June 14, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Attention: Docket Number: FDA-2016-D-1113

Subject: FDA DRAFT GUIDANCE: Data Integrity and Compliance with CGMP Guidance for Industry

Dear Sir or Madam:

ISPE (International Society for Pharmaceutical Engineering) would like to submit comments for the FDA DRAFT GUIDANCE: Data Integrity and Compliance with CGMP Guidance for Industry.

The draft guidance provides additional clarity on many of the data integrity issues that have been the subject of FDA and other Health Authority regulatory actions. The draft guidance also references several regulations, including 21 CFR Part 211, “Current Good Manufacturing Practice for Finished Pharmaceuticals.” The draft guidance provides application for current technology that did not exist at the time these regulations were promulgated.

Further, the draft guidance references 21 CFR Part 11, “Electronic Records; Electronic Signatures” (Part 11), which provides legal sanctity to electronic records and signatures. Part 11 also issues requirements to preserve the content and meaning of records. It puts many of these requirements into perspective and encouraged risk-based approaches. FDA issued the *Part 11 Scope and Applications Guidance* to enable enforcement discretion in key areas and to promote innovation (rather than stifle it). We believe that these important risk based principles should remain in effect and be complemented by the current FDA draft guidance on data integrity.

The eventual implementation of this data integrity guidance, when finalized, should help FDA prioritize the revision of Part 11 (as well as any resulting, related guidance that is now pending FDA’s reexamination of Part 11). This is a vital consideration, given the continued emphasis on promoting emerging technologies while ensuring availability of legacy products and preventing drug shortages.

ISPE appreciates the opportunity to submit these comments for your consideration.

Sincerely,

Dora Kourti, PhD
Senior Vice President for Global Regulatory Affairs, ISPE

FDA draft Guidance for Industry - Data Integrity and Compliance with CGMP, Docket No. FDA-2016-D-1113

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf

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	GENERAL COMMENTS ON THE DOCUMENT
	Overall, the document provides additional clarity on many issues that surround data integrity.
	While there are many citations to 21CFR Part211, clearly many are interpretive considering the technology in existence today that did not exist at the time that the CGMP regulations were prepared. 21CFR Part 11 was written to provide legal sanctity to electronic records. Within that, were requirements meant to preserve the content and meaning of records, ALCOA principles, and other expectations for electronic records. Many were put into perspective by the 2003 Scope and Applications Guidance. Those important risk based principles should remain in effect in this current guidance when finalized. Also, updating of the Part 11 regulation is long overdue. Part 11 and the guidance **need to capture important risk based principles**.
	The draft guidance should clarify how metadata related to advanced monitoring is expected to be maintained and archived. Of particular concern is the **voluminous data that can result from advanced analytical monitoring** such as spectroscopy and/or multivariate statistical process control. Expectations to retain all metadata in an unreduced form can have unintended consequence of discouraging implementation of advanced manufacturing approaches.
	A glossary should be added to include definitions for: raw data, data, and true copies (not an all-inclusive list).

	GENERAL COMMENTS ON THE DOCUMENT
Page 7, Lines 278 - 280	The paragraph regarding control strategies for paper and electronic records requires further clarification (with examples if possible) in relation to the requirements for second person review of original paper and electronic records. The term "control strategy" has a specific definition for the manufacturing process in ICH Q10. May be another term could be used here. For example, earlier in Question #10 the case of pH meters and balances that may create a paper print out or static image is noted. Specifically, for a balance without a printer, how should the second person review be implemented? Similar direct digital display of results occurs with pH meters and Karl Fischer titrators, not equipped with printers or controlled with data systems where the original test result is obtained by direct read out from the instrument display. In these cases, is a second person, real time, observation of the displayed result required, followed by documented written verification of the result in the notebook of other hard copy record? Additionally, the agency need clarify its requirements for "control strategies" related to second person review of electronic records in more modern instrument systems then the examples provided above. For example, for original electronic records in the form of chromatographic results, would it be possible for the agency to describe an acceptable sequence of events which includes the second person review. Does the second person review need to be performed by Quality Assurance as part of the batch review and release process, in whole or in part, or would it be acceptable for this review to be performed and documented in the QC Laboratory? <u>Suggested new sentence</u>: Documentation must ensure that original laboratory records, including paper and 279 electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain 280 that all test results are appropriately reported. That review can be performed as part of the record review performed to release the batch. A firm can utilize the logic expressed in 211.68 (d) whereby automated systems allowing for one person to perform the operation/test in conjunction with a validated system.
Scope	The scope of applicability of the draft guidance is explicitly limited to data required for CGMP (i.e. CFR Title 21, parts 210, 211 and 212). The principles set out in the guidance appear to be equally applicable to data required for all of the Good Practice requirements set out in Title 21 (e.g. Good Laboratory Practice, Good Clinical Practice, Quality System for Medical Devices etc.). Should this guidance be considered as applicable for the data required by other parts of Title 21 (as for example, the requirements set out is 21 CFR Part 11 are)?
Terminology	Another concept that we would have liked to be discussed was to include <u>all</u> of the terms that are generally associated with ALCOA +, but it appears that within the definition of data integrity there is no inclusion of the term 'enduring.'

	GENERAL COMMENTS ON THE DOCUMENT
Terminology	CFR Title 21, Part 11 and subsequent Guidance to Industry 'Electronic Records, Electronic Signatures Scope and Application' establish a helpful definition of an Electronic Record. In Part 11 and the Scope and Application Guidance an Electronic Record is differentiated from other data in a computerized system by the Narrow Interpretation statement – i.e. electronic data is an Electronic Record only when it is used in lieu of a paper GxP record. Using the more general term 'Data' in this guidance creates a likelihood of confusion and the possible wide interpretation (i.e. the application of this guidance to all data in a computerized system, not just the Electronic Records used in Lieu of GxP Paper Records). In order to ensure that regulated companies' focus is on GxP impacting data, specific and differentiated terminology could be employed, for example 'Record' and 'electronic Record'.
Question 6	Please specify whether this section applies only to paper, and if not, please be more specific about how it would apply to electronic forms.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Line Number	Current Text	Proposed Change	Rationale or Comment
36		Suggest including drug substances in the guidance. Reference to ICH Q7 and/or the FDCA 501(a)(2)(B) would help to clarify that data integrity problems impact drug product AND drug substance.	The scope of the guidance document only covers finished products. Yet, many of the data integrity breaches of note have involved manufacturers of drug substances/Active Pharmaceutical Ingredients.
42		End of sentence line 42: While not in the scope of this guidance, data integrity related CGMP violations can also have an effect or be directly linked to application filing. (See FDA AIP Webpage)	Comments: Add sentence relating to effect on application filing
98	An audit trail is a chronology of the "who, what, when, and why" of a record. For example, the audit trail for a high performance liquid	This definition of the use of the audit trail differs from 21 CFR Part 11 in that Part 11 focuses on the creation, alteration and deletion of electronic records rather than	This could lead to system upgrades / technology changes that are not necessary. There is nothing wrong with the general expectation but it may be better to state a record of parameters

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	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.	the recording of parameters that are just being used. Many systems do not provide this feature. The intent of the current text is sensible but the recording of such information should be part of the lab record rather than the "audit trail" which is synonymous with Part 11.	used and who executed the run rather than specifically referring to an audit trail.
104	Electronic audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).	This is not aligned with Part 11 and Annex 11, and existing FDA (including the Part 11 Scope and Application Guidance) and other regulatory (e.g. MHRA), and ISPE GAMP guidance and current industry good practice.	It may be true in some cases, especially for small simple systems, but is impractical for large IT systems, and is usually and much more effectively achieved through other mechanisms and logs. We believe that maintaining a distinction between the primary data audit trail and other system transaction logging and other technical or procedural mechanisms is useful and good practice. This view and interpretation is supported by the statement later in the Guidance that states "Audit trails are considered part of the associated records" which points towards a data audit trail orientation, and also the analogy used later that audit trail review is similar to the expectation that "cross-outs on paper" be assessed when reviewing data. If these various other types of information were to be regarded as a required part of the GxP audit trail, then all these logs etc. would be subject to the Part 11 requirement that "Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.". This may be possible (although impractical) for some small lab instruments, but impractical and undesirable

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			for IT system of any importance (including ERP, MES, EBRS, LIMS, etc.). This would create a very expensive and almost unachievable expectation that technical records of events like attempts to access the system must be retained for a period as long as the GxP record on the system with the longest retention period. We believe there should be a clear distinction between data audit trails as required and clearly described by Part 11 (and guidance) and Annex 11 (and MHRA guidance), and various technical system logs, transaction logs, etc. which have a different purpose and use.
105	…. and those that track actions at the record or system level ….	Again as defined in Part 11, system level access is not necessarily recording in the audit trail	It may be better to state that recording of system access is beneficial to providing information about system use
111	….can fulfill these CGMP requirements.	….can **support** these CGMP requirements.	Technology controls alone cannot ensure data integrity.
126-135	FDA uses the term backup in § 211.68(b) to refer to a true copy of the original data that is maintained securely throughout the records retention period (for example, § 211.180). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format. This should not be confused with backup copies that may be created during normal computer use and temporarily maintained for disaster	Clarify that use of the term backup in § 211.68(b) to refer to a true copy of the original data that is maintained securely throughout the records retention period is non-standard, and that the terms archive or retained record or record retention are most often used by regulators and industry. Clarify the distinction between backup and archive.	We suggest maintaining the standard and useful distinction between backup and archive process, as reflected in current industry usage and good practice An archive is a copy of the original record for the purpose of long-term retention and retrieval. Records are often deleted from the system following verification of the archive. A backup is a copy of data (and/or software) that may be used to restore the original in the event the latter is lost or damaged. A backup solution is intended to satisfy short-term needs for operational recovery and not intended to meet long-term retention requirements.

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	recovery (e.g., in case of a computer crash or other interruption). Such temporary backup copies would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.		It is acknowledged that under some specific and unusual circumstances backups may also act as archival records. If established correctly the routine backup will include an up to date and true copy of electronic records, and thus the ability to reconstruct the records. Redefining the term backup as requiring backup files to be maintained throughout the records retention period and satisfy long-term retention requirements contradicts industry standards and normal good practice. Determining specific strategies for backup and archive processes should be the responsibility of the regulated company.
127			Please clarify what is meant by the term "securely" particularly as it pertains to data integrity. Is it related to a system administrator's role in maintaining control over who can change data? Does it mean that we should have redundant storage of all data or does it mean we should keep an offline copy? And how often should we synchronize in the latter case?
172	FDA recommends you implement appropriate controls to manage risks associated with each element of the system. Controls that are appropriately designed to validate a system for its intended use address software, hardware, personnel, and documentation.	Would suggest adding the clarification that: "all workflows supporting CGMP operations are validated."	For example, in an ERP system we may not validate financial workflows in the same way as product manufacturing workflows.
180 - 185	FDA recommends that you restrict the ability to alter specifications,	Would suggest adding further clarification regarding the way in which alterations are	Now while this seems like a logical and practical method, there could be a number of issues with

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	process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data). FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content. To assist in controlling access, FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.	requested should be provided: • The need for a documented request to change data should be requisite, as a record for authentication by the requestor, or a driver for authorized personnel to confirm/reject the request.	the wording: • The 'system administrator' individual could be misled by the data owner/operator into making a change/modification to the data: o This may occur accidently i.e. identifying the incorrect batch affected o This may be intentional i.e. to 'hide' the use of equipment which is out of calibration • It should also be noted that the 'system administrator' may not know the context of the data or the change being requested i.e. the specific equipment code, and may make a modification which is not understood within/by the system.
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 reviewing the list of authorized individuals and their access privileges for each CGMP computer system in use at a frequency that reflects 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.
224			Comment: Need to define requirements for electronic raw data review, data review, and audit trail review
226		Please add a definition of the term critical data.	Comment: It is important to align understanding of the term critical data.
226-230	FDA recommends that audit trails that capture changes to critical data	~~FDA recommends that audit trails that capture changes to critical data be~~	The proposed text aligns with the risk-based approach documented in the 2003 FDA Scope

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	be reviewed with each record and before final approval of the record.	~~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.**	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. For reference (from Part 11 preamble): The agency considers such operator actions as activating a manufacturing sequence or turning off an alarm to warrant the same audit trail coverage as operator data entries in order to document a thorough history of events and those responsible for such events. Although FDA acknowledges that not every operator ''action,'' such as switching among screen displays, need be covered by audit trails, the agency is concerned that revising the rule to cover only ''critical'' operations would result in excluding much information and actions that are necessary to document events thoroughly. For reference (from FDA 2003 Scope and Application Guidance): The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

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			Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and reliability of the records. We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation. **Excerpt from Draft guidance:** FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record. Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters. FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.

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232	FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.	Would suggest including some form of wording to indicate that the rationale be also based upon “value”.	It would be useful to expand the audit trail review schedule include some consideration that such an activity has in terms of adding value to the overall organisation / quality and the appropriate use of resources rather than just been seen as a drain on such resources.
232-233	FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.	**Additionally, FDA recommends routine** ~~scheduled audit trail review based on the complexity of the system 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 and safety and record integrity.**	The proposed change is intended to clarify when routine audit trail review should occur in addition to 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.
233		Add " The periodic review should look for non-data changes; such as changes to the configuration of the system, changes to security (users, user types etc.) to promote access levels, such as giving analyst administrator rights; review of failed logins"	Comment: Need more content about why a periodic review is needed and where it should be inserted in the guidance.
316-319	Similarly, it is not acceptable to store data electronically in temporary memory, in a manner 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.	Similarly, it is not acceptable to store data electronically in temporary memory, in a manner 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.**	Many manufacturing execution systems (MES) are designed with input checks to reduce manual entry of invalid records. In these cases, data is not permanently saved until it "passes the input check" (e.g., weights are pre-checked and if a value is not within a certain range, the operator can choose not to permanently save that entry...these entries are not audit trailed as they are saved in temporary memory until permanently saved). These input checks are intended to improve data integrity by filtering out invalid values. This provides clarification that input checks routinely implemented in manufacturing

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			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. For reference (from Part 11 preamble): The agency intends that the audit trail capture operator actions e.g., a command to open a valve) at the time they occur, and operator information (e.g., data entry) at the time the information is saved to the recording media (such as disk or tape), in much the same manner as such actions and information are memorialized on paper. The audit trail need not capture every keystroke and mistake that is held in a temporary buffer before those commitments. For example, where an operator records the lot number of an ingredient by typing the lot number, followed by the 'return key'' (where pressing the return key would cause the information to be saved to a disk file), the audit trail need not record every ''backspace delete'' key the operator may have previously pressed to correct a typing error. Subsequent ''saved'' corrections made after such a commitment, however, must be part of the audit trail.
361			Comment: Please clarify what is meant by reprocessing data. It is somewhat clear that this doesn't refer to retesting- is this "reintegration"?
379		Add sentence: It does not matter if the data integrity issue was due to malfeasance or	Comment: Add sentence to clarify the need to include tips regarding guidance issues.

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		poor training. Regardless of intent all data integrity issues should be handled appropriately within the context of CGMP.	
381			Comments: Encouragement here should be for individuals to avail themselves of company's internal speak up lines conduct codes to alert management so issue can be promptly addressed in addition to inviting FDA notification. In addition FDA invites should be changed to FDA recommends individuals have the opportunity to …. This helps to clarify that notification to FDA is not required and that FDA intends to protect the identity of the individual.
407	….hiring a third party auditor ...	….appointing an independent auditor (without interest or involvement in the operations or quality assurance of the data concerned) …	The enforcement of using third party auditors is already creating a bubble in the consulting market, leading to inrush on inexperienced players and some unhelpful practices such as exaggeration of requirements. Many organizations have sufficient breadth to be able to appointment and internal audit team that is both qualified and impartial.
408		Delete last phrase or change to consideration of personnel actions appropriate to remedy situation and prevent recurrence.	Comment: This is too unilateral and can preclude if done too soon getting information, investigations or could be directed against wrong individuals.
410		This is important to determine the root cause, investigate objectively any possible malfeasance or serve as a strong step to achieve sustainable voluntary compliance.	Comment: Add sentence justifying why third party may be needed.