



# **Did we consider the world around us? A GCP and Informed Consent perspective**

**Cecilia Arfvidsson, on behalf of the EBF**

## Paragraph from ICH M10

➤ In 1.3 Scope

*“For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the bioanalysis of study samples should also conform to their requirements.”*



## Changes to current guidelines

- EMA Guideline on bioanalytical method validation also includes a statement around GCP with a reference to the EMA reflection paper:

*“The validation of bioanalytical methods and the analysis of study samples for clinical trials in humans should be performed following the principles of Good Clinical Practice (GCP). Further guidance that will help clinical laboratories develop and maintain quality systems which will comply with relevant European Union Directives, national regulations and associated guidance documents can be found in the “Reflection Paper for Laboratories That Perform The Analysis Or Evaluation Of Clinical Trial Samples.” (EMA/INS/GCP/532137/2010).”*



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# Good Clinical Practice - GCP

- All aspects of a clinical study should comply with Good Clinical Practice (GCP).
- GCP is a collection of ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Compliance with GCP provides public assurance that the rights, safety and well-being of trial subjects are protected and that the trial data are credible.
- Different regulatory guidelines available and followed - all with the fundamental principle origin from Declaration of Helsinki.



Respect for the individual – patient in focus

# Guidance on Good Clinical Practice



- **Declaration of Helsinki** – original adopted by World Medical Association (WMA) in 1964
- **European Clinical Trials Directive 2001/20/EC** – established to standardise the research activities in clinical trials within the European community
- **Good Clinical Practice Directive 2005/28/EC** – supplement the EU CTD with purpose to strengthen the legal basis to comply with the GCP principles
- **International Conference on Harmonisation Guidance on Good Clinical Practice (CPMP/ICH/135/95)** - Unified standard for the European Union (EU), Japan, the United States, Canada and Switzerland to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. First adopted in 1996, addendum adopted in 2016
- **Code of Federal Regulations** – FDA has built GCP into their CFR, title 21
- Additional guidelines available from WHO, CIOMS, UNESCO...

# Good Clinical Practice principles

1. GCP, part of EU Directives, national regulations and associated guidance documents, to be considered as law (administrative law)
2. GCP principles are not in scope of validation – as for the GLP principles, appropriate quality management system needs to be in place
3. Sample analysis to be conducted in accordance with study protocol and only to include work covered by the informed consent

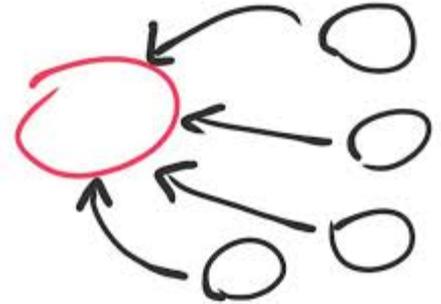


reference to GCP in ICH M10 should be limited to referring to bullet 3



## ICH M10 conclusion read from a GCP perspective

- *This harmonised guidance on the validation of bioanalytical methods and analysis of study samples, **reduces the need for carrying out additional bioanalytical experiments.** This may **accelerate development and drug approval** and may lower the costs*



Respect for the individual – patient in focus

## Opportunity with ICHM10 – added value for the patients

➤ Best possible use of time, cost and resources through:

- Worldwide harmonisation
- Removal of ambiguities and perceived issues
- Simple and easy to understand
- Regulators and industry has the same interpretation
- Clear scope
- Flexibility allowed when scientifically justified

 Safe and effective medicines reach the patients more quickly

# ICH M10 discussions, with the patients in focus

- Avoid adding the extremes into routine validation
  - Co-medication stability
  - Bracketed vs extrapolated long term stability
  - Whole blood stability
  - Evaluation of hemolysed and/or lipaemic matrix
  
- Evaluate overall impact on data quality and patient safety
  - Excessive use of ISR
  - Multiple aliquots for stability assessment

# ICH M10 discussions, with the patients in focus

- Evaluate relevance for downstream PK evaluation
  - Acceptance criteria based on end use vs platform dependent
  
- Consider patient confidentiality and consent
  - Use of individual vs pooled incurred samples during cross-validation
  - Co-medication interference testing
  
- Consider minimum use of matrix
  - No of replicates/individuals requested
  - Surrogate matrix (where applicable)
  - Use of pre-dose samples vs trying to source relevant patient matrix

# Good Clinical Practice principles

- The GCP guidelines provide no direct guidance or details for how the GCP principles should be applied to bioanalysis of clinical study samples
- This gap filled by the **EMA Reflection paper** adopted by EMA, GCP Inspectors Working Group in 2012.
- Reflection paper **referred to in current EMA Guideline on Bioanalytical Method Validation** as the source to find *“...guidance that will help clinical laboratories develop and maintain quality systems which will comply with relevant European Union Directives, national regulations and associated guidance documents”*
- In Global CRO Council (GCC) survey from 2016<sup>1</sup> half of all respondents had been audited by a regulatory agency against the expectations outlined in the reflection paper – even when auditing agency was the FDA



28 February 2012  
EMA/INS/GCP/532137/2010  
GCP Inspectors Working Group

Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

Draft agreed by GCP Inspectors Working Group	10 June 2010
Adopted by GCP Inspectors Working Group for release for consultation	10 June 2010
Start of public consultation	23 September 2010
End of consultation (deadline for comments)	28 February 2011
Adopted by GCP Inspectors Working Group	28 February 2012

Keywords: Clinical laboratory, Laboratory analysis, Clinical Trial

# GCP vs GLP

- GCP standards similar to those of GLP with regards to:
  - Organisation, QA and QC, Personnel and Facilities
  - Method validation and Repeat analysis
  - Computerised systems and data recording/reporting/retention
  
- Important difference is in the sponsor's legal responsibility of the clinical study conduct adding additional care with regards to:
  - Contracts incl. roles and responsibilities, lines of communication, availability of all relevant study documentation and avoiding any conflicting information
  - Bioanalysis during study conduct incl. reporting of any potential serious breaches, communication of serious deviations, ensure blinding is not compromised and withdrawal of consent



# A Bioanalytical lab's struggle with GCP compliance

- Having access to all relevant information and documentation
  - Copy of the full clinical protocol (incl. Amendments)
  - Confirmation of consent in place
  - Sample identification discrepancies and any missing samples
  - Randomisation codes
  - Sample handling and storage at the clinical site
  
- Having relevant procedures in place
  - Manage of withdrawal of consent
  - Protection of any personal identifiers
  - Blinded vs unblinded and investigation on anomalous results
  - Reporting of potential breaches and clinically significant results

# Informed Consent

- One of the core principles of GCP
- A process by which a subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.
- Documented in a written, signed and dated informed consent form
- Challenges
  - Process for ensuring informed consent is in place prior to analysis
  - Process that also manages changes and/or withdrawal of consent
  - Understanding of the expiration of consent

# GCP considerations ... outside the guidance

- Continuous **improvement of the clinical study protocol quality** as well as other study documentation to include all necessary information and directives with regards to GCP
- Continuous **advancement of the processes** for informed consent, reporting of GCP breaches, protection of blinding of the study teams ...
- Continuous **advancement in the GCP training** provided for all bioanalytical lab personnel involved in the analysis and/or evaluation of clinical study samples



# Feedback from EBF and the workshop delegates

- GCP was not specifically called out in the Scope discussions at the EBF strategy meeting
- Feedback from workshop delegates in the survey sent out in preparation for ICH M10 meeting highlight that there is ambiguity in the GCP paragraph

*“Based on EMA Guideline, in case of studies conducted in GLP or GCP, also the method validation should be conducted according to applicable GLP and GCP principles”*

*“For the purpose of use in clinical studies, the bioanalytical method validation can be declared to GLP or GCP is necessary?”*



# Summary and recommendations to EMA/EWG

- All aspects of a clinical study should comply with Good Clinical Practice (GCP)
- EMA reflection paper adopted as the “standard” for how to apply the GCP principles to bioanalysis of clinical study samples – by industry as well as the regulatory agencies
- GCP principles is not in scope of validation
- Challenges within the bioanalytical lab to be resolved through continuous improvement and advancement of relevant GCP processes and trainings
- Recommendation to EMA/EWG

Current text in ICH M10 draft	Suggested change
For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the bioanalysis of study samples should also conform to their requirements.	Add: For GCP, this implies that Sample analysis to be conducted in accordance with study protocol and only to include work covered by the informed consent

## Remaining questions for panel discussion

- Any questions?

# Acknowledgement and questions

- EBF community and ICH M10 focused workshop delegates for their feedback
  
- Any questions: please send questions to [info@e-b-f.eu](mailto:info@e-b-f.eu), before 31 May for consideration in meeting feedback to EMA/EWG