PDA
Parenteral Drug Association

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1946
70TH ANNIVERSARY
2016

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June 17, 2016

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Draft Guidance for Industry: Data Integrity and Compliance with CGMP; Docket: FDA-2016-D-1113

Dear Sir/Madam:

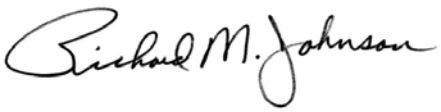
PDA is pleased to provide comments to this docket and appreciates FDA's efforts to clarify their current expectations around Data Integrity with the questions and answers in this guidance document. Detailed comments are attached and a few general issues are highlighted below.

With regards to the current draft we conclude data integrity concerns go well beyond quality control laboratories because data and metadata are generated in all departments. PDA recommends the scope of this guidance be enlarged to represent the spectrum of issues seen in warning letters and has made some specific suggestions in the attached comments. PDA also recommends FDA add a question and answer explaining the concept of data lifecycle for additional clarity and has provided a suggestion.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical and biological manufacturing including members representing our Data Integrity Task Force, Regulatory Affairs and Quality Advisory Board, and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President and CEO, Parenteral Drug Association

Cc: Richard Levy, PDA; Denyse Baker, PDA

Food and Drug Administration Draft Guidance
Data Integrity and Compliance with CGMP
June 14, 2016

General Comments

General Comments	Rationale	Critical Comment? Y/N
PDA recommends this guidance include data integrity examples more representative of the spectrum of issues seen in warning letters e.g. (1) Failure to record activities at the time they are performed. *Your employees did not complete batch production and control records immediately after activities were performed. When QA reviewers noticed missing entries in the batch records, they made a list of all the missing items on separate, uncontrolled pieces of paper that were provided to the production manager. Data were later entered into CGMP documents after operations had already ended as though they had been entered at the time of the operation.* (2) Your firm failed to ensure that all quality-related activities are recorded at the time they are performed. *For example, an "unofficial" notebook found in the engineering office stated, "Pseudomonas present in water system" on November 26, 2014 and "water system (Activity) investigation" on November 25, 2014. Your firm was unable to provide the investigators with any documentation regarding Pseudomonas sp. found in your water system and the related investigation.*	Data and metadata is generated at all departments, and data integrity goes well beyond quality control laboratories, hence it will be beneficial for all departments to have a representative example quoted as reference.	**Yes**
The guidance does not discuss the concept of data lifecycle nor provide a definition.	PDA recommends FDA adds a question on What is data lifecycle? With the following answer: All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, review, data retention,	Yes

General Comments	Rationale	Critical Comment? Y/N
	archive/retrieval and destruction.	

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Q1 Line 98	For purposes of this guidance, *audit trail* means… "who, what, when, and why"…	"who, what, and when ~~and why~~"	Please add reference to indicate this definition comes from Part 11. Existing technology does not always allow information on why the change was made to be captured in the system itself. All metadata will not be located within the audit trail.	Yes
Q1 Line 100	For example, the audit trail for a high performance liquid chromatography (HPLC) run **could** include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any, including change justification for the reprocessing.	For example, the audit trail for a high performance liquid chromatography (HPLC) run ~~could~~ **should** include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any, including change justification for the reprocessing.	Wording changed to be consistent with line 98 which requires "who, what, when and why". The inclusion of the metadata in the audit trail should not be optional.	Yes
Q2 Lines 147-149	Any data created as part of a CGMP record must be evaluated by the	Any data created as part of a CGMP record must be evaluated ~~by the~~	There should be some flexibility to allow a firm's Quality System to 1)	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180).	~~quality unit as part of release criteria (see §§ 211.22 and 212.70)~~ and maintained for CGMP purposes (e.g., § 211.180).	define which GMP data should be evaluated by the quality unit and 2) define which GMP data needs to be reviewed as part of release criteria.	
Q3 Lines 157-159	Does **each workflow** on our computer system need to be validated? **Yes,** a workflow, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation (see §§ 211.63, 211.68(b), and 211.110(a)).	Does each workflow on ~~our~~ **a** computer system need to be validated? "Yes, **for systems used for GMP purpose in the manufacturing, testing, release, storage, distribution of materials, or in creation of data for validation, regulatory submissions, or surveillance/monitoring,** the intended use of the system should be checked through validation (see §§ 211.63, 211.68(b), and 211.110(a)).	The combination of "each workflow" and "yes" is misleading Only systems used for GMP purpose in the manufacturing, testing, release, storage, distribution of materials, or in creation of data for regulatory, validation, studies or surveillance need to be validated. Use of the term "our" is not appropriate for a general guidance.	Yes
Q4 Lines 178-181	You must exercise appropriate controls to assure that changes to computerized MPCRs, or other records, or input of laboratory data into computerized records,	You must exercise appropriate controls to assure that changes to computerized ~~MPCRs~~, or other records, or input of ~~laboratory~~ data into computerized records,	The text as written gives the appearance of leaving out a broad section of GMP data such as PM/Cal data, and inventory records, and seems to be focused	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	can be made only by authorized personnel (§ 211.68(b)). FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible	can be made only by authorized personnel (§ 211.68(b)). FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible. **Examples include MPCRs, laboratory data, EBRs, inventory records, PM or calibration data.**	narrowly on batch related data. PDA recommends inclusion of other examples to ensure clarity on scope of data included.	
Q4 Lines 185-187	FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.	~~FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.~~ FDA recommends maintaining and **reviewing the list** of authorized individuals and their access privileges for each CGMP computer system in use **including the ability to track changes to access. This review frequency should reflect the risk of the access privileges (e.g., more frequently for privileged or administrative access).**	The original text could be interpreted to mean that a list must be maintained manually. Access changes should be tracked. The list should be maintained and reviewed.	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Q7 Lines 226-230	FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.	~~FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.~~ **FDA recommends applying audit trails or other physical, logical, or procedural security measures based on predicate rule requirements and on criticality of the data. The criticality of the data should be determined based on the potential of the data to effect product quality and safety and record integrity and the extent and types of security measures should be based on a justified and documented risk assessment. Audit trails that capture changes to critical data should be reviewed with each record and before final approval of the record.**	The proposed text aligns with the risk-based approach documented in the 2003 FDA Scope and Application guidance, which provides criteria for identifying which data is critical and reinforces that the predicate rules should be relied upon to define the scope of records that must be audit trailed.	Yes
Q7 Lines 232-233	FDA recommends routine scheduled audit trail review based on the complexity of the system	**FDA recommends routine** ~~scheduled audit trail review based on the complexity of the system~~	The proposed change is intended to clarify when routine audit trail review should occur in addition to	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	and its intended use.	~~and its intended use.~~ **monitoring of audit trails, where frequency is based on the intended use and potential of the data to effect product quality, safety and data integrity.**	the audit trail review of each critical record prior to approval and to remove "complexity of the system" as a consideration for audit trail review.	
Q7 Line 226	Current Text: FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.	Proposed Change: Please add a definition of the term "critical data" Proposed definition below. Critical Data – all authentic and original data and metadata needed to represent a given action or decision, which fulfill the requirements to satisfy policies, procedures, applicable laws and regulations.	Rationale: It is important to align the understanding of the term "critical data" in the guidance.	Yes
Q9 Line 254	True copies of dynamic electronic records may be made and maintained in the format……	True **electronic** copies of dynamic electronic records may be made and maintained in the format……	Clarification that the true copies of dynamic electronic records cannot be paper copies. It is recommended that this document (question 1.a.) includes a definition for "true copy". There isn't global alignment on understanding of this term. 21 CFR	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			211.180 mentions only "photocopies, microfilm, microfiche, or other accurate reproductions". This definition does not seem adequate in the context of modern systems anymore. **True Copy:** An exact verified copy of an original record. Data may be static (e.g. a 'fixed' record such as paper or pdf) or dynamic (e.g. an electronic record which the user / reviewer can interact with).	
Q12 Line 305	When does electronic data become a CGMP record? When generated to satisfy a CGMP requirement, all data become a CGMP record.	~~When generated to satisfy a CGMP requirement, all data become a CGMP record.~~ **Electronic data generated to satisfy or support a CGMP requirement becomes a CGMP record at the time of its creation. This is what is meant by "contemporaneous recording of data".**	Adds a clear concise answer to the question Note: Paper copies of electronic data or analyses should not be considered original records and not subject to the same retention policies.	Yes
Q12 Lines 316-319	Similarly, it is not acceptable to store data electronically in temporary memory, in a manner	Similarly, it is not acceptable to store data ~~electronically in temporary memory,~~ in a manner	This requirement might be misleading. It uses terminology from computer science, like	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	that allows for manipulation, before creating a permanent record. Electronic data that are automatically saved into temporary memory do not meet CGMP documentation or retention requirements.	that allows for manipulation, before creating a permanent record. Electronic data that are automatically saved into temporary memory do not meet CGMP documentation or retention requirements. **The implementation of input checks (e.g., drop-down lists, restricted numeric ranges, or date ranges) which generally improve the quality of the data are allowed.**	"temporary memory" which might be translated by somebody into RAM and HDD... But the intention of the requirement is about modification of data. So this requirement asks for personalized user accounts for all systems that allow data modification after acquisition. The additional text at the end of the statement provides clarification that input checks routinely implemented in manufacturing execution systems (MES) are allowed even though values in this case may be saved in temporary memory in order to perform the check before permanently saving the record. The original text may lead to the interpretation that input checks are a way to manipulate data.	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Q15 Lines 381-383	FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. "CGMP data integrity" should be included in the subject line of the email.	FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. "CGMP data integrity" should be included in the subject line of the email. This reporting method designed for individuals is not intended to supersede Field Alert Reports (FAR) or Biological Product Deviation Reports (eBPDR).	For clarity, it should be noted that this invitation for reporting of suspected DI issues by individuals is not intended to replace the formal methods used by firms (FAR and eBPDR).	
Q16 Lines 391-394	**16. Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?** Yes. Training personnel to detect data integrity issues is consistent with the personnel requirements ….	**16. Should personnel be trained in preventing and detecting data integrity issues as part of a routine CGMP training program?** Yes. Training personnel to prevent and detect data integrity issues is consistent with the personnel requirements ….	Individuals should be trained on both, preventing and detecting data integrity issues. It is important to be capable of detecting issues, but it is just as important to be able to prevent them, and not rely on every issue to be detected.	Yes
Q18 Line 406	FDA encourages you to demonstrate that you have effectively remedied your problems by: hiring a third party auditor, determining the scope of	FDA encourages you to demonstrate that you have effectively remedied ~~your problems by: hiring a third party auditor, determining the scope of~~	The current proposed wording is overly prescriptive and may not be appropriate for all variations of data integrity issues. Data Integrity issues may require	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	the problem…. implementing a corrective action plan (globally), and removing at all levels individuals responsible for problems from CGMP positions.	~~the problem…. implementing a corrective action plan (globally), and removing at all levels individuals responsible for problems from CGMP positions~~ **the data integrity issue by determining the root cause, assessing impact to patient safety and product quality and implementing appropriate corrective and preventative actions.**	different approaches to address the root cause. For example, placing more control over operations may not address the mindset or behavioral issues. The need to hire a third party auditor should be determined by the firm on a case by case basis.	