P-248 データインテグリティガイダンスに対する日本のGLPデータ管理のギャップ

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Gaps for GLP data management in Japan to Data Integrity Guidance

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Introduction

Since a Data Integrity Guidance for GMP (MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015) was issued by the Medicines & Healthcare Products Regulatory Agency (MHRA), UK in March 2015, several related guidance documents have been issued. In March 2018, Data Integrity Guidance for GXP, including GLP (‘GXP’ Data Integrity Guidance and Definitions), was issued by MHRA. Considering the possibility that similar guidance will be issued by the OECD in the near future, we analyzed the gaps between the MHRA’s guidance and the current situation of Japanese GLP-compliant facilities. As a result, we identified gaps that could have a significant impact on domestic facilities, particularly in the requirements regarding the following three points: governance systems, computerized systems, and blank formats.

History of Data Integrity Guidance

Prologue of Data Integrity（DI）Regulation

- **Outbreak of Quality issues in India and China**
  - **India**
    - > Data falsification has been discovered one after another in the GMP area.
  - **China**
    - > Frequent falsification has been observed in the GMP and GCP field.

Authorities tighten regulations

FDA
- > Warning Letter (WL) increased from around 2010.

CFDA (Chinese authorities)
- > Several regulations for DI have been issued from around 2015.

History of FDA Part 11

YYYY/MM	Guidance	Remarks
1997/8	Execution of 21CFR Part 11 Electronic Records Electronic Signatures	Regulations of electronic records and signatures
1999/4	Issuance of Computerized System Used in Clinical Trials	Requirements for using a computerized system in clinical trials
2002/8	Issuance of Pharmaceutical cGMPs for the 21st Century :A Risk-Based Approach	Declaration of a new approach to scientific guidance based on risk base approach
2003/3	Issuance of Guidance for Industry Part11, Electronic Records Electronic Signatures - Scope and Application	Focus on high-risk electronic data, considering costs that were not initially assumed
2003/9	**Suspension of issuance of Warning Letter related to 21CFR Part 11**	The reason is that the scope of application was reviewed due to an increase in application cost.
	7 years blank	
2010/7	**Resumption of inspection based on 21CFR Part 11**	Recent GMP inspections have found cases where data integrity has been compromised, which is the reason for the resumption.

Scope of DI Regulation

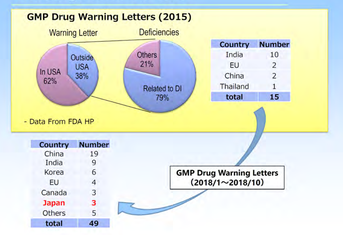
- **Row data**
  - Original or authentic copy of the record
    - ✓ Is it the same as the data originally acquired?
- **Metadata**
  - Information needed to explain / understand the data
    - ✓ Is there any missing information that gives meaning to the data?

DI requirements

Completeness of both static data (paper / PDF) and dynamic electronic data

※Original electronic data may not be excluded from DI regulation even if electronic data is printed on paper.

Warning Letters in GMP



History of DI Guidance

YYYY/MM	Authorities	Guidance
2015/3	**MHRA**	**Data Integrity Definitions and Guidance for Industry**
2016/4	FDA	Guidance for Industry Data Integrity and Compliance With CGMP (Draft)
2016/5	**WHO**	**Guidance on Good Data and Record Management Practices**
2016/7	MHRA	MHRA GxP Data Integrity Definitions and Guidance for Industry (Draft)
2016/8	PIC/S	Good Practice for Data Management and Integrity in Regulated GMP/GDP Environments (Draft 2)
2016/10	CFDA	Draft CFDA Guidance on Drug Data Management Practices (Draft)
2018/3	**MHRA**	**‘GXP’ Data Integrity Guidance and Definitions**
2018/11	PIC/S	Good Practice for Data Management and Integrity in Regulated GMP/GDP Environments (Draft 3)
2018/12	**FDA**	**Data Integrity and Compliance With Drug CGMP**
20XX/??	**OECD**	**Publication of Data Integrity documentation for GLP**

Definition of Raw Data in DI

Excerpt from MHRA GXP Draft DI Guidance

System complexity	Simple system					Complex system
	pH meter	Filter integrity test			Interactive response technology	Enterprise resource planner
		UV spec	HPLC systems	LC-MS-MS	LIMS	
	Balance	FTIR		Pharmacovigilance database		Bespoke systems
		ECG machines	Electronic trial master file		Clinical database	
		Spreadsheet			Statistical analysis tools	
	Min/Max thermometers	Data loggers	Building management system			
Software	No software	Simple software				Complex software
Printouts	Printouts may represent original data	Printouts not representative of original data				

Electronic data should be defined as raw data.

Gaps for MHRA’s ‘GXP” Data Integrity Guidance

Governance systems

In Japan, the GLP organization has been required to be managed separately from the company organization, but MHRA’s guidance required that the senior management in the company organization be involved in the data governance. Therefore, many of the GLP facilities in Japan are not currently in a situation that meets the requirement of this guidance. However, if the test facility management (TFM) is regarded as the management who can manage resources for data governance (budget, tasks, etc.), the governance system required by the guidance can be completed within the GLP organization (Case 1 and Case 2). If not, we believe that the facilities may enable their GLP organizations to respond to the requirement of the DI guidance by establishing a reporting system on the data governance from the TFM to the management (Case 3).

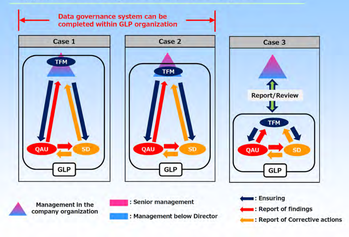
Computerized systems

Many facilities output dynamically collected electronic data to paper and define it as raw data. In the future, it is necessary to aim to define dynamic data as raw data. However, in order to define dynamic data (electronic data) as raw data, enormous costs such as “change of process,” “purchase of equipment,” and “purchase of access rights” are incurred. For this reason, we show practical measures, such as hybrid operations, focusing on access rights management and audit trail. Eventually, it will be important to assess the risks of devices and systems that do not meet data integrity requirements, prioritize countermeasures, and proceed with dynamic data management in a medium-term plan.

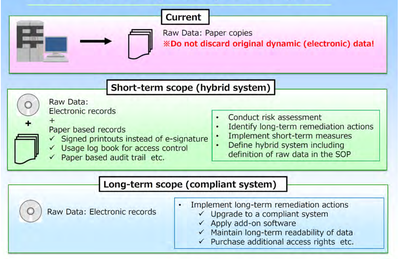
Blank formats

Management of blank format may include "stamping, punching, signatures, etc. by administrative departments," "book format," and "complete digitization of records by computerized system.“ There are various obstacles for these management approaches, but in the future some measures to prevent tampering should be considered. It would be ideal to digitize the records completely with a computerized system. However, since the situation of the blank format varies depending on the facility, it is necessary to consider the methods appropriate for each.

Typical GLP Organizations in Japan



Management of Dynamic (Electronic) Data



Aspects of Managing Method for Blank Format

Methods	Pros & Cons
Cut sheets (Signatures, Stamps or Punching by administrative departments)	**Cost:** minimum ~ moderate **Task:** moderate ~ high **Remark:** applicable to all type of study
Book-like Format	**Cost:** minimum **Task:** moderate **Remark:** not applicable to some type of study (induction of mistakes due to inefficient procedure)
Digitization of records	**Cost:** high (both installation and maintenance) **Task:** high (both installation and maintenance) **Remark:** complete control to blank format

There are major obstacles to applying either method to GLP facilities.

Future countermeasures for DI

Ultimate Image of the Future

- **Fully integrated electronic system* including:**
  - Test data management system (LIMS, electronic lab notebook, etc.)
  - Exam information and document management system
  - Animal management system
  - Asset management system
  - Consumables and reagent management system
  - Education system etc.

*FDA Part 11 concept: Prevents tampering by avoiding human intervention

Data integrity issues are not limited to GXP, but social issues
Steel strength, inspection qualification, exhaust gas data, pile driving data, seismic isolation data, accounting data, Fuel efficiency data, political activity data, food data (food disguise), expiration date data, Basic research data

What to Do in the Near Future

- Check the regulatory trends
  - FDA severities continue, as WLs in India and China have not decreased
  - PMDA's view on DI in GLP
  - GCP trends in clinical sample measurement
- In-house education for DI
- Check the status of CRO for DI as a sponsor
- Enact data governance rules in company
  - Document your company's policies and present them during inspections
- Assess the requirements needed for your company
  - Those that do not require large resources will respond first
    - > Access right setting (including access to PC clock), use of audit trail, blank template management, etc.
  - Risk-based assessment, preparation of improvement plan
    - > Prepared for presentation during inspection

General overview

Assuming that GLP Data Integrity Guidance will be issued by the OECD in the near future, we analyzed the gaps between the MHRA’s Data Integrity Guidance and the current situation of Japanese GLP-compliant facilities. Gaps that could have a major impact on domestic facilities were seen in the requirements of “governance system,” “computerized system” and “blank formats.” Regarding the gap for the governance system, it was thought that the impact could be mitigated by investigating the situation of the GLP organization of each facility and responding flexibly. On the other hand, it is assumed that high costs and a large amount of tasks will be incurred to fully address the gaps for the requirements of “computerized system” and “blank formats.” At this time, it is unclear when the GLP Data Integrity Guidance by OECD will be issued, but in the next few years, it will be necessary to establish a policy of data integrity for each facility while deepening the understanding of the principles of data integrity.