Pharmaceutical
Quality Group

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Data Integrity for Pharmaceutical Grade Excipients

IPEC Data Integrity Position Paper for Excipients

Pharmaceutical Quality Group

22 September 2020

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The views, thoughts, and opinions expressed in the text belong solely to the authors, and not necessarily to the author's employer, organization, committee or other group or individual.

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IPEC Position Paper on Data Integrity for Pharmaceutical Grade Excipients

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IPEC Position Paper on Data Integrity for Pharmaceutical Grade Excipients

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Note: comments were also provided from **IPEC Japan**

Guidance Documents and ALCOA principles

How it works =

Legislation and Regulatory functions place requirements on Finished Drug Manufacturers to ensure the safety, quality and efficacy of their products = Protect the patient.

Finished Drug Manufacturers must comply to legally sell their product. They ask their suppliers to follow appropriate GMP according to the risk level for the material supplied = Protect the patient.

Excipient Manufactures need to define how data integrity applies to their operation based on the risk to product quality and safety if the integrity of the data was compromised = Protect the patient.

What our customers have been reading

Medicines & Healthcare products
Regulatory Agency

MHRA

Medicines & Healthcare products
Regulatory Agency (MHRA)

'GXP' Data Integrity Guidance and Definitions

March 2018

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018
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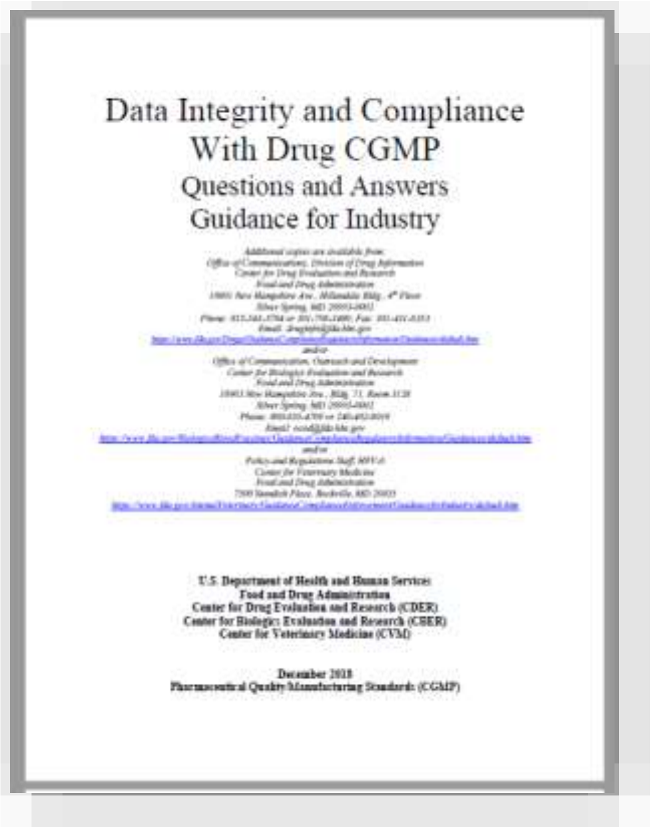

Data Integrity and Compliance
With Drug CGMP
Questions and Answers
Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
[illegible]
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
[illegible]
and/or
Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place, Rockville, MD 20855
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

December 2018
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Guidance and Industry Standards

- FDA: Data Integrity and Compliance with CGMP Guidance for Industry, December 2018.
- MHRA: GxP Data Integrity Definitions and Guidance for Industry, Rev. 1 March 2018.
- EMA: Data integrity, August 2016.
- PIC/S: Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, August 2016.
- WHO: TRS 996, Annex 05, Guidance on good data and record management practices, 2016.
- TGA: Data Management and Data Integrity (DMDI), 2017
- Health Canada: Letter to Stakeholders, 2015
- Rx360: Data integrity library
- ISPE: Data Integrity: Testing Into Compliance

The overall goal of Data Integrity

Prevent the manipulation of data or repeat testing to achieve the desired outcome with limited opportunity for detection.

Necessary in order for the data to provide an accurate review of the decisions made in the past through the data available at the time the decision was made.

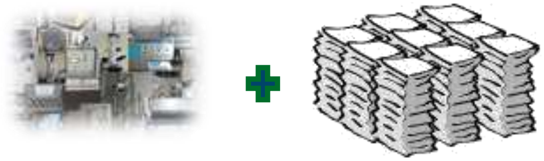
Like an action video game for Quality Decisions.

What is Data Integrity

Data integrity is “the extent to which all data are complete, consistent and accurate throughout the data lifecycle.”*

the accuracy, completeness, content and meaning of data is retained throughout

Applies to both electronic and paper records



Applies to data creation, processing/manipulation, temporary storage and long-term storage/archiving.

*MHRA GMP Data Integrity Definitions and Guidance for Industry, March 2018

ALCOA+
The Principles of Data Integrity

ALCOA

Attributable to the person generating the data

Legible and permanent

Contemporaneous (recorded at time of the task or measurement)

Original (or "true copy" of file or format, preserving the integrity)

Accurate (reliable)

4 elements of the "+"

Complete: The data must be whole; a complete set (including any test, repetition or re-analysis performed).

Consistent: The data must be self-consistent. All elements of the analysis, such as the sequence of events, are date or time stamped in the expected sequence.

Enduring: A sustainable record (systematically documented) in laboratory notebooks or validated systems.

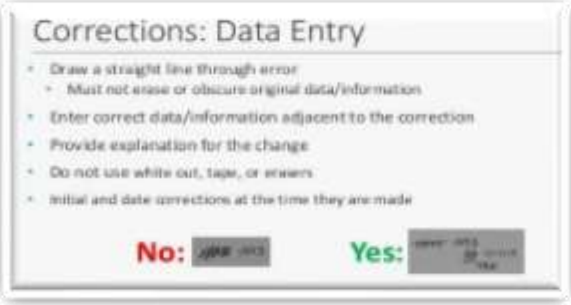
Available: Can be accessed for review and audit or inspection over the lifetime of the record.

Attributable

It should be possible to identify the individual who performed the recorded task.

The need to document who performed the task / function, is in part to demonstrate that the function was performed by trained and qualified personnel.

This applies to changes made to records as well: corrections, deletions, etc.



Corrections: Data Entry

- Draw a straight line through error
  - Must not erase or obscure original data/information
- Enter correct data/information adjacent to the correction
- Provide explanation for the change
- Do not use white out, tape, or erasers
- Initial and date corrections at the time they are made

No: [illegible] Yes: [illegible]

Legible

All records must be legible –
the information must be readable
in order for it to be of any use.

This applies to all information that would be required to be considered Complete, including all Original records or entries.

Where the ‘dynamic’ nature of electronic data (the ability to search, query, trend, etc.) is important to the content and meaning of the record, the ability to interact with the data using a suitable application is important to the ‘availability’ of the record.

Contemporaneous

The evidence of actions, events or decisions should be recorded as they take place.

This documentation should serve as an accurate attestation of what was done, or what was decided and why, i.e. what influenced the decision at that time.

ALC**O**A+

Original

The original record can be described as the first-capture of information, whether recorded on paper (static) or electronically (usually dynamic, depending on the complexity of the system).

Information that is originally captured in a dynamic state should remain available in that state.

ALCO**A**+

Accurate

Ensuring results and records are accurate is achieved through many elements of a robust Pharmaceutical Quality Management System. This can be comprised of:

- equipment-related factors such as qualification computer validation calibration maintenance

- policies and procedures to control actions and behaviors, including **data review procedures** to verify adherence to procedural requirements

- deviation management including root cause analysis impact assessments CAPA

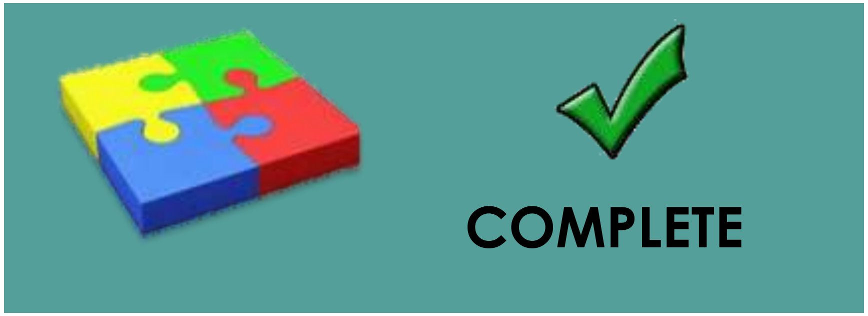
- **trained and qualified personnel** who understand the importance of following established procedures and documenting their actions and decisions.

Together, these elements aim to ensure the accuracy of information, including scientific data, that is used to make critical decisions about the quality of products.

ALCOA+

Complete

All information that would be critical to recreating an event is important when trying to understand the event. The level of detail required for an information set to be considered complete would depend on the criticality of the information. A complete record of data generated electronically includes relevant metadata.



ALCOA+

Consistent

Good Documentation Practices should be applied throughout any process, without exception, including deviations that may occur during the process. This includes capturing all changes made to data.

- You don’t throw away bad data or failed analysis – you keep it and justify the exclusion from use in decision making
- Data may only be excluded where it can be demonstrated through valid scientific justification that the data are not representative of the quantity measured, sampled or acquired.
- In all cases, this justification should be documented and considered during data review and reporting. All data (even if excluded) should be retained with the original data set, and be available for review in a format that allows the validity of the decision to exclude the data to be confirmed.

Enduring

Part of ensuring records are available is making sure they exist for the entire period during which they might be needed. This means they need to remain intact and accessible as an indelible/durable record.

ALCOA+

Available

Records must be available for review at any time during the required retention period, accessible in a readable format to all applicable personnel who are responsible for their review whether for routine release decisions, investigations, trending, annual reports, audits or inspections.

What else is the guidance telling us?

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018

3.4

Implement, design and operate a documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. An example of a suitable approach is to perform a **data integrity risk assessment** (DIRA) where the processes that produce data or where data is obtained are mapped out and each of the formats and their controls are identified and the **data criticality** and **inherent risks** documented.

3.6

The effort and resource applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure to the patient or environment. Collectively these arrangements fulfil the concept of **data governance**.

5.1

Systems and processes should be designed in a way that facilitates compliance with the **principles of data integrity.**

IPEC Data Integrity Position Paper for Excipients

Position Paper Purpose

This paper describes IPEC's position on the relevance of data integrity guidance documents to the manufacture and supply of excipients.

NOTE: Within this paper, supplier will refer to both the excipient manufacturer and distributor

IPEC Position Paper

Data Integrity for Pharmaceutical Grade Excipients

30 April 2020

Purpose of Position Paper

This paper describes IPEC's position on the relevance of data integrity guidance documents to the manufacture and supply of excipients.

NOTE: Within this paper, supplier will refer to both the excipient manufacturer and distributor

The Issue

Current regulatory guidance documents on data integrity emphasize drug products (DP, also known as medicinal products) and drug substances (DS, also known as active pharmaceutical ingredients, APIs). Their scope does not explicitly include or exclude excipients. However, since critical data, Good Manufacturing Practice (GMP) compliance, and confidence in the quality of the excipient is based on the integrity of data, it is important for all parties involved in the manufacture and supply of excipients (e.g. warehousing, distributing, testing and packaging) to develop and implement appropriate strategies to manage the integrity of critical data in order to provide confidence in the quality and GMP compliance of the excipient.

Many excipients are produced in facilities that manufacture products for a variety of markets (e.g., pharmaceutical, food, cosmetic and industrial). The manufacturing controls and instruments probably were:

- designed for products other than excipients
- designed and constructed with some open access components
- built with sophisticated process automation systems designed to handle highly hazardous materials
- primarily designed for manufacturing efficiency and compliance with environmental, occupational health and process safety regulations
- installed before data integrity expectations were explicitly defined.

Background Information

Maintaining data integrity is fundamental to the application of GMP. Published regulatory guidance defines data integrity requirements for finished drug/medicinal products and active ingredients [1-5]; however, these guidance documents include requirements that may not be easily adaptable to the manufacture of excipients.

What is data integrity?

Data integrity is the extent to which data are complete, consistent and accurate and maintained as such throughout the data lifecycle [6].

Data integrity applies to GMP and critical data in the manufacturing process including testing, packaging, storage and distribution.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
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www.ipec-federation.org – +32 (0)2 213 74 40 – info@ipec-federation.org
VAT [illegible] – RPM Brussels Capital Region

The Issue

Current regulatory guidance documents on data integrity emphasize drug products and drug substances

The functionality of excipients in formulation are often share with similar uses in food, cosmetics, feed, and industrial products (paints, glue, rubber compounding, etc.)

Many excipients are produced in facilities with these characteristics:

- primarily designed for manufacturing efficiency and compliance with environmental, occupational health and process safety regulations
- manufacture products for a variety of end markets (pharma, food, cosmetic, industrial, etc.)
- built with sophisticated process automation systems designed to handle highly hazardous materials
- installed before data integrity expectations were explicitly defined.

Data integrity concepts explicitly included in excipient GMP Standards and Guides

A. IPEC & PQG, The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2017

B. EXCiPACT™ Certification Standards for Pharmaceutical Excipient Suppliers: GMPs, GDPs, 2017

C. NSF/IPEC/ANSI 363 – 2019 GMPs for Pharmaceutical Excipients

Excipient GMPs

A. IPEC-PQG
B. EXCiPACT™
C. NSF/IPEC/ANSI-363

ALCOA+ principles	Data Integrity Requirement	A	B	C
Attributable	Entries in records should be signed and dated by the person making the entry. Consideration should be given to the integrity and audit trail of electronically retained data.	4.2.4	7.5.2	7.5.3
	Records for both batch and continuous processing, where critical to excipient quality, should include: identification of persons (e.g. initials traceable to signature log) performing and directly supervising or checking each significant step, operation or control parameter.	7.5.1.1	8.5.1	8.5.1
Legible	Records should be understandable. Entries in records should be clear and indelible.	4.2.4	7.5.2	7.5.3
Contemporaneous	Entries in records should be made directly after performing the activity (in the order performed)	4.2.4	7.5.2	7.5.3
Original	Corrections to entries should be signed and dated, leaving the original entry legible. Measures should be taken to maintain data integrity at all times. For example, analytical results and calculations should be traceable to original data and measurements.	4.2.4	7.5.2	7.5.3
	Laboratory controls should include a record of raw data secured during each test including printouts such as graphs.	8.2.4.1	8.6	9.1.4.1

Excipient GMPs

A. IPEC-PQG

B. EXCiPACT™

C. NSF/IPEC/ANSI-363

ALCOA+ principles	Requirement	A	B	C
Accurate	Retention of accurate, suitable and regular back-up or archival systems such as copies of the program and file	6.3.2.3	7.1.3	7.1.3.5
	The excipient manufacturer should have procedures in place to ensure data is authentic, complete and accurate.	8.2.4.1	ISO 9001:2015 7.5*	7.5
+Complete	Records should be available for each batch of excipient produced and should include complete information relating to the production and control of each batch.	7.5.1.1	8.6	8.5.1
	Laboratory controls should include all data related to the entry.	8.2.4.1		9.1.4.1
+Consistent	Entries in records should be clear, indelible, made directly after performing the activity, signed and dated by the person performing the observed task.	4.2.4	7.5.2	7.5.3
+Enduring	Records should be kept for a defined period.	4.2.4	7.5.3.1	7.5.3
	Records should be stored in facilities that provide a suitable environment to minimize deterioration or damage.	4.2.4	ISO 9001:2015 7.5.3.2*	7.5.3
	Retention of accurate, suitable and regular back-up or archival systems such as copies of the programme and files,	6.3.2.3	7.1.3	7.1.3.5

* ISO 9001 is a prerequisite to the EXCiPACT™ GMP/GDP Certification

Excipient GMPs

A. IPEC-PQG

B. EXCiPACT™

C. NSF/IPEC/ANSI-363

ALCOA+ principles	Requirement	A	B	C
+Available	Records should be stored and maintained in a manner that they are readily retrievable.	4.2.4	ISO 9001:2015 7.5.3.1*	7.5.3
	Records should be available for each batch of excipient produced and should include complete information relating to the production and control of each batch.	7.5.1.1	ISO 9001:2015 8.5.1*	8.5.1
	The excipient manufacturer should have procedures in place to ensure data is authentic, complete and accurate; that it can be traced to its source and that it is readily available	8.2.4.1	8.6	9.1.4.1

* ISO 9001 is a prerequisite to the EXCiPACT™ GMP/GDP Certification

ISO 9001

7.5.3 Control of documented information

.1

a) it is available and suitable for use, where and when it is needed

b) It is adequately protected (e.f. from loss of confidentiality, improper use, or loss of integrity)

.2

Documented information retained as evidence of conformity shall be protected from unintended alterations

Comparison in Application of Data Integrity Principles for API vs excipients

Same journey but different modes of transportation

Different ability to detect & correct along the way

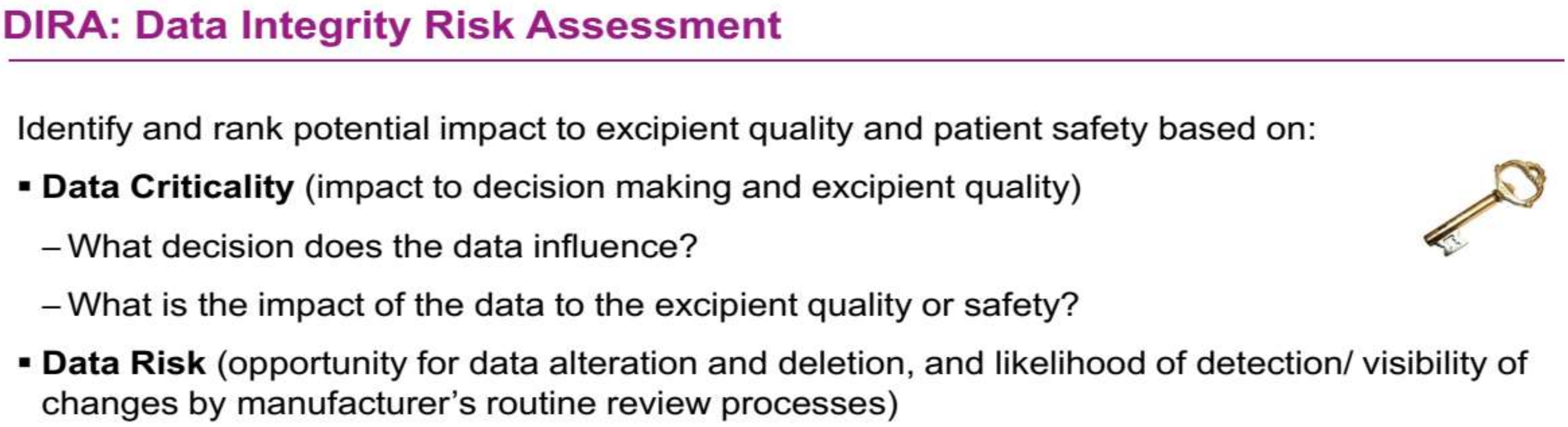
Data Integrity Principles	DP/DS	Excipients
Process Computer system restrictions/ access	Computer access requires unique usernames and passwords	Process control systems managing excipient quality critical parameters are often subject to restricted access control; however, they often require access by multiple operators for safety reasons and may have shared passwords base on roles/responsibilities.
Validation & compliant computers (electronic records and signatures)	DP/DS computer systems must be validated and meet requirements for electronic records and signatures (e.g. U.S. 21 CFR Part 11)	Computer systems impacting excipient quality are commissioned, which includes ensuring that the systems operate in the way for which they were intended and ensures that only authorized parties have access to data input and/or the capability to make changes.
Audit trails for computer systems/operations	Complete audit trail review prior to each batch release	Audit trails may be electronic, or paper based
Storage/retention of metadata	Collection, review, storage and retention of all metadata	Metadata may not be captured electronically by some legacy systems. Manual measures may be used to ensure compliance and maintenance of DI.
Attributable and original records	All records are accountable and under document control.	Excipient suppliers may use paper systems to record information.

IPEC Federation Position

Although DI is clearly relevant to excipient mfg and distribution, excipient suppliers may implement different DI controls than DP manufacturers.

DI should be applied to excipient manufacturing processes, distribution or other activities where the loss of DI would jeopardize compliance with excipient GMPs/GDPs, impact confidence in excipient quality, pose potential harm to the patient, or cause the failure or rejection of the DP.

Excipient suppliers should identify risks to their critical data and establish and document controls to implement mitigating measures wherever feasible and appropriate.



DIRA: Data Integrity Risk Assessment

Identify and rank potential impact to excipient quality and patient safety based on:

- **Data Criticality** (impact to decision making and excipient quality)
  - What decision does the data influence?
  - What is the impact of the data to the excipient quality or safety?
- **Data Risk** (opportunity for data alteration and deletion, and likelihood of detection/ visibility of changes by manufacturer's routine review processes)

Excipient Supplier Recommendations

Establish a data integrity approach based on identified risks to relevant critical data. Effort/resources should be commensurate with risk and impact of a data integrity failure.

Data integrity approaches may consider the following:

- Ensure data life cycle, from development of data through destruction.
- Create a list of records and data (by type or specific function) covered by the documented data integrity controls.
- Monitor to ensure compliance with the documented data integrity controls (e.g., culture, training and internal auditing).
- Implement measures to ensure the integrity of data from those systems already in-use and not designed to meet modern-day data integrity requirements

Excipient User Recommendations

Users should manage expectations appropriately when auditing excipient suppliers and realize that requirements from regulatory guidance may be addressed differently.

Users should evaluate the excipient supplier’s controls for quality critical data to determine if data integrity concepts have been addressed.

Excipient Makers and User

<u>What we have in common</u>

Facilities and operations.

- packing area is the start of customer's processing area
- storage area is the customer's ingredient storage area
- finish product testing lab is the customer's incoming ingredient testing lab

Need to supply

- The reliability of the Maker's product is the reliability of our User's drug product supply
- Supplying product generates cash flow needed to continue operations

Knowledge

- Makers are experts in their excipient
- Users know why they use it

<u>The differences</u>

Makers starts with raw commodities consumed by processes to make an excipient

- Raw materials, Ingredients, Specialty Ingredients
- Heavy purification and processing to make final product

Users start with APIs & excipients to make finished products consumed by people

- Blending, light processing, and packaging

cGMP for making excipients will be different from cGMP for making finished drugs

Filling in the Gaps

Excipient Manufacturers should:

- Make a data integrity plan.
- Build the plan from existing QMS controls for document and record controls.
- Include additional procedural steps to ensure ALCOA+ principles are met.

Use DIRA

Clearly limit which of the many documents, records, and data are critical for GMP and need to be included under the plan.

Include data integrity in internal audit plan.

DIRA:
Data Integrity Risk Assessment

Identify and rank potential impact to excipient quality and patient safety based on:

Data Criticality (impact to decision making and excipient quality)

- What decision does the data influence?
- What is the impact of the data to the excipient quality or safety?

Data Risk (opportunity for data alteration and deletion, and likelihood of detection/ visibility of changes by manufacturer’s routine review processes)

DIRA:
Data Integrity Risk Assessment

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018

4.1
Implement, design and operate a documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. An example of a suitable approach is to perform a **data integrity risk assessment** (DIRA) where the processes that produce data or where data is obtained are mapped out and each of the formats and their controls are identified and the **data criticality** and **inherent risks** documented.
3.6
The effort and resource applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure to the patient or environment. Collectively these arrangements fulfil the concept of **data governance**.

5.1
Systems and processes should be designed in a way that facilitates compliance with the **principles of data integrity.**

DIRA:
Data Integrity Risk Assessment

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018

4.1

Data has varying importance to quality, safety and efficacy decisions. **Data criticality** may be determined by considering how the data is used to influence the decisions made.

4.2

The risks to data are determined by the potential to be deleted, amended or excluded without authorization and the opportunity for detection of those activities and events. The risks to data may be increased by complex, inconsistent processes with open-ended and subjective outcomes, compared to simple tasks that are undertaken consistently, are well defined and have a clear objective.

4.4

Reduced effort and/or frequency of control measures may be justified for data that has a lesser impact to product, patient or the environment if those data are obtained from a process that does not provide the opportunity for amendment without high-level system access or specialist software/knowledge.

Creating a Data Integrity Plan
LIMIT THE SCOPE

Do the documents/records involve data used to:

- Make product safety decisions.
- Make product quality decisions.
- Prove compliance with a:
  - Particular regulation;
  - Statute;
  - Guidance document;
  - Commitment made to a Customer (CoA) or
  - Commitment your firm made to a regulatory authority (or our customer using CoA data).

5.1

Systems and processes should be designed in a way that facilitates compliance with the **principles of data integrity.**

Creating a Data Integrity Plan

Data Integrity Risk Assessment (DIRA)

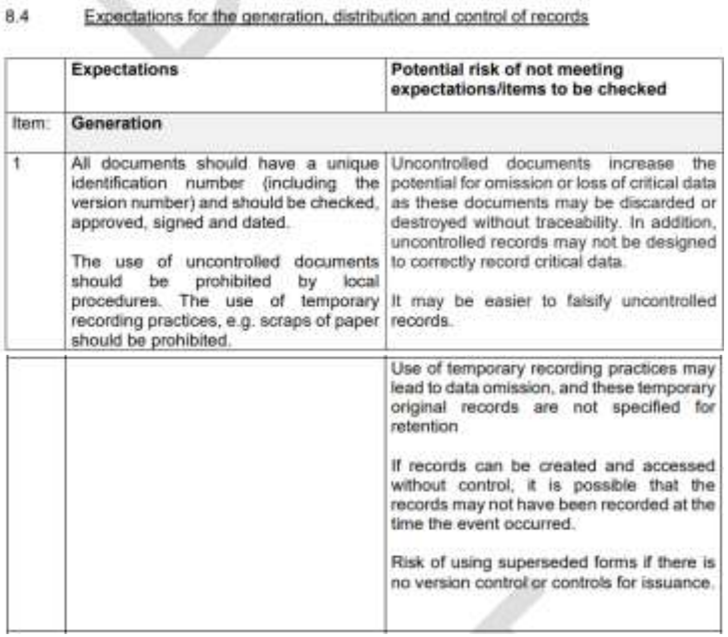
Answer the basic question –

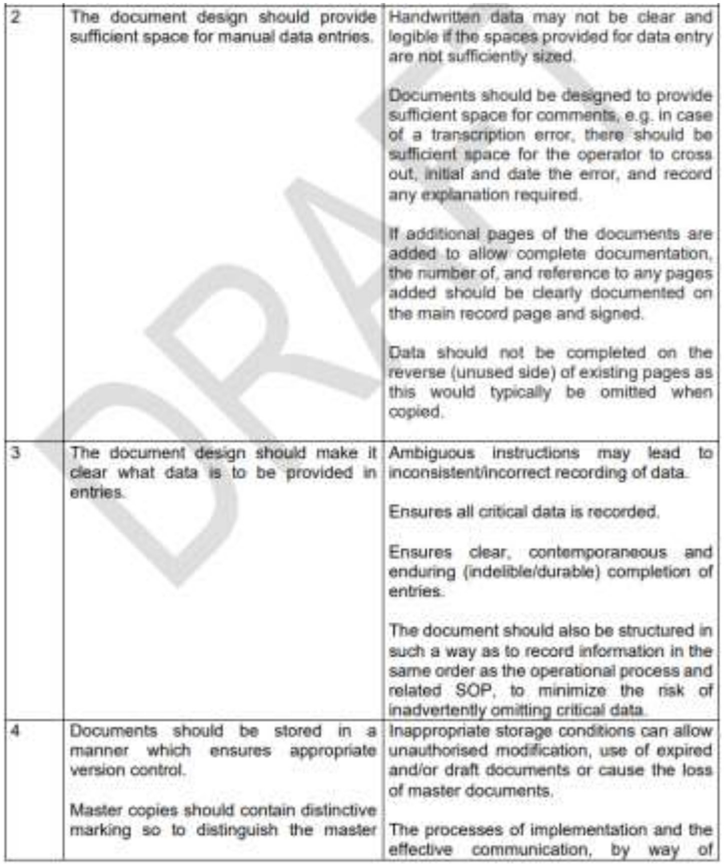
IF our data (the paper record or in a digital system) loses integrity, will…..

- Patients/consumers likely be injured?
- Product Quality be jeopardized?
- We be in noncompliance with any cGXP?
- Our risk of product liability litigation increase?
- We have to deal with significant extra costs and headaches to clean-up?

Internal Audit

Look at the PIC/S document starting on page 14 @ section 8.4





8.4 Expectations for the generation, distribution and control of records

	Expectations	Potential risk of not meeting expectations/items to be checked
Item:	**Generation**	
1	All documents should have a unique identification number (including the version number) and should be checked, approved, signed and dated. The use of uncontrolled documents should be prohibited by local procedures. The use of temporary recording practices, e.g. scraps of paper should be prohibited.	Uncontrolled documents increase the potential for omission or loss of critical data as these documents may be discarded or destroyed without traceability. In addition, uncontrolled records may not be designed to correctly record critical data. It may be easier to falsify uncontrolled records.
		Use of temporary recording practices may lead to data omission, and these temporary original records are not specified for retention If records can be created and accessed without control, it is possible that the records may not have been recorded at the time the event occurred. Risk of using superseded forms if there is no version control or controls for issuance.
2	The document design should provide sufficient space for manual data entries.	Handwritten data may not be clear and legible if the spaces provided for data entry are not sufficiently sized. Documents should be designed to provide sufficient space for comments, e.g. in case of a transcription error, there should be sufficient space for the operator to cross out, initial and date the error, and record any explanation required. If additional pages of the documents are added to allow complete documentation, the number of, and reference to any pages added should be clearly documented on the main record page and signed. Data should not be completed on the reverse (unused side) of existing pages as this would typically be omitted when copied.
3	The document design should make it clear what data is to be provided in entries.	Ambiguous instructions may lead to inconsistent/incorrect recording of data. Ensures all critical data is recorded. Ensures clear, contemporaneous and enduring (indelible/durable) completion of entries. The document should also be structured in such a way as to record information in the same order as the operational process and related SOP, to minimize the risk of inadvertently omitting critical data.
4	Documents should be stored in a manner which ensures appropriate version control. Master copies should contain distinctive marking so to distinguish the master	Inappropriate storage conditions can allow unauthorised modification, use of expired and/or draft documents or cause the loss of master documents. The processes of implementation and the effective communication, by way of

What to do when Data Integrity Failures are discovered

- Assess the impact on decisions made with the data or from data where this data was used to calculate data
- Take appropriate action
- Document the basis of the action, what was done, and the outcome

Questions and Answers