Bioanalysis and GLP: A Regulatory Perspective

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Introduction

• Introduction to the MHRA
• Guidelines, guidance and regulatory perspectives
• Analytical quality and GLP
• Method development considerations
• Validation and analysis considerations
• Data integrity and security
• Regulatory initiatives and scientific advice
Overview

http://www.mhra.gov.uk

An Executive Agency of the Department of Health

Around 1200 staff

total budget of ~£140 million. Funded mostly by fees charged to industry

Regulates medicines and medical devices in the UK and EU, ensuring that medicines sold in the UK for human use are safe and effective medical devices – from heart valves to walking frames – are safe and meet performance standards

Runs scientific committees which advise UK Government Ministers on safety of medicines and devices
Organisational structure

Medicines and Healthcare Products Regulatory Agency (The agency)

CPRD  NIBSC  MHRA

- Devices
- IE&S
- Licensing
- VRMM

Corporate

- Communications
- Directorate
- Finance & Procurement
- Human Resources
- Information Management
- Policy
Guidance and regulatory perspectives
Guidelines

Regulatory guidelines are a bit like the modern map of the London Underground.

They don’t completely represent the “real” world.

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Guidelines

There’s almost always more than one way to reach an objective and the recommended route might not be the one you should follow!

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Guidelines

Whereas legislation defines the process by which applications are made, guidelines are generally written in order to provide an element of flexibility and not to place undue legislative restraints on scientific progress.

HOWEVER, IF THERE IS A GOOD SCIENTIFIC RATIONALE, A REGULATORY GUIDELINE MAY NOT BE FOLLOWED!!
EMA Bioanalytical method validation guidance: EMEA/CHMP/EWP/192217/2009 Rev 1
Analytical Quality

• All studies should be conducted according to acceptable current protocols. Each study should be planned and designed taking into account the properties and indications of the drug concerned.

• Requirements of GLP/GMP/GCP etc guidelines should be met when appropriate.
Analytical Quality

• Measurement of drug concentrations in biological matrices (such as serum, plasma, blood, urine, and saliva) is an important aspect of medicinal product development.

• The results of animal toxicokinetic studies and of clinical trials, including bioequivalence studies are used to make critical decisions supporting the safety and efficacy of a medicinal drug substance or product.
Analytical Quality

• It is therefore paramount that the applied bioanalytical methods used are well characterised, fully validated and documented to a satisfactory standard in order to yield reliable results.

• Acceptance criteria wider than those defined in the guideline may be used in special situations.

• This should be prospectively defined based on the intended use of the method.
GLP

- Validation of bioanalytical methods used in non-clinical studies carried out in compliance with GLP should be performed following the Principles of GLP.
- Aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated.
- Methods used in non-clinical studies not required to be performed to GLP should be “fit for purpose”, but not necessarily developed in a GLP facility.
THE GOOD NEWS
Guidance and regulatory perspectives

• A number of in vitro and bioanalytical methods have been accepted for regulatory use via numerous and adaptable approaches, either as pivotal, supportive or as exploratory studies.
Guidance and regulatory perspectives

Get Early Regulatory Input

Validation

Give it Time!
1. Defined test methodology/standard protocol
2. Reliability
3. Relevance

Good Laboratory Practice

Regulatory Acceptance

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Bioanalysis

Method Development
- Identification of key parameters to validate method

Validation
- Documentation
- Regulatory guidance
- Sample Preparation
- Sample Analysis

Analysis
- Documentation
- Regulatory guidance
- Sample Preparation
- Sample Analysis

Data
- Acquisition
- Processing
- Management
- Reporting

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Method Development

Does method development have to be conducted to regulatory standards?

NOT ALWAYS!

But may cause problems later in the project
Method Dev Examples - I

- Error identified incorrect $C_{\text{max}}$
  - Method validated on appropriate model of LCMS instrument
- Analysis started and sample concentrations below LLOQ and capabilities of the instrument
- Revalidation and repeat analysis required
- Issue not fully documented

Development is the starting point.
Are you sure it is correct?
If something goes wrong how does it look to regulators?
How is it documented?
What is the risk?
Method Dev Examples - II

- Endogenous compounds not considered in method development (or validation)
- No documentation (e.g. in report) as to how this was considered
- Was it endogenous or carry over?

Are you confident that you can reconstruct and justify your decision making?
Validation and analysis
Sample Preparation

• Balances
  • Results recorded by hand on a worksheet
  • Check weights not recorded
  • Equipment not level or poorly positioned

Where are the risks to your data?

Is it something as simple as recording a weight from a balance?
Validation and analysis

Design

- Incorrect calculation of No. samples required for Incurred Sample Reanalysis
- No justifiable reason to repeat the analytical run
- In this case – there was a failure to follow the EMA Bioanalytical Method Validation Guidance

Are you sure what the analysis is for and the regulatory requirements?
Validation and analysis
Analytical Batch

- Is the QC added to analytical run adequate enough to address the sample processing methods used?
- Is the QC approach to constructing analytical runs and their subsequent acceptance documented (e.g. SOP).

There are risks associated with equipment and people. Do you have adequate controls in place?

How robust is your documentation to support the study/work?
Validation and analysis
Quality

• Internal Standard Responses from LC/MS

  • Potential effects of anticoagulants used
  • If seen, an assessment of response will be required

Do you have SOPs to review Internal Standard Performance?

Can you justify your decision making?
Validation and analysis
Calibration Curves and QC Samples

• Inappropriate use of Calibration Curves Standards
  • Calibration curves being used for different analytical runs
  • Correct calibration curve failed

Can your process or systems allow this to happen?

Could it happen?
Validation and analysis
Calibration Curves and QC Samples

- Inappropriate use of Calibration Curves and Standards
  - Calibration standard rejected from data
  - No justifiable reason for rejection
  - When Standard put back into analysis, the run failed
Validation and analysis Calibration Curves and QC Samples

- Inappropriate rejection of multiple Calibration Standards
  - No process to control the removal of multiple Calibration Standard failures
  - Different results achieved depending on approach used.
  - No SOP for consistency

How can this be reconstructed? Is there an SOP and do you check?
Validation and analysis
Integration – Quantification

• Transparent and controlled by procedures
• Controlled by SOP and consistent across a run
• Audit trailed and reviewed
• Smoothing justified and reflect validation

Quantification needs to be fully transparent and consistent.

How can it be reconstructed and verified?
Data Risks

• Once quantified on the instrument, data can be processed in a number of ways before reporting and archiving
  • Spreadsheets used to process analytical data not validated
  • Data transmitted (to sponsor) without QC checks (or QA checks for GLP studies)
  • Lack of control to protect the data prior to reporting
  • Content of report not reflecting the raw data

Do you understand the risks to your data?
Data Security

- Access right to analytical equipment controlled by administrator

- Issues arise from management of security settings
  - Shared log in
  - Administrator responsible for analysis and could deactivate audit trail
  - Records of access rights incomplete
  - Instrument audit trail for analytical run deleted.

Do you understand the risks associated with the controls in place on your instruments and their limitations?
Data Audit Trails

- Instrument creates an audit trail
  - Contains key information to reconstruct and verify the study
  - Instrument performance
  - User
  - Security

- Archived and available for inspection

Are all audit trails adequately archived? Are they accessible for inspection?
Validation Report

- Summary
- Description of method and where appropriate, source/references,
- Assay procedure (analyte, IS, sample pre-treatment, extraction and analysis).
- Reference standards
- Calibration standards and QC samples (matrix, anticoagulant if applicable, preparation, preparation dates, and storage conditions),
- Run acceptance criteria (including chromatographic criteria)
- Analysis Tables
- All runs, with dates, passed and failed, with reasons for failure
- Calibration results, range, response function, back-calculations, accuracy
- QC results
- Stability data
- Selectivity, LLOQ, carry-over, matrix effects, dilution integrity
- Unexpected results, Deviations from method
Analytical Report

• Should refer to validation report
• Reference standards
• Calibration standards and QC samples (storage conditions),
• Run acceptance criteria (including chromatographic criteria)
• Assay procedure
• Sample Tracking
• Analysis Tables
  – All runs, with dates, passed and failed, with reasons for failure
  – Calibration results - passed
  – QC results – passed
  – Failed analytical runs
  – Deviations
  – Re-assay due to analytical reasons
  – Incurred sample re-analysis (or in validation or separate report)
• Chromatograms, including corresponding QC and calibration samples
Global regulatory initiatives

Precise regulatory help and advice via dedicated procedures can ultimately ease the path for the qualification and gain consensus on clinical relevance
Scientific advice

• The MHRA, and many other EU Member States, have, for many years, provided scientific and regulatory advice to sponsors.

• Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.
Scientific advice

- European Medicines Agency (EMA) & Committee for Human Medicinal Products (CHMP) - Scientific Advice Working Party (SAWP)
  - written procedure, usually initiated in anticipation of clinical studies intended to support eventual registration

- Scientific Working Party (SWP)
  - the SWP occasionally invites/accepts offers from organisations wishing to discuss new paradigms in drug discovery/development.
  - SWP members also participate in numerous organisations/initiatives in all fields of toxicology
Scientific advice

• National Competent Authorities offer scientific advice procedures too
  – face-to-face meeting with written answers (non-binding)

• UK & some other agencies also have an Innovation Office – for unusual things or early in development where comment is not specific to one medicinal product

• You don’t have to listen to Regulators… but it does help!
• We do like it when people take notice of what we’ve said.
• However, don’t be afraid of standing up for yourselves if you’re certain you’re right!
Summary

• A rigid adherence to good science is far more important than a rigid adherence to Regulatory Guidelines.

• Regulatory help and advice via dedicated procedures can ultimately ease the path for the qualification and gain consensus on clinical relevance

• There are risks associated with conduct of analysis
  • Systems
  • Procedures
  • People

• Can result in accidents or fraudulent behaviour
Summary (cont.)

• Regulatory Inspectors still see common findings regarding the quality and conduct of analytical studies

• Consideration must be given to how a study can be reconstructed and adequately verified

• An important step in producing robust analysis is to understand this requirement and where the risks are
Everything was going along fine until they discovered their HeLa cell line expressed Y chromosome markers.
ANY QUESTIONS

DO YOU HAVE?
Any Further Questions?

Please Feel Free to Contact the MHRA If You Have Any Further Queries:

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