EBF Open Symposium

N° 13 From Cyberspace - Staying Connected

17-20 November 2020

GCP - From challenges into opportunities

Philip Timmerman
on behalf of the EBF

http://www.e-b-f.eu
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).

– Bioanalysis is not mentioned in any of the OECD guidelines

http://www.chakoteya.net/StarTrek/7.htm
Stardate: 1704.2
Airdate: 29 Sep, 1966
MCCOY: Definitely not drugs or intoxication. The bio-analysis on the tapes prove that conclusively.
The wonderful world of regulations: GLP

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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).

– 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 the relationship between Bioanalysis and GLP
– We still see labs preforming “GLP Bioanalysis” even though there is no such thing…it’s the other way 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
21 CFR 58 (1979)


WHO Handbook 1997
OECD-1
OECD Principles of GLP

- No 1: OECD Principles on Good Laboratory Practice

GLP consensus documents
- No 4: Quality Assurance and GLP (revised 1999) (See also Frequently asked questions: FAQ)
- No 5: Compliance of Laboratory Suppliers with GLP Principles (revised 1999)
- No 6: The Application of the GLP Principles to Field Studies (revised 1999)
- No 7: The Application of the GLP Principles to Short Term Studies (revised 1999)
- No 8: The Role and Responsibilities of the Study Director in GLP Studies (revised 1999)
- No 13: The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies

Guidance Documents for Compliance Monitoring Authorities
- No 2: Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice
- No 3: Revised Guidance for the Conduct of Laboratory Inspections and Study Audit

Advisory Documents of the Working Group on GLP
- No 11: The Role and Responsibility of the Sponsor in the Application of the Principles of GLP
- No 12: Requesting and Carrying Out Inspections and Study Audits in Another Country
- No 14: The Application of the Principles of GLP to in vitro Studies
- No 15: Establishment and Control of Archives that Operate in Compliance with the Principles of GLP
- No 16: Guidance on the GLP Requirements for Peer Review of Histopathology
- No 17: Application of GLP Principles to Computerised Systems

[Note: this document replaces Consensus Document No. 10: The Application of the]

Position Papers
- No. 18: OECD Position Paper Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025
- No. 21: OECD Position Paper Regarding Possible Influence of Sponsors on Conclusions of GLP Studies
OK….to the point…why this GLP example?

Guideline on bioanalytical method validation

<table>
<thead>
<tr>
<th>Event</th>
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<tr>
<td>Draft agreed by the Efficacy Working Party</td>
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<td>31 May 2010</td>
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<td>Agreed by Pharmacokinetics Working Party (PKWP)</td>
<td>June 2011</td>
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<td>21 July 2011</td>
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Connecting 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

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).

In essence referring to OECD 1 and 2
But…when browsing OECD-1 and 2

- No reference to Bioanalysis at all

- 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

- For Bioanalytical support, this boils down to OECD-1, 8, 10 (15) and 13
  = planning, performing, monitoring, recording, reporting and archiving
  = documented communication

- There are no additional or different criteria added in OECD 1-15 with respect to science or other expectations already in the BMV…except ensuring the data fit the structure on documenting/communicating decisions, changes/deviations to planned and \textit{a priori} described procedures, all within within a clear hierarchy of responsibilities (the TFM, SD, PI…). BMV doesn’t have this laid out.
Not that all believed it... so there was a fears discussion

- We invented “GLP Bioanalysis”

- And on BMV Chapter 3... “Thou shalt comply with OECD-1...” had (have) believers and non-believers
  - Some thought/continue to believe that for BMV \( \rightarrow \) GLP...
    - 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)*

    - Case closed
But some are persistent

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (2010)

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....
All in all, for GLP

- OECD-1: a very clear 40-y old document still keep us busy.

- There is of course 21 CFR 58, which are in in many aspects identical but at the same time are significantly different.
  - Also this has confused the global community,
  - major differences being
    - 21 CFR 58 has no “certification” (compliance monitoring program) as in OECD
    - Management of multi site studies is not included of 21 CFR 58
  - Both differences have complicated work around the globe in communication

- We won’t dive into other regions…China was certainly a big one on GLP, and still is.
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, who should be our point of focus in all discussions.
The world of GCP
A déjà vu
Simple….ICH E6(R2)

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 #: T9-105427-311

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;

Guideline for good clinical practice E6(R2)

Step 5

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ICH E6(R2) GCP – the 13 Principles

1. Ethics
2. Trial risk vs trial benefit
3. Trial participants
4. Information on the Medicinal Product
5. Good quality trial
6. Compliance with the study protocol
7. Medical decisions
8. Trial staff
9. Informed consent
10. Clinical trial data
11. Confidentiality
12. Good Manufacturing Practice
13. Quality assurance
1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
What does 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).
History repeating

Guideline for good clinical practice E6(R2)
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What else does EMA BMV 2012 expect on GCP?

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9. Informed consent
10. Clinical trial data
11. Confidentiality
12. Good Manufacturing Practice
13. Quality assurance
Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples
Have we missed this in the draft back in 2009

In 2009, it wasn’t there, but industry commented on below challenging paragraph:

“The validation of bioanalytical methods and the analysis of study samples should be performed in accordance with the principles of Good Laboratory Practice (GLP). However, as human bioanalytical studies fall outside of the scope of GLP, as defined in Directive 2004/10/EC, the sites conducting the human studies are not required to be monitored as part of a national GLP compliance programme. 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).
  - Note for guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95).”
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- 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...

CPMP/GCP/532137/2010...

which in essence originates from MHRA GCP Guidance
For the BMV, it came late and the reflection paper missed a good discussion and training (certainly outside of the UK)...

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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 |
The reference to GCP in final EMA BMV was highlighted as a ambiguity by EBF …

• … in our 2012 publication
  • The European Bioanalysis Forum community’s evaluation, interpretation and implementation of the European Medicines Agency guideline on Bioanalytical Method Validation, Peter van Amsterdam, Arjen Companjen, Margarete Brudny-Kloeppe, Michaela Golob, Silke Luedtke and Philip Timmerman Bioanalysis (2013) 5(6), 645–659

• … in the 5th EBF Open Symposium, 2012:
From 2012 onwards...MHRA taking the lead

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- Start of public consultation: 29 September 2010
- End of consultation (deadline for comments): 28 February 2011
- Adopted by GCP Inspectors Working Group: 28 February 2012
But when coming new in the game, it’s not necessarily made easy
Good Clinical Practice (GCP)
Regulations and Guidelines

Regulations
New Clinical Trials Regulation - EU No. 536/2014 (repealing Directive 2001/20/EC)
Declaration of Helsinki

UK Legislation
The Medicines for Human Use (Clinical Trials) Regulations 2004 - Statutory Instrument 1031
The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 - Statutory Instrument 1928
The Medicines for human Use (Clinical Trials) Amendment (No.2) Regulations 2006 - Statutory Instrument 2984
The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 - Statutory Instrument 941

USA Regulations
FDA Regulations relating to GCP and clinical trials

Guidelines
ICH E6 Guidelines for Good Clinical Practice
Medicines for Human Use - Eudralex
MHRA Serious Breaches Guidance
Clinical Trials Toolkit
MHRA Good Clinical Practice Guide (Grey Guide)


How to prepare for an inspection for Good Clinical Practice by the Medicines and Healthcare products Regulatory Agency (MHRA): a guide for organisations that sponsor or host non commercial clinical trials of medicinal products

An updated guide incorporating the Medicines for Human Use (Clinical Trials) Amendment Regulations (the Amendment Regulations) 2006 which transpose the EU Directive (2005/28/EC) on Good Clinical Practice.
Experience is building, again in UK

In 2018, the MHRA received a total of 115 serious breach notifications, of which:
– 76 were determined by the inspector as a serious breach
– 24 were determined as not being a serious breach
– 15 referrals were still awaiting further information from the reporter in order for the inspectorate to make a final assessment of whether the issue met the definition of a serious breach

In 2019, MHRA received a total of 112 serious breach notifications, of which:
– 75 were deemed to be a serious breach
– 36 deemed not to be a serious breach
– 1 awaiting further information to enable final determination

If you want to have a look…
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.
GCP in BA “goes global”
How should we read this?

What are the requirements?
- EMA reflection paper
- WHO Handbook
- ICH E6(R2)
- MHRA (and is this the EMA reflection paper)
- Others?
  - From the ICH M10 draft: The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

With
- A BA community outside UK BA inspectorate in essence not having real experience
- A BA community struggling with some expectations
- GLP experience potentially contaminating GCP expectations, certainly in labs that stopped support of GLP studies

And above all…learning at the past, have we really discussed this globally?
Let’s turn the challenge into an opportunity

- Learning from the past
  - Prevent making the mis/over-interpretations
  - How did we struggle to bring GLP on board?

- Come together on understanding what GCP for BA means
  - As for GLP, what is the interplay between GCP and BMV?
  - Where are the ambiguities and where is the conflict?
  - Who owns what, and why?

- Learn from MHRA inspections
  - Where is it difficult to comply for a BA lab scientist?

Or…are we at risk of losing our focus on the value for the patients in favour of procedures becoming too rigid?
And no misunderstanding

All 13 GCP principles are paramount
But at the same time, just as there is no « GLP Bioanalysis » 

GCP Bioanalysis 

doesn’t exist

Let’s get it right – let’s do this together
Acknowledgement

- The EBF community
- Delegates at the several EBF Meetings discussing ICH M10