance provides general recommendations for bioanalytcal method validation. The recommendations can be adjusted or modified depending on the specific type of analytical method used.”

Guidance documents

- Why do we need them?
- Provide us with a framework in which to do good science - to ensure bioanalytical methods are fit for their intended purpose
- 2001 FDA Guidance was initially designed to support bioequivalence testing
- They are advisory, not legal documents – but they are the Gold Standard for bioequivalence studies

Regulatory compliance (UK/EU)

Non-clinical	Clinical
The UK Good Laboratory Practice Regulations (Statutory Instrument 1999 No. 3106, as amended by Statutory Instrument 2004 No. 994). OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17. EC Commission Directive 2004/10/EC of 11 February 2004 (Official Journal No. L 50/44).	The Medicines for Human Use (Clinical Trials) Regulation 2004, UK Statutory Instrument 2004 No. 1031 and as amended. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 and Directive 2005/28/EC of 8 April 2005. ICH Guideline for Good Clinical Practice 1 May 1996. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95

Regulatory compliance documents

- Legal documents
- “GLP is a quality system concerned with the organisational processes and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded and reported” – OECD
- “GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects” – EU Clinical trials Directive

Compliance and validation?

- GXP regulatory documents specify very little about the extent that a method needs to be validated/qualified or how to approach analysis of samples eg:
  - UK MHRA GCP guidance for labs that perform analysis of clinical trial samples – “analysis should be performed using appropriately validated methods with defined acceptance criteria”
- GXP regulations are quality management systems that cover a variety of different study types

How much validation?

- The extent of the method validation experiments should be driven by the objectives of the study – not based on whether the study is GLP or GCP compliant
- Understanding the purpose of the study is essential to ensure your method is fit for purpose

Validation and compliance

- Fully validated method can be used to support a non-regulatory study
- A qualified method can be used to support a regulatory compliant study – and a compliance claim can still be made for the data generated
- Qualified method – is a method for which you understand the variation in the critical parameters

Same study – different objectives

- GLP compliant toxicology study in rodents
  - Plasma samples obtained for TK analysis
  - Tissue samples collected to check for presence of drug
- Full validation performed for plasma method
- Qualification performed for tissue method
- GLP compliance claimed for plasma and tissue measurements

GLP compliant pre-clinical studies

- ADME studies – PK measurements on unlabelled drug. Limited sample numbers – how much method validation/qualification?
- Protein binding and blood-plasma partitioning studies. Multiple species and matrices. Limited sample numbers – how much method validation/qualification?
- Tissue sample in toxicology studies – how much method validation/qualification?

Measurement of metabolites

- It may be necessary to measure a metabolite of a drug if its exposure is greater than 10% of parent or if it's a unique metabolite to humans
  - US FDA. Guidance for Industry: Safety Testing of Drug Metabolites and CPMP/ICH/286/95 ICH Topic M3 (R2)

How much validation?

- No regulatory guidance on the degree of validation required for methods used to demonstrate the abundance of metabolites in preclinical or clinical samples
- EBF recommends a tiered approach to metabolite quantification, for example:
  - Known active metabolite – validated method used to support preclinical and clinical development
  - Activity of metabolite unknown – qualified method used to support development up to Phase I

Validation and compliance?

- GLP compliant preclinical studies and GCP compliant Phase I studies may be supported using qualified methods

Biomarker bioanalytical criteria

- No regulatory criteria about how to approach method validation and sample analysis
- Industry best practice
  - Lee *et al*
  - EBF recommendations
- Process similar to PK analysis but criteria for acceptability can be different

Understand the purpose of the study

- How extensively validated does the method have to be?
- Depends on the objective of the study and where it is in the development pathway
- Tendency to automatically use BMV validated biomarker methods to support GLP/GCP studies
- Can still claim compliance using methods that are qualified/validated fit for purpose

Care with terminology

- Regulated bioanalysis defined as "Determination of drug concentrations in biological matrices for regulated studies" for example:
  - follow BMV guidance
  - use validated assays for sample analysis
  - But not always the case!
- "GLP light" – used in lead compound optimisation and early development studies
  - Implies link between reduced validation/qualification of method and compliance status

Conclusion

- In order to marry good science with regulatory compliance, it is important to understand the distinction between the bioanalytical guidance documents and the various GXPs
- The extent of method qualification or validation should be based on the objective of the study that the method will be used to support and not the compliance status of the study
- Qualified methods can be used to support regulatory compliant studies