Autumn Focus Workshop
Managing GCP in Regulated Bioanalysis

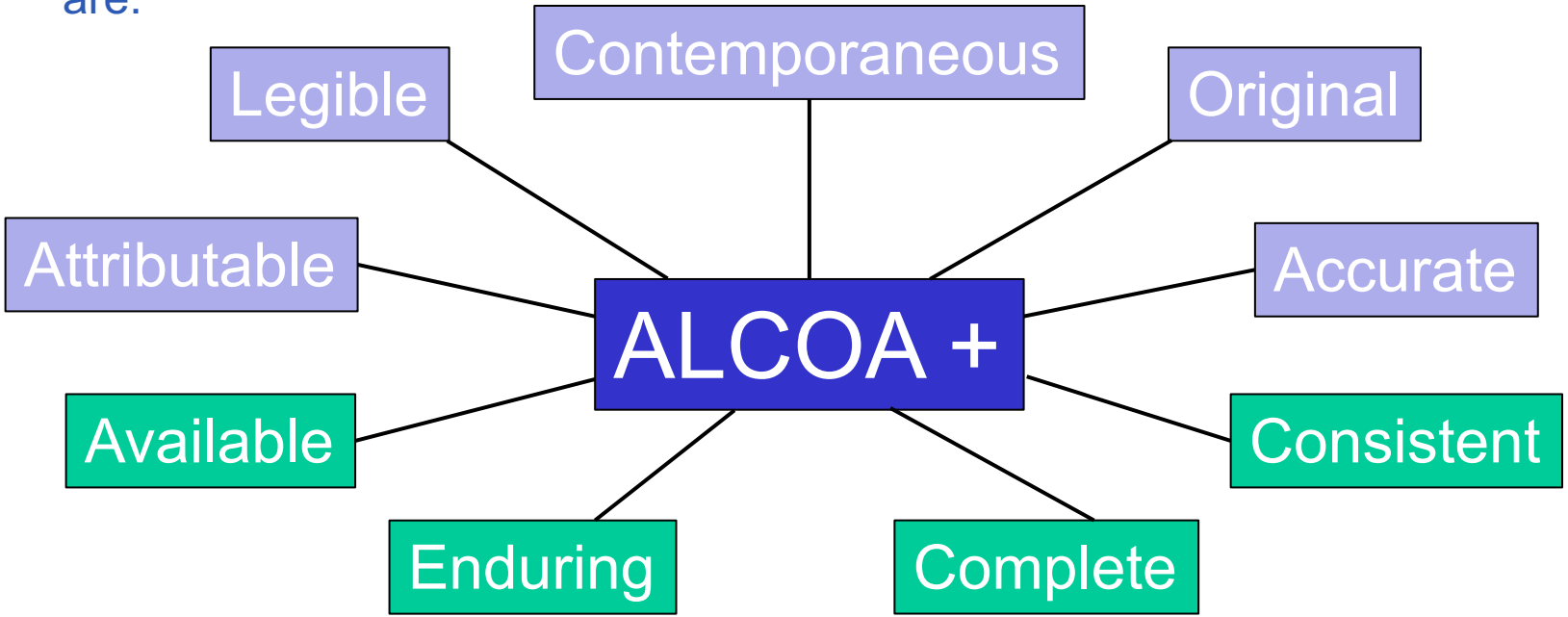
Feedback from EBF GCP team discussions on equipment maintenance and validation (incl GCP relevant info from EBF e-data and Data Integrity team)

Cecilia Arfvidsson, on behalf of the EBF

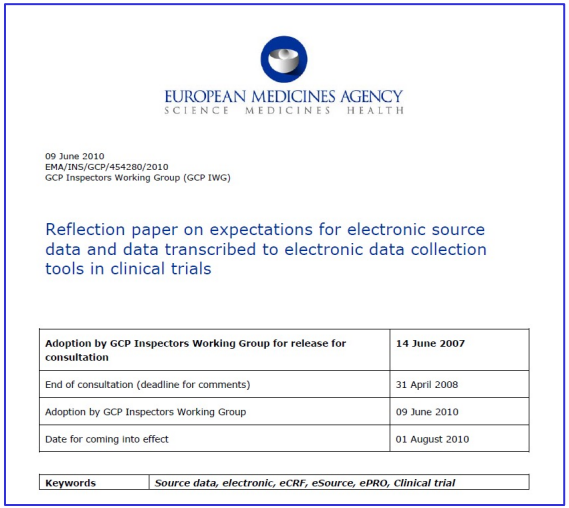
15-16 September 2022 – Malaga, Spain

Introduction

- A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:



Reflection papers into guidelines



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

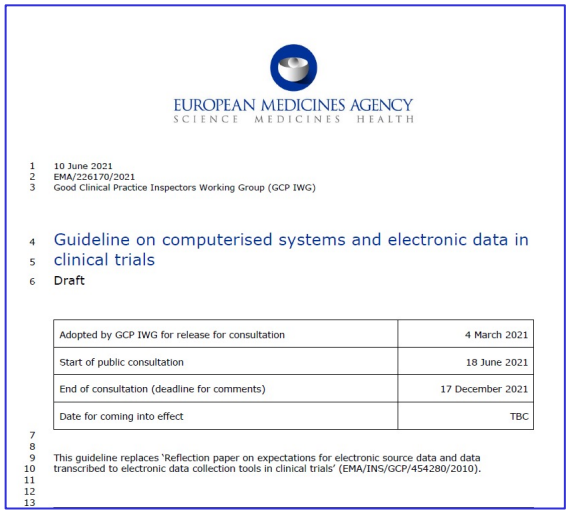
09 June 2010
EMA/INS/GCP/454280/2010
GCP Inspectors Working Group (GCP IWG)

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

Adoption by GCP Inspectors Working Group for release for consultation	**14 June 2007**
End of consultation (deadline for comments)	31 April 2008
Adoption by GCP Inspectors Working Group	09 June 2010
Date for coming into effect	01 August 2010

Keywords	***Source data, electronic, eCRF, eSource, ePRO, Clinical trial***

EMA reflection paper (2010) for electronic source data in clinical trials – general principles and some specific requirements



EUROPEAN MEDICINES AGENCY
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10 June 2021
EMA/226170/2021
Good Clinical Practice Inspectors Working Group (GCP IWG)

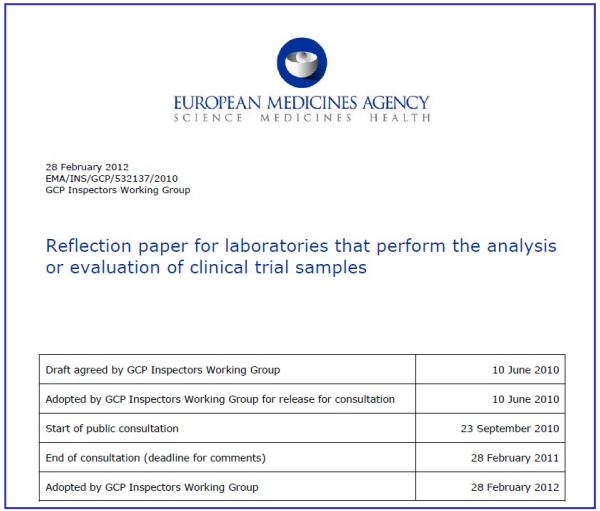
Guideline on computerised systems and electronic data in clinical trials

Draft

Adopted by GCP IWG for release for consultation	4 March 2021
Start of public consultation	18 June 2021
End of consultation (deadline for comments)	17 December 2021
Date for coming into effect	TBC

This guideline replaces 'Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials' (EMA/INS/GCP/454280/2010).

Draft EMA guideline (2021) on computerised systems and electronic data in clinical trial – more up to date guideline out for consultation



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

EMA reflection paper (2012) for laboratories in clinical trial – expectations on the BioA lab on equipment maintenance and csv

The reflection paper on equipment maintenance

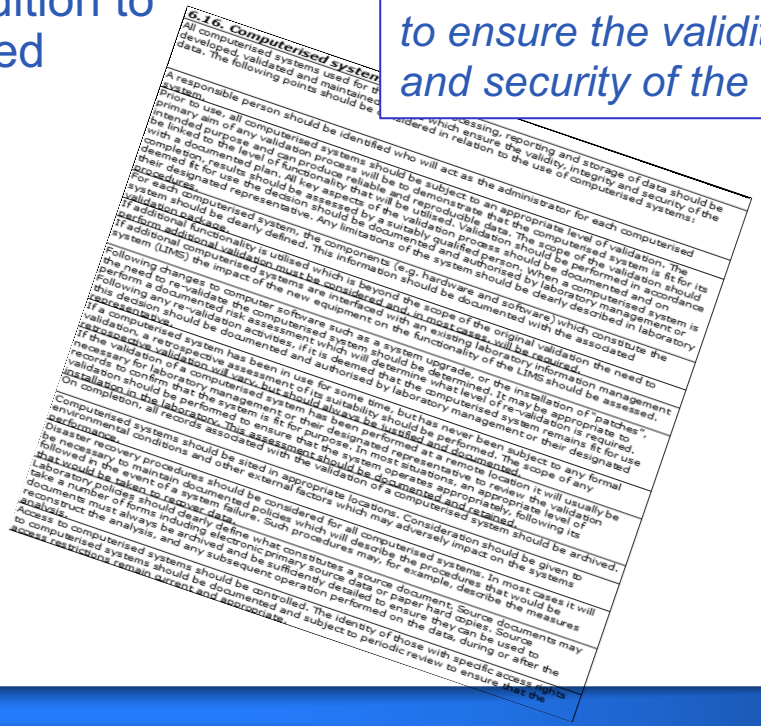
- Identified overinterpretation risk:
  - GLP principles and GMP requirements are applied in GCP settings

6.15. Equipment maintenance
All equipment used to conduct clinical analysis should be fit for its intended purpose. As a minimum, equipment should be regularly maintained by suitably qualified persons and any maintenance documented.
Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing, by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose. Any such tests should be documented and the records retained as long as the trial records to which the sample analyses relate (i.e. it may be necessary to retain the records beyond the decommissioning and retirement of the equipment).
Apparatus should be periodically inspected, cleaned, maintained and calibrated according to standard operating procedures or the manufacturer's manuals. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement. Calibration frequency will be determined by management or their representatives and should be designed to ensure that all equipment remains fit for purpose.

The reflection paper on computerised systems

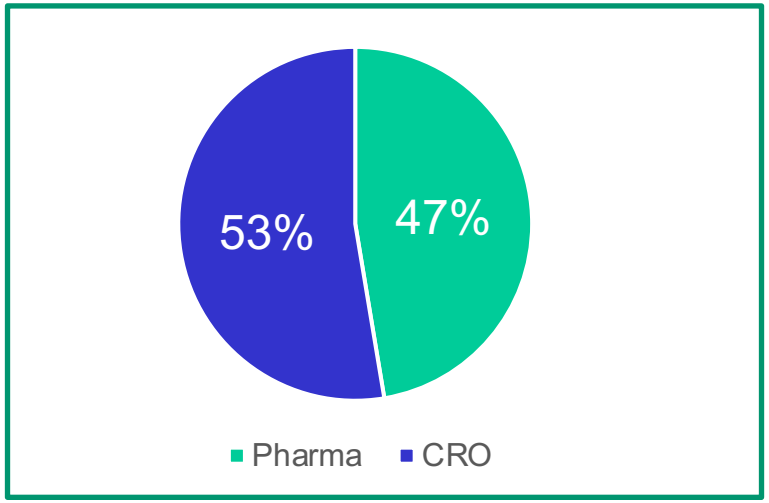
- Identified overinterpretation risk:
  - GLP principles are applied in GCP settings and separate re-validation in addition to manufacturer validation performed

…*should be developed, validated and maintained in ways to ensure the validity, integrity and security of the data*



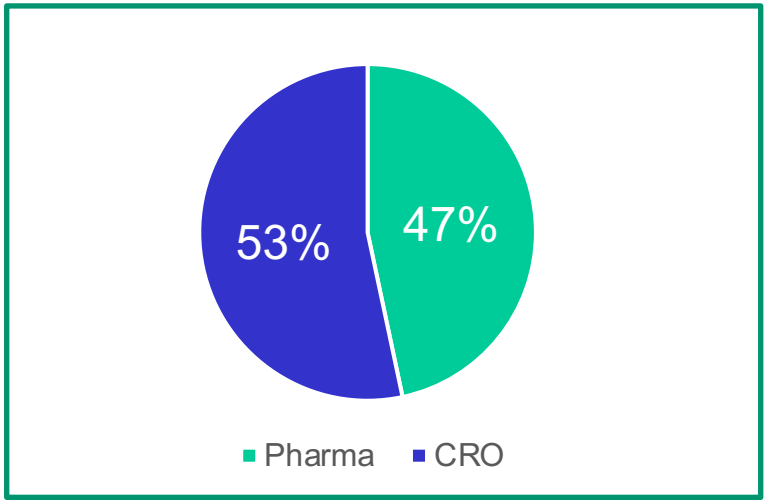
FotP - Feedback from core community on…

Equipment Maintenance survey



- Response: 38 member companies

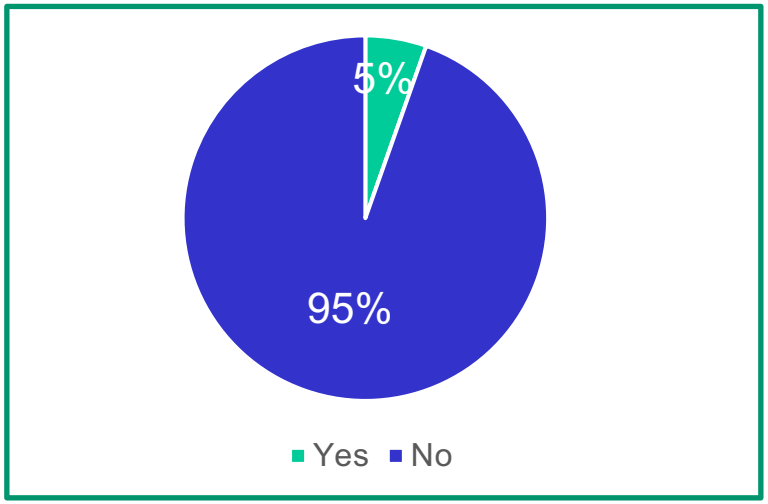
Computerised systems validation survey



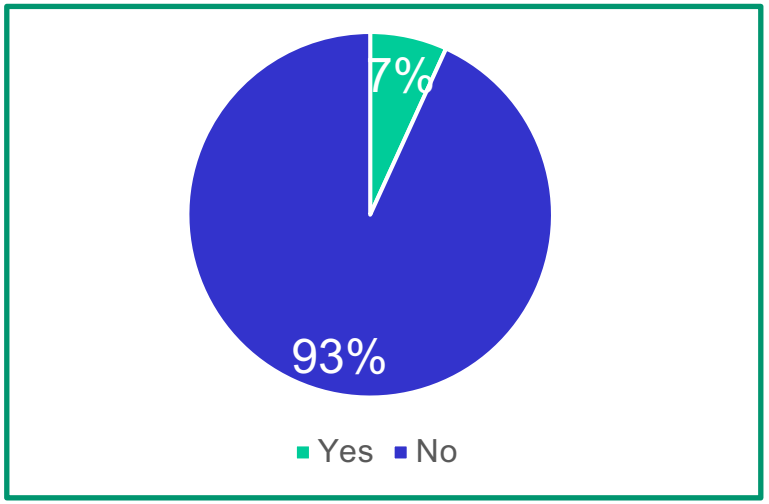
- Response: 47 member companies

Do you implement different requirements for Computerized system validation / Equipment maintenance in GCP setting compared to GLP?

Equipment Maintenance



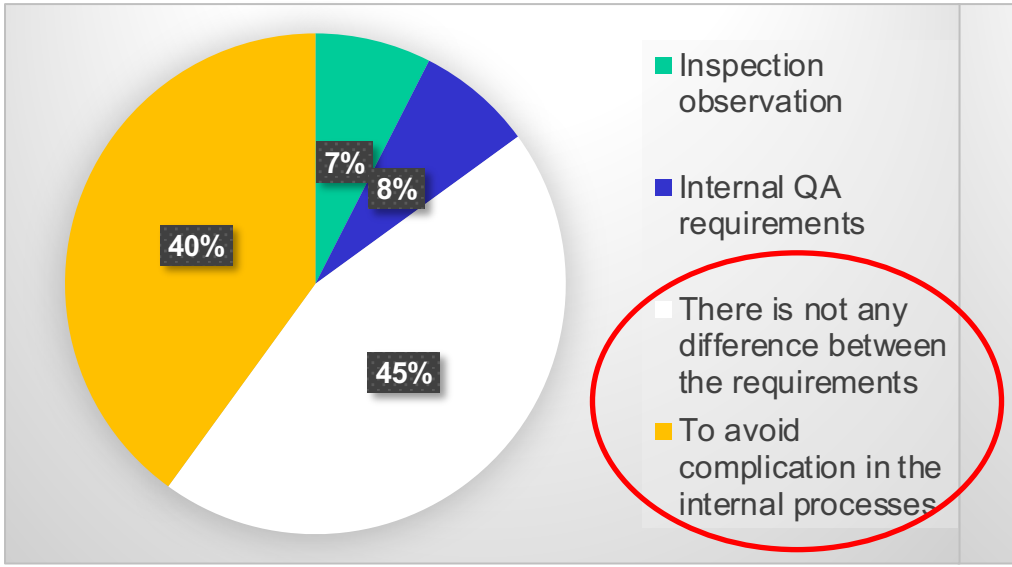
Computerised systems validation



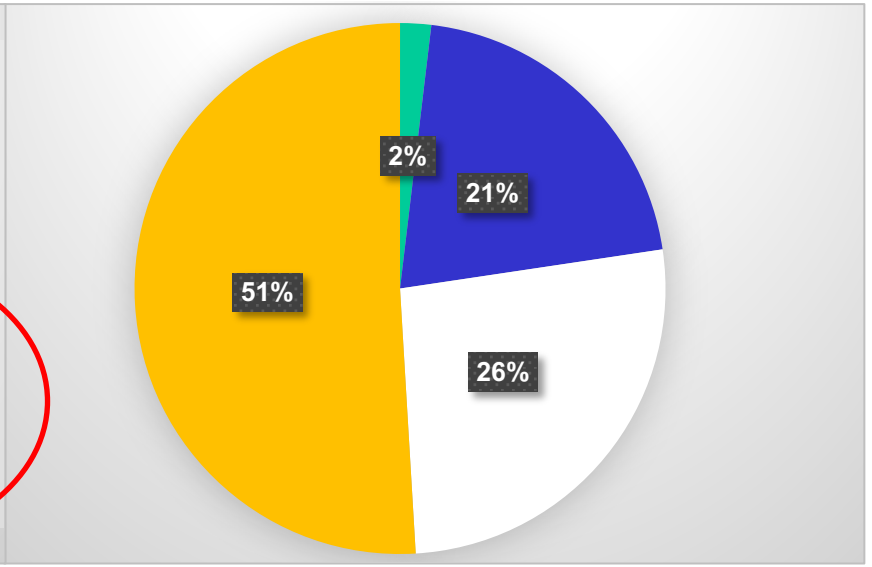
Most EBF labs apply the same requirements in GCP setting as in GLP

What is the main reason for applying the GLP requirements also in GCP settings?

Equipment Maintenance



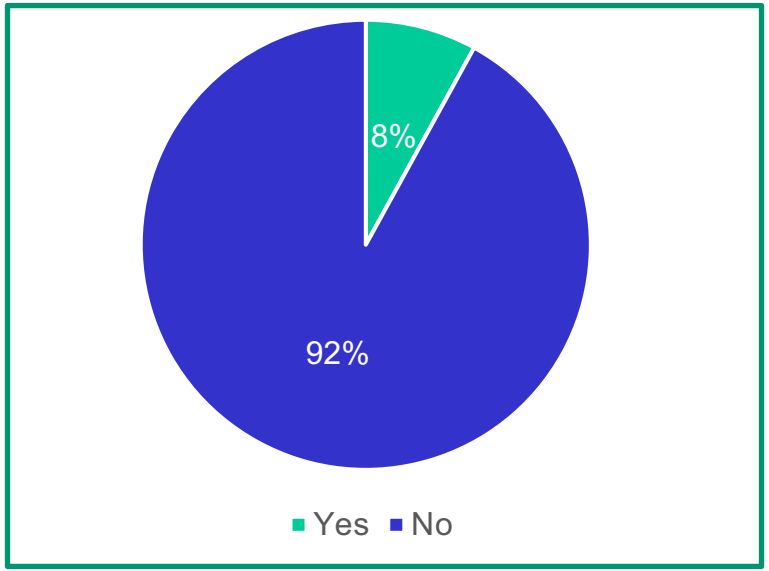
Computerised systems validation



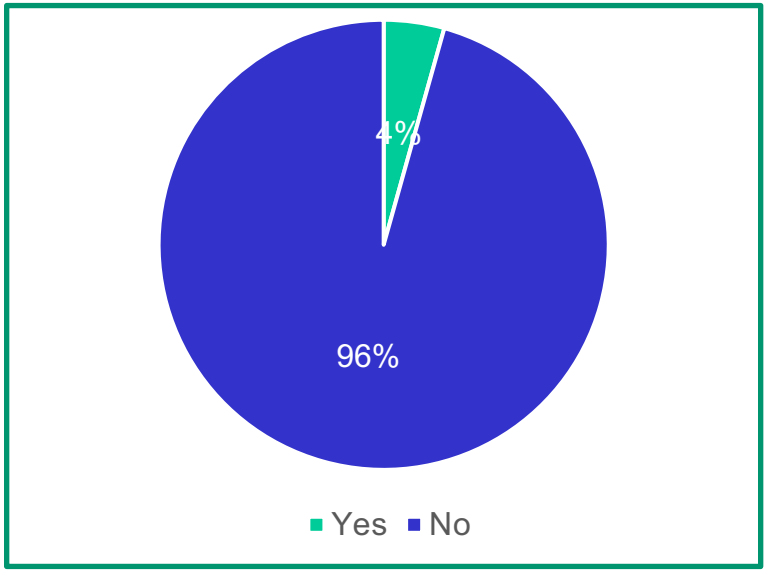
Why? There is no difference in requirements or to facilitate in the internal processes

Have you had any comments with regards CSV / equipment maintenance approach during HA inspection?

Equipment Maintenance

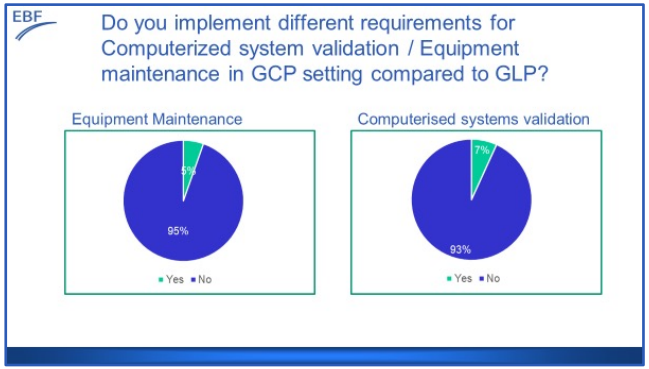


Computerised systems validation



Comment - HA inspection focus is on the equipment and software to ensure data integrity requirements are being met this applies equally to all GxP

Overinterpretation of refection paper



≠ Fit for its intended purpose

Possible reasons?

- Fit-for-purpose approach not clearly defined
- Labs think that this is the ‘easy way out’
- To be on the ‘safe side’

Equipment maintenance - overinterpretation noted

- GLP principles and GMP requirements are applied in GCP settings

6.15. Equipment maintenance
All equipment used to conduct clinical analysis should be fit for its intended purpose. As a minimum, equipment should be regularly maintained by suitably qualified persons and any maintenance documented.
Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing, by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose. Any such tests should be documented and the records retained as long as the trial records to which the sample analyses relate (i.e. it may be necessary to retain the records beyond the decommissioning and retirement of the equipment).
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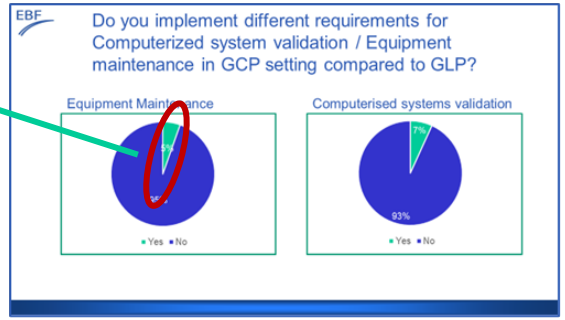
- Solution:
  - Define the 'lean', fit for purpose approach as it is stated in the refection paper. Approach to be based on the equipment's intended use and associated level of risk.

Equipment maintenance – GCP specific approach

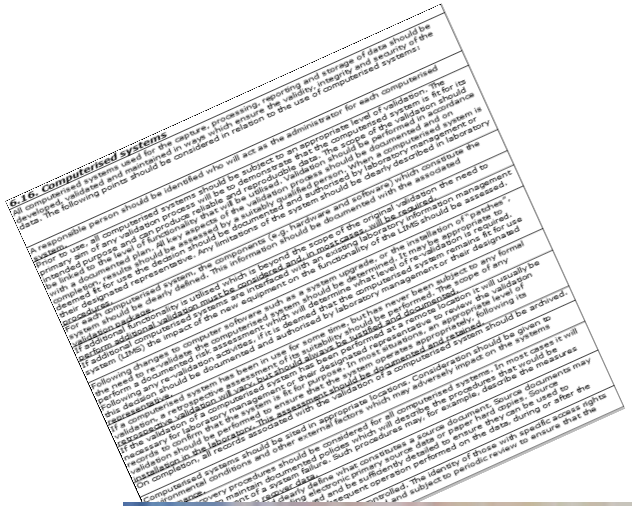
- One example of a GCP specific approach descibed for a non-GLP lab that measures biomarkers with a reduced quality maintenance concept, focusing on:



- Validation determination
  - main function and intended use of the instrument,
  - definition of electronic analytical data and their storage
  - risk assessment for use of derived data
  - data integrity
  - Roles and authorization concept/access
  - functional checks and tests
- Training documentation for user
- Installation qualification + functional tests

- Equipment folder (logbook) for tracking of use;
  - regular separate functional tests
  - preventive maintenance
  - error/problem handling and repair
  - technical changes
  - configuration management
  - decommissioning

Computerised systems - overinterpretation noted

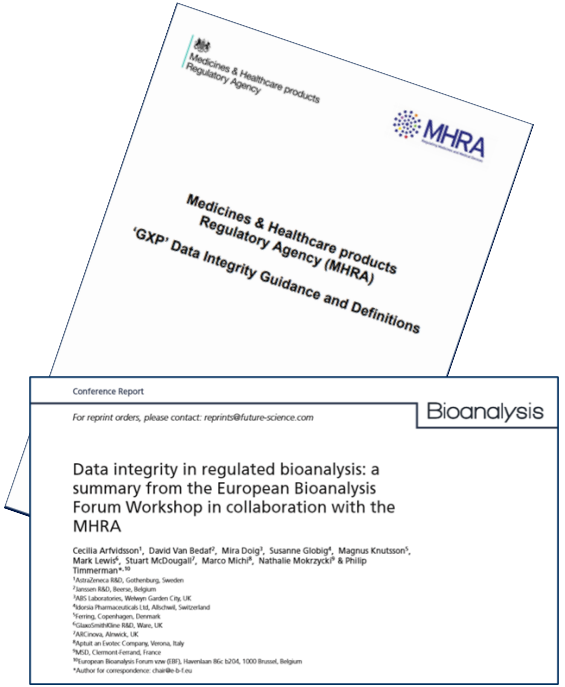


- GLP principles are applied in GCP settings and separate re-validation in addition to manufacturer validation performed

- Solution:
  - To define a pragmatic, risk-based approach for CSV for GCP settings
  - The recommendation should consider GCP specific recommendations (EMA Notice to Sponsors (2020), Draft Guideline on Computerised Systems (2021) and periodic review principles should be included.

EBF e-environment & Data Integrity team

- Despite continuously evolving systems the purpose of the regulatory requirements remains the same;
  - confidence in the quality and integrity of the data
  - being able to reconstruct activities
- The team has since 2018 arranged workshops and sessions at the EBF Open Symposium to provide increased insight and understanding of regulatory data integrity expectations
- To provide further insight and guidance on how to implement adequate levels of data integrity control dependent on the criticality of the data generated



Key messages relevant for GCP setting

- Key message 1 - know your software system data and processes
  - Two data integrity concepts are critical:
    - **data lifecycle** incl data collection, processing, reporting, review and archiving
    - **data governance** incl the process, the systems used and the ownership

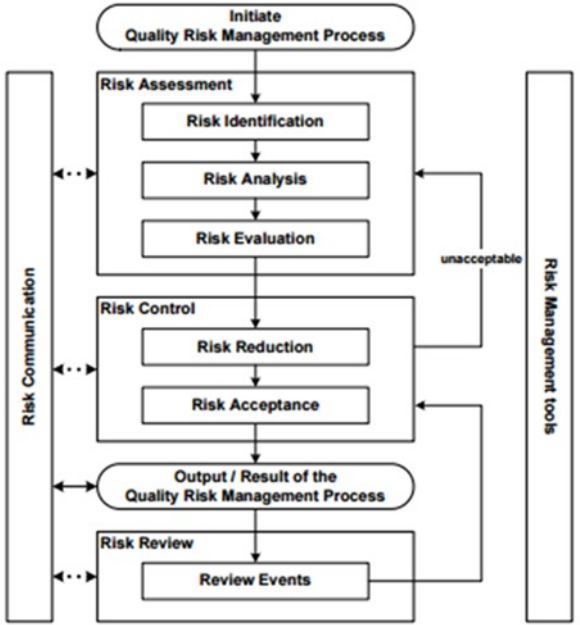
- Key message 2 - define your software systems through a process map exercise to understand:
  - your systems/processes/equipment/people
  - your data transfers/touchpoints/imports/exports
  - time/process/data criticality

  This to identify the potential risks and weaknesses

Key messages relevant for GCP setting

- Key message 3 - Understand the use of the data in each step of the map to identify the critical data and the controls/ oversight measures required for risk mitigation
  - Not all data is equal! Data criticality is determined by the intended use of the data and there's an expectation of using risk management principles to assess the risks and to identify the necessary mitigation steps

- Key message 4 - reduce the risk by implementing solutions that have been identified as a result of improved software awareness and knowledge



Key questions discussed, relevant for GCP setting

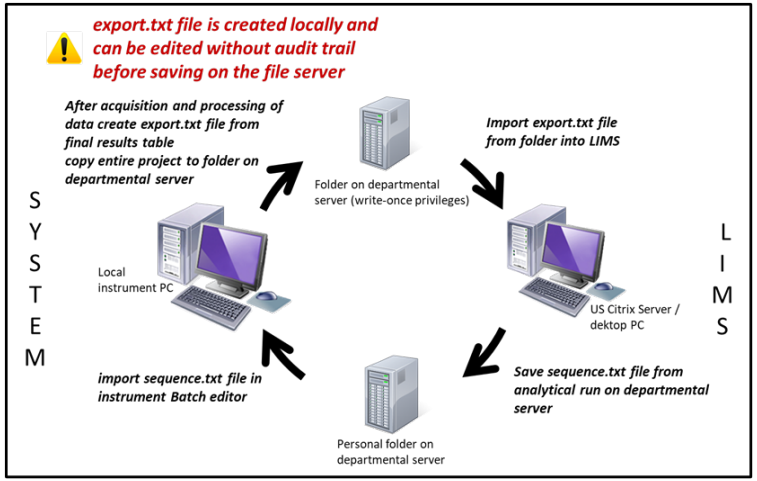
- How to optimise the data transfer process in order to be in line with regulatory expectations - keeping a balanced workload?
  - *Know your 'universe' and visualize the data flows through process mapping + risk assessment to identify the critical steps and the mitigation steps required*

- How to find the adequate level in your data integrity efforts?
  - *As above. The mitigation steps should then be regularly monitored to evaluate the applied mitigation efforts and minimize any overdoing*

- What is essential to QC check to ensure data integrity?
  - *This will all depend on your risk assessment what deemed necessary and not. Outcome of QC check should be regularly monitored to verify if the applied process and frequency is appropriate*

Building Common Understanding for Future System Solutions

The 2018 workshop was the starting point for enhanced interaction between system vendors, pharma/CROs and regulatory authorities to understand current, and define future, system data integrity capabilities.



- Highlight current key DI challenges, focusing on the data transfers in the LC/MS workflows
- What are the missing functionalities in today's process?
- What can the software developers do to help improve the current situation?

Improved Data Integrity in the LC/MS workflows

Following the e-environment workshop at the EBF OS 2019 the EBF proposal for a generic data transfer specification was published in Bioanalysis[1]

White Paper

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Improving data integrity in regulated bioanalysis: proposal for a generic data transfer process for LC–MS from the European Bioanalysis Forum

Cecilia Arfvidsson[1], David Van Bedaf[2], Susanne Globig[3], Magnus Knutsson[4], Mark Lewis[5], Stuart McDougall[6], Marco Michi[7] & Philip Timmerman*,[8]

[1]Clinical Pharmacology & Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden
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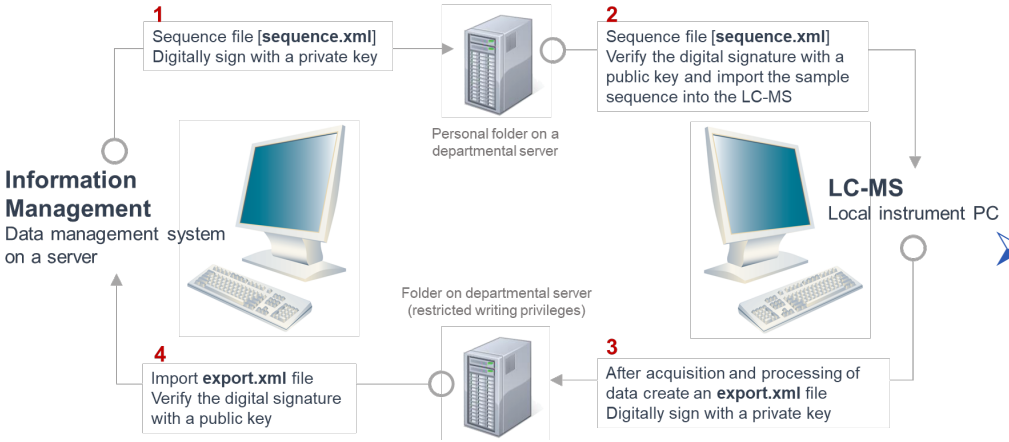
[4]Bioanalysis, Ferring, Copenhagen, Denmark
[5]Bioanalysis Immunogenicity & Biomarkers, GlaxoSmithKline R&D, Ware, UK
[6]Bioanalytical Services, ARCinova, Alnwick, UK
[7]Pharmacokinetics & Drug Metabolism, Menarini Ricerche S.p.A., Pomezia, Italy
[8]European Bioanalysis Forum vzw (EBF), Havenlaan 86c b204, 1000 Brussel, Belgium
*Author for correspondence: chair@e-b-f.eu

[1]Arfvidsson C, Van Bedaf D, Globig S *et al*. *Bioanalysis* 12(14), 1033-1038 (2020).

- Highlighting the need for improved data integrity compliance in today's LC/MS workflow
- Focus on the bi-directional data transfers between information management (IM) system and LC/MS, using only a **minimum data set, strictly required to safeguard DI**
- Progress can be made if/when all agree on a common lean standard and a pragmatic approach.

Towards a vendor neutral bi-directional data transfer process

A vendor neutral data transfer model has since then been presented by a joint software developer / instrument vendor team as a response to EBF paper.



- Replacing current use of .txt files with digitally signed vendor neutral .xml files to significantly increase data security
- Remove manual and time-consuming quality-control steps to mitigate the DI risks
- Data transfers more secure, but also easier to audit and with a near zero impact for any user experience

E-environment team's ´ideal´ instrumentation /software

- **Data storage and transfer**
  - Data transfer in a secure file format
  - A direct interface to and from LIMS or at least a "standard output format" that can be used as a template for any LIMS
  - Flexibility within database to be able to select what files to export
  - Possibility to export and re-import raw data into database
  - Database for file storage
- **User access levels**
  - Built-in application account
  - Lock options at several stages
  - Data and user management within a database
- **Audit Trail**
  - Full audit trail available and within a database (not file based)
  - A more extensive system audit trail filter
- **Archiving of study data**
  - An opportunity to archive individual parts of the database

In summary ….

- Your equipment and computerised systems should be fit for their intended purpose. To define this approach, you need to:
  - Understand your equipment/system
  - Know the intended use of the data
  - Consider the GCP specific recommendations and guidelines

- Do a risk assessment to identify the critical steps and the mitigation steps required

- Include a periodic review to verify that the applied process is appropriate

…and to consider for the discussion

- "*There is no real difference between GLP and GCP requirements for equipment maintenance and computerized system validation*" – Is this true??

- "*HA inspection focus is on the equipment and software to ensure data integrity requirements are being met and this applies equally to all GxP* " - Is this true??

Acknowledgements

- EBF GCP team
- EBF e-environment team
- EBF core community

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw

www.e-b-f.eu