Autumn Focus Workshop
Managing GCP in Regulated Bioanalysis

15-16 September 2022

Can we learn from GLP?

Philip Timmerman,
on behalf of the EBF

Was this really the intention?

Dear Study director,

during the sample analysis of the 1-m study with reference Arghh-12-2238, the autosampler AC-N° 2212 stopped because of a power failure. The event was documented in the log file, audit trail and study file and signed and dated by myself as PI. Do you allow me to continue analysis?

Waiting for your response and advise.

Kindest regards

The wonderful world of regulations: GLP

- Since 1981, we are trying to master OECD GLP in the bioanalytical laboratory

  The Principles of Good Laboratory Practice (**GLP**) are a managerial quality control system covering the organisational process and the conditions under which non-clinical health and environmental studies are **planned, performed, monitored, recorded, reported and retained (or archived).**

  – However, bioanalysis is not mentioned in any of the OECD guidelines

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- However, bioanalysis is not mentioned in any of the OECD guidelines
- As a community, we have struggled (and many still are) to understand the essence of GLP and its relationship to Bioanalysis
- Trying to get their head around "*when supporting a GLP study, your work BA needs to comply with the principles of GLP*". It's may sound like semantics, but it has caused some misunderstanding
- GLP doesn't control **how** how to validate an assay or define scientific criteria for acceptance of data.

The wonderful world of regulations: GLP

- GLP doesn't control **how** how to validate an assay or define scientific criteria for acceptance of data.

- It's about documented *a priori* decided testing which is executed as planned and reported accordingly…
- So for the sake of argument, if scientific decision making only requires an assay to 50% accurate, and this is documented GLP conform, it's OK for GLP (and for the decisions taken in the study)

OK….to the point…why passing by GLP? → EMA BMV

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**
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

Can we connect the EMA-BMV and GLP?

EMA BMV -2012. Chapter 3. Legal Basis

- Non-clinical (pharmaco-toxicological) studies submitted in a marketing authorisation application shall be carried out in conformity with the provisions related to **Good Laboratory Practice**, Directive **2004/10/EC** on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances and Directive **2004/9/EC** on the inspection and verification of good laboratory practice (GLP).

Connecting BMV and GLP

EMA BMV-2012. Chapter 3. Legal Basis

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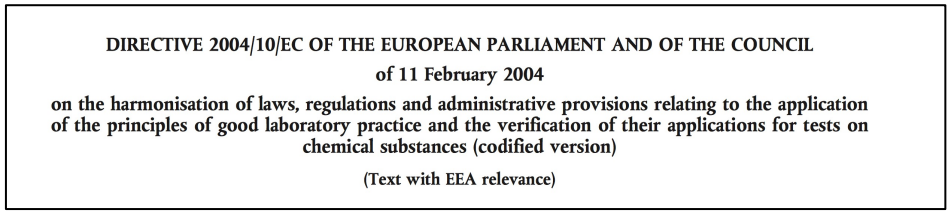
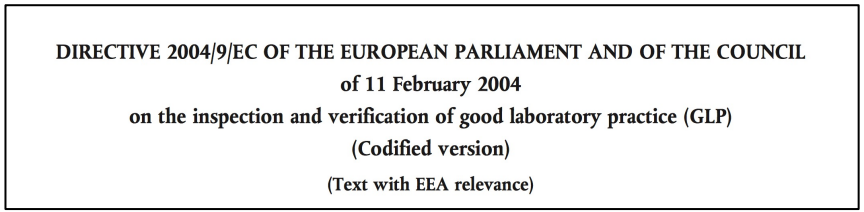


DIRECTIVE 2004/10/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 11 February 2004
on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)
(Text with EEA relevance)



DIRECTIVE 2004/9/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
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on the inspection and verification of good laboratory practice (GLP)
(Codified version)
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In essence refering to OECD 1 and 2

But…when browsing through OECD-1 and 2

- We cannot find any reference to Bioanalysis, and why should it
- This brings us to the essence of GLP in BA or in any environment:
  - when (Bioanalytical) data are generated in support of a non-clinical safety study, they need to be in compliance with the OECD regulations
- There are no additional/different scientific criteria/expectations in OECD 1-22 adding to the BMV →
  - GLP prescribes ensuring the data fit the structure "**planned, performed, monitored, recorded, reported and retained (or archived)** within within a clear hierarchy of responsibilities (the TFM, SD, PI…).
  - **BMV doesn't have any of this laid out in that level of detail desired by GLP, and why should it**.

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  - **BMV doesn't have any of this laid out in that level of detail desired by GLP, and why should it**.

DONE

However….

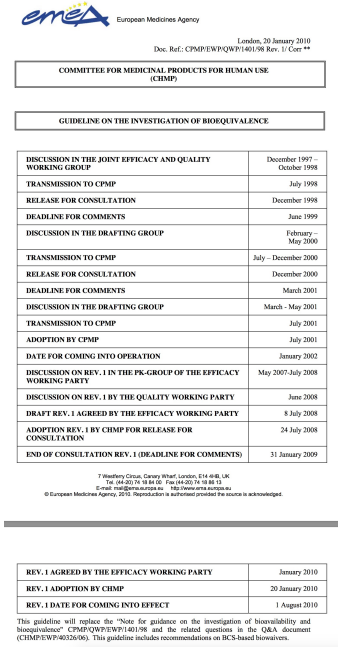
- And on EMA BMV Chapter 3…"*Thou shalt* comply with OECD-1…" had (have) believers and non-believers
  - Some thought/continued to believe that for BMV → GLP is a regulatory requirment → It's NOT
    - This was clarified in an OECD FAQ (http://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm)

6. What standard should be applied to the validation of methods which are used in GLP studies and how should it be applied?

Unless stipulated in national regulations, there is no requirement to perform method validation in compliance with GLP. Since parameters of the validated method are used in the GLP study (for example threshold, linearity, accuracy, precision, stabilities, equipment settings, etc.), data should be accurately recorded and stored in a manner that protects its integrity. Validation data may be required for study reconstruction and, consequently, it should be retained for an appropriate period of time. (posted on 21 January 2016)

But some are persistent

- GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (2010)
  https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf



European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002
DISCUSSION ON REV. 1 IN THE PK-GROUP OF THE EFFICACY WORKING PARTY	May 2007-July 2008
DISCUSSION ON REV. 1 BY THE QUALITY WORKING PARTY	June 2008
DRAFT REV. 1 AGREED BY THE EFFICACY WORKING PARTY	8 July 2008
ADOPTION REV. 1 BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION REV. 1 (DEADLINE FOR COMMENTS)	31 January 2009

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REV. 1 AGREED BY THE EFFICACY WORKING PARTY	January 2010
REV. 1 ADOPTION BY CHMP	20 January 2010
REV. 1 DATE FOR COMING INTO EFFECT	1 August 2010

This guideline will replace the "Note for guidance on the investigation of bioavailability and bioequivalence" CPMP/QWP/EWP/1401/98 and the related questions in the Q&A document (CHMP/EWP/40326/06). This guideline includes recommendations on BCS-based biowaivers.

4.1.7 Bioanalytical methodology

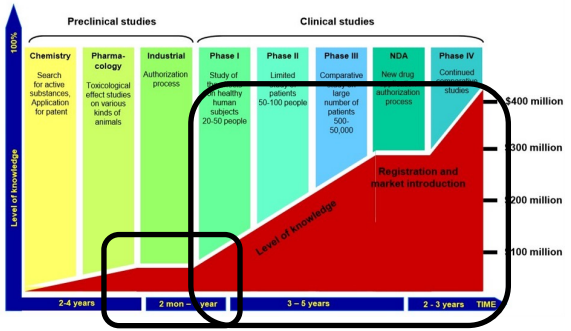
The bioanalytical part of bioequivalence trials should be performed in accordance with the principles of Good Laboratory Practice (GLP). However, as human bioanalytical studies fall outside the scope of GLP, the sites conducting the studies are not required to be monitored as part of a national GLP compliance programme.

It cannot get more confusing….

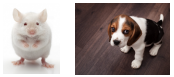
The long GLP introduction was an introduction to understand the challenges and similarities we face in GCP today

It shows how multiple and poorly aligned guidelines, lack of timely and expert communication or “fear for non-compliance” can be a real enemy to deliver diligent and efficient compliance and value for the patient

The world of GCP



GLP



GCP

A déja vu

Pictures removed

Simple….ICH E6(R2)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)

Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

Implementation status:

ANVISA, Brazil - Implemented; Date: 1 November 2019; Reference: Notification at Anvisa´s Website

EC, Europe - Implemented; Date: 1 December 2016; Reference: CHMP/ICH/135/1995

FDA, United States - Implemented; Date: 1 March 2018; Reference: Federal Register Vol. 83, No. 41, p. 8882-3

HSA, Singapore - Implemented; Date: 1 January 2016; Reference: HSA, Singapore website

Health Canada, Canada - Implemented; Date: 3 April 2019; Reference: File #: 19-105427-311

MFDS, Republic of Korea - Not yet implemented;

MHLW/PMDA, Japan - Implemented; Date: 5 July 2019; Reference: PSEHB/PED Notification No. 0705-3, PSEHB/PED Notification No. 0705-5, PSEHB/PED Notification No. 0705-7, PSEHB/PED Administrative Notice

NMPA, China - Implemented; Date: 1 July 2020; Reference: NMPA & NHC Joint Announcement on the Issuance of Good Clinical Practice of Pharmaceutical Products (No. 57 of 2020)

Swissmedic, Switzerland - Implemented; Date: 1 November 2016; Reference: Swissmedic, Switzerland press release

TFDA, Chinese Taipei - Implemented; Date: 31 December 2017;

The analogy with GLP (using the EMA Guideline as an example)

EMA-2012

– 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**).

History repeating

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)

Step 5

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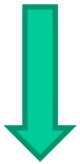
Reference to BMV



Not there

What else did EMA BMV 2012 expect on GCP?

- EMA-2012
  - 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**).


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

13 Principles of ICH GCP

1. **Ethical considerations - Helsinki**
2. **Trial risk *vs* trial benefit**
3. **Integrity and safety of trial participants**
4. **Information on the Medicinal Product**
5. **Good quality trial described in a clear protocol**
6. **Compliance with the study protocol**
7. **Medical decisions**
8. **Treained and experienced trial staff**
9. **Informed consent**
10. **Accurate recording, interpretation and handling of trial data**
11. **Confidentiality protecting trail participant**
12. **Good Manufacturing Practice**
13. **Quality assurance program**

Have we missed it when commenting on EMA draft in 2009?

Nope…in 2009, it wasn't in the draft.
industry could only commented on *below challenging paragraph* :

"…….. In addition, for clinical trials in humans the principles of Good Clinical Practice (GCP) should be followed.

- *Furthermore, reference is made to the following EMEA guidelines:*
- *Note for guidance on good clinical practices (CPMP/ICH/135/95)* ***= ICH E6***
- *Note for guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95).* **= ICH Q1**

But…in the final Guideline…since in the meantime MHRA had removed their GCP requirements in favour of EMA reflection paper

CPMP/GCP/532137/2010…

which in essence originates from MHRA GCP Guidance

So, for the EMA-BMV, we were too late and the Guideline missed a good discussion and training on GCP with industry.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

OK… ICH M10…

ICH Member

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2022
EMA/CHMP/ICH/172948/2019
Committee for Medicinal Products for Human Use

ICH guideline M10 on bioanalytical method validation and study sample analysis

Step5

Transmission to CHMP	28 February 2019
Adoption by CHMP	28 February 2019
Release for public consultation	14 March 2019
End of consultation (deadline for comments)	1 September 2019
Final adoption by CHMP	21 July 2022
Date of coming into effect	21 January 2023

1. INTRODUCTION

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.

- For GLP: we know how to read this…see previous EMA slides

- For GCP: since we never had a proper discussion, this is maybe the time to have it, considering:
  - There is no GCP Guideline on BMV criteria
  - The EMA GCP reflection paper is only a reflection paper, and for the sake of argument, any *a priori* agreed criteria which meet the scientific needs would be OK.
  - Copying GLP into GCP may be convenient to prevent “double standards” in a lab, but a thorough risk/benefit discussion still need to happen considering the resource needs involved
  - And what to do in case your lab only runs clinical samples and there is no GLP to build on?

Do we really want this?

Dear Doctor (I guess you are the study director ☺),

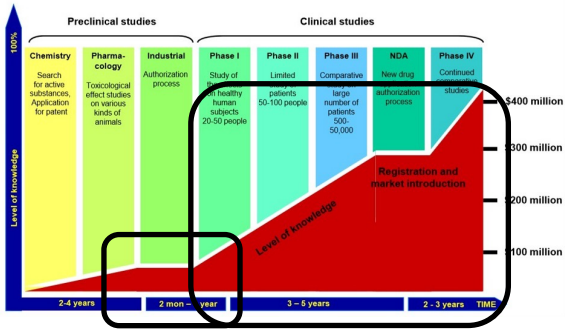
during the sample analysis of the bioequivalence study with reference Arghh-12-2238, the autosampler AC-N° 2212 stopped because of a power failure. The event was documented in the log file, audit trail and study file and signed and dated by myself as PI (I guess I am PI in this mail☺). Do you allow me to continue analysis.

Waiting for your response and advise.

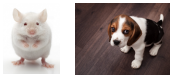
Kindest regards

And we see this terminology being referred to by some in the GCP world…so it's not ridiculing the problem

Considering the size of the GCP world



GLP



GCP

So, work ahead to get it right