

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 drugs/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.

Application of Data Integrity Principles to Excipients

Specific data integrity requirements for excipients have not been described in regulatory documents or guidance. Only recently have references to a definition for and concepts of data integrity been explicitly included in excipient GMP Standards and Guides [6-8]; however, the basic principles (often referred to as “ALCOA¹ or ALCOA+”) have always been inherent in the GMPs.

For example, the following requirements (which include ALCOA+ principles) can be found in the “Control of Records”, “Laboratory Controls”, “Production Instructions and Records” and “Computer Systems” sections of excipient GMP Standards and Guides [6-8]:

Table 1 – Comparison of ALCOA+ Principles

ALCOA+ principles	Requirement	IPEC-PQG [8]	EXCiPACT™ [7]	NSF/IPEC/ANSI-363 [6]
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	8.2.4.1	8.6	9.1.4.1

¹ Attributable, Legible, Contemporaneous, Original, Accurate (ALCOA)

ALCOA+ principles	Requirement	IPEC-PQG [8]	EXCiPACT™ [7]	NSF/IPEC/ANSI-363 [6]
	each test including printouts such as graphs.			
Accurate	Retention of accurate, suitable and regular back-up or archival systems such as copies of the programme 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
+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	8.2.4.1	8.6	9.1.4.1

ALCOA+ principles	Requirement	IPEC-PQG [8]	EXCiPACT™ [7]	NSF/IPEC/ANSI-363 [6]
	data is authentic, complete and accurate; that it can be traced to its source and that it is readily available			
* ISO 9001 is a prerequisite to the EXCiPACT™ GMP/GDP Certification				

IPEC Federation Position

Although data integrity is clearly relevant to excipient manufacturing and distribution, excipient suppliers may implement different data integrity controls than DP manufacturers. Data integrity should be applied to excipient manufacturing processes, distribution or other activities where the loss of data integrity 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

Recommendations

For Excipient Suppliers:

Excipient suppliers should establish a data integrity approach based on identified risks to relevant critical data. Effort and resources applied to assure the integrity of the data should be commensurate with the 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.

For Excipient Users:

Users should manage expectations appropriately when auditing excipient suppliers and realize that requirements from regulatory guidance [1-5, 9,10] may be addressed differently. Users should evaluate the excipient supplier's controls for critical data to determine if data integrity concepts have been addressed.

For IPEC:

Data Integrity principles are already incorporated into most IPEC guides. As these guides are revised, IPEC will update them to ensure the content is consistent with these explicitly data integrity principles.

References (if applicable):

1. FDA: Data Integrity and Compliance with CGMP Guidance for Industry, December 2018.
<https://www.fda.gov/media/119267/download>
2. EMA: Data integrity: key to public health protection, August 2016.
<https://www.ema.europa.eu/en/news/data-integrity-key-public-health-protection>
3. MHRA: GxP Data Integrity Definitions and Guidance for Industry, July 2016.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf
4. PIC/S: Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, August 2016.
<https://picscheme.org/layout/document.php?id=1566>
5. WHO: TRS 996, Annex 05, Guidance on good data and record management practices, 2016.
https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
6. NSF/IPEC/ANSI 363 – 2019 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients.
<https://webstore.ansi.org/Standards/NSF/NSFIPECANSI3632019>
7. EXCiPACT™ Certification Standards for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices, Good Distribution Practices, 2017.
https://www.excipact.org/files/EXCiPACT/Downloads/20180123%20EXC%20Standard_Final-webversion.pdf
8. The International Pharmaceutical Excipient Council & The Pharmaceutical Quality Group, The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2017.
<https://ipeccamericas.org/reference-center/document-depot>
9. U.S. FDA Code of Federal Regulation, Title 21 Part 11 (21 CFR 11) Electronic Records; Electronic Signatures;
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1>
10. U.S. FDA Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application.
<https://www.fda.gov/media/75414/download>