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28 Feb. 2019

Mr. Jeffrey Hodgson
Pharmaceutical Inspection Co-operation Scheme
14 Rue du Roveray
CH-1207 Geneva
Switzerland

Reference: Draft PIC/S Guidance on Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (PI 041-1 (Draft 3))

Dear Mr. Hodgson:

PDA appreciates the opportunity to comment on the revised Draft PIC/S Guidance on Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (PI 041-1). PDA's responses to the questions posed by PIC/S are detailed in the attached PIC/S comment form.

We note that the attached comments are submitted by PDA as an organization. PDA also is collecting comments on behalf of PIC/S, which we will forward to you separately.

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 have been prepared by a committee of experts in regulatory affairs and data integrity including members of the Regulatory Affairs and Quality Advisory Board.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,

Richard Johnson
President and CEO

cc: Tina Morris, PDA; Ruth Miller, PDA

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PS/INF 38/2018
30 November 2018

PIC/S CONSULTATION

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS

Editor: PIC/S Secretariat

web site: http://www.picscheme.org

1. Introduction:

A PIC/S working group was established in 2015 to develop guidance for inspectorates on the topic of data management and integrity. The Data Integrity Working Group (DI-WG) includes participants from over 15 PIC/S Participating Authorities, and the remit of the group is to develop harmonised guidance for inspectorates with regard to the expectations for Data Management and Integrity for GMP and GDP regulated entities.

A draft of the PIC/S guidance Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (PI 041-1) developed by the DI-WG was published by PIC/S on a trial basis in August 2016. The guidance document was designed to facilitate a harmonised approach to data integrity elements of routine GMP inspection. Following the receipt of feedback from PIC/S Participating Authorities in February 2017, a revised document was published on 30 November 2018.

Due to widespread interest from industry following the August 2016 publication of the PIC/S draft guidance, the PIC/S Committee has agreed to engage with stakeholders with an external consultation on the updated draft guidance (version 3). This revised draft will be available for PIC/S Participating Authorities to continue to use on a further trial basis while the external consultation is held in parallel.

2. Scope and duration of the consultation:

The consultation seeks stakeholder feedback on the following questions relating to the proportionality, clarity and implementation of the guidance requirements. Any comments regarding harmonisation difficulties with other regulatory guidance are also welcomed.

Stakeholders are requested to use the structured question format to facilitate collation and assessment of responses. Where ‘yes’ or ‘no’ responses are provided, please elaborate as necessary to explain.

The draft guideline (version 3) is downloadable on the PIC/S website and has been formatted with prescribed line and page numbers.

To submit feedback, please provide feedback **exclusively on this dedicated template** which is available on the websites of the below associations and submit by e-mail with subject line "PIC/S Focused Public Consultation – Data Management and Integrity" to one of the following associations which will collect and compile responses. Stakeholders should **only reply once**.

• ECA (European Compliance Academy) Foundation:	heimes@gmp-compliance.org
• IFPMA (International Federation of Pharmaceutical Manufacturers & Associations):	s.adam@ifpma.org
• ISPE (International Society for Pharmaceutical Engineering):	regulatorycomments@ispe.org
• PDA (Parenteral Drug Association):	tmorris@pda.org

The consultation period will last 3 months and run from **30 November 2018** to **28 February 2019**

3. Reviewer (name, position, full contact details):

Richard Johnson, President and CEO, Parenteral Drug Association. 4350 East West Highway, Suite 600, Bethesda MD 20814, USA. +1 (301) 656-5900. johnson@pda.org.

4. Questions for stakeholders:

PI 041-1 section	PI 041-1 paragraph	Question	Stakeholder response
All		**Q1.** Are any sections of the guidance document unclear as to the expectations for what should be achieved?	We recommend that PIC/S clarify to investigators that large parts of this guidance are intended to provide context but do not reflect regulatory obligations. We are concerned that the document may not adequately differentiate between best practices and legally binding requirements. Without further clarification, the document might cause confusion among investigators and/or inadvertently lead investigators to request documents outside the scope of their authority. For example, much of sections 5 and 6 reflect sound practices that enhance data integrity but are not required by law or regulation in the United States and other countries.

All		**Q2**. Are there any sections of the guidance that introduce unreasonable or onerous expectations?	Although the expectations set in the guidance are largely reasonable, many of the sections, including 5, 6, 9 and 10, contain expectations that are not required by law in many jurisdictions, including the United States. As noted, we recommend adding discussion to avoid confusion about the requirements. As a specific response to Q2, we note that regulators generally allow destruction of original records where certified true copies of data are maintained. The proposed change to section 8 would add a new requirement to maintain these records. This change is more strict than regulatory requirements.
All		**Q3**. Is the document format sufficiently generic to clearly apply to the range of GMP and GDP operations subject to inspection?	Yes
All		**Q4.** Is any further (specific) guidance required?	We are not certain that it is always clear what PIC/S is recommending to the inspector. We suggest that the guidance could be strengthened by including specific information on inspectional and audit techniques and ways for investigators to evaluate/measure "compliance." PIC/S could include discussion of what an inspector is to look for in practice, and communicate the need for an inspector to relate citations or recommendations to the governing legal and regulatory requirements. For example, one generally accepted worldwide requirement is for deviations to be opened and resolved in accordance with GMP principles. PDA believes that it would be helpful for this document to provide guidance to inspectors on how to evaluate deviations and CAPAs in the data integrity context. Additionally, many investigators could use practical guidance on how to evaluate audit trails. The discussion of data governance in section 5.2.3 also could benefit from such specific advice. In a future revision, PIC/S might also consider providing examples of data integrity or data governance issues, describing how they link to explicit legal or regulatory requirements, and discussing the severity that may lead to an inspector's citation consistent with law and regulation.
All		**Q5.** Are there any sections of the guidance that appear contradictory?	We have some concerns about the descriptions of hybrid systems, as further discussed in response to Q31.
Sections 3 and 4		**Q6.** Is the purpose and scope of the document clear?	PIC/S might consider revising section 3.1.3 to clarify whether the intent is to integrate good data management into the inspection process (for regulators) or to provide tools to inspectors to harmonize inspections with regard to the evaluation of good data management practices. Otherwise, PIC/S may wish to review the document with an eye to assuring that it achieves the purposes described in section 3, as described in our response to Q4 above.
Section 5		**Q7.** Does the description of the 'data governance system' provide sufficient background to the requirements for achieving an enabling environment?	PIC/S may wish to define "data management" to distinguish this term from "data governance," if such distinction is intended, and ensure that the terms are used according to those definitions. For instance, consider whether, in section 5.3.1, the second sentence should refer to the "contract acceptor's data governance policies" rather than data management. In section 5.1.1, we recommend that you define or clarify the term "record" to express any distinction from data. In that same section, PIC/S might wish to consider revising this sentence for clarity: "These arrangements ensure that data….. will ensure a attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available record throughout the data lifecycle." To clarify section 5.3.2, we suggest that PIC/S further consider how an inspector might evaluate a company's allocation of effort and resources to data governance while balancing "other quality resource demands." How does PIC/S recommend a company make this evaluation? Is a documented rationale adequate?
Section 5		**Q8.** Are the principles of data lifecycle, data criticality and data risk clearly described?	In general, yes. However, it may be beneficial to describe when a risk assessment should be performed, to help inspectors understand what to look for. In section 5.5.3, we suggest PIC/S consider whether this sentence is appropriate in the list of risk assessment factors to consider: "The outcome of a comparison between electronic system data and manually recorded events could be indicative for malpractices…."
Section 5		**Q9.** Is it clear as to how these can be applied in practice?	Yes
Section 5		**Q10.** Is the difference between 'data governance system review' and 'data review' clearly explained?	We believe that the guidance would benefit from additional discussion of the distinction. In addition, PIC/S might consider expanding the discussion in section 5.6, Data governance system review, to discuss other methods of review including management review, trending of investigations, utilization of established reporting mechanisms; to provide more examples to guide inspectors; and to clarify the legal requirements. Also in section 5.6.2, PIC/S may wish to revise this bullet point for clarity of meaning and expectation: "In situations where routine computerised system data is reviewed by a validated 'exception report', a risk-based sample of computerised system logs / audit trails to ensure that information of relevance to GMP activity is reported accurately." PIC/S also might consider adding discussion of the potential benefits of an independent evaluation, independent compliance function, or third party audit in some circumstances. While a routine internal audit program may be able to address some of the items listed, it may not be able to provide an independent perspective.
Section 5		**Q11.** Is the guidance relating to the use of quality risk management in data management and integrity sufficiently clear?	We find this text to be slightly ambiguous, and believe that the inclusion of examples would help provide clarity.
Section 6		**Q12.** Does the description of organisational influences help to explain the impact of management behaviour on data integrity control measures?	Subject to our responses to Q1 and Q4 above, we suggest that section 6.3.3 could mention, as an additional example, periodically auditing for data integrity issues and assessing the site's quality culture. We also urge PIC/S to further consider the inspector's role regarding evaluation of attributes of quality. Certain factors can be assessed and evaluated to reflect the current status and trends in the organization's quality culture, as well as corrections and improvements. But what is the role of the external inspector? The discussion in 6.1.1 and 6.1.2 begins to get at the complexity of the inspector's role.

Section 6		**Q13.** Are there any concepts that are not clearly described?	This section includes mention of performance indicators/quality metrics as addressed above, but examples would be helpful, especially for soft attributes like culture.
Section 6		**Q14.** Does the guidance for dealing with data integrity issues (sections 6.7 and 12) adequately outline the expectations for and management of the risk of data integrity issues?	Subject to our responses to Q1 and Q4, we recommend adding more detail on the use of root cause analysis, identification and prevention of repeat issues, CAPA effectiveness checks, and the use of metrics. We also note that data integrity investigations, although handled within the PQS, may have attributes that require specific actions, such as human resources, sensitivity to discovery of executive level breaches, etc.
Section 6	6.6.3	**Q15**. Is the importance of appropriately configured modern equipment/software used for management of GMP / GDP data clearly described?	Yes, but we suggest that PIC/S consider whether additional language would be helpful in describing the selection of modern equipment with advanced features.
Section 6	6.6.4	**Q16.** Is the need for sufficient numbers of personnel to permit appropriate segregation of duties described in a manner relevant to large and small organisations?	PIC/S might consider rephrasing the first sentence of section 6.6.4 to be clear that companies may train a target group of employees whose activities are related, rather than strictly segregating training.
Section 7		**Q17.** Is the explanation of general principles, including ALCOA+ requirements, clear?	Yes, but comprehension may be better if PIC/S were to add examples for each activity.
Section 7		**Q18.** Can these principles be understood in the context of different GMP activities (e.g. quality system, production QC, warehousing, etc.) and data formats (paper or digital)?	Yes
Section 8		**Q19.** Are the expectations for control of paper-based records clear?	We suggest some ways to clarify the expectations. In section 8.1, you may wish to note that duplicate records may be issued in case of damage. Footnote 7 in section 8.6 discusses the exceptional circumstances in which activities can be recorded by a second person on behalf of another. You might consider clarifying that this generally should not be allowed in critical activities (CPP and CQA). In section 8.8, we suggest that you consider including elements regarding the review of analytical documents. In section 8.9, you might consider including discussion of hybrid system controls. PIC/S might consider whether some of the text of section 8.10 is appropriately located. Specifically, some of the content of section 8.10 relates to computerized systems data, but section 8 overall relates only to “Paper-based systems.” Likewise, PIC/S may wish to consider moving the following text to section 9: “In the case of printouts which are not permanent (e.g. thermal transfer paper) a verified (‘true’) copy should be retained, along with the non-permanent original.” This text (which is in the table following section 8.12.2, in item #2), relates to computer-based systems, not paper-based.
Section 8		**Q20.** Do the requirements place an unreasonable burden on industry?	No, subject to our response to Q2.
Section 8		**Q21.** Do the concepts of ‘true copy’, ‘static data’ and ‘dynamic data’ create technical difficulty in retaining data throughout the required retention period?	PIC/S might consider defining "raw data" and further discussing the situations in which paper storage of electronically-created raw data may be appropriate. It is our understanding that raw data from electronic devices such as computers cannot be maintained in paper format. In the discussion in the table following 8.10.5, PIC/S may wish to consider whether storage in PDF format might be appropriate when chromatographic software creates PDF versions that include all images, raw data, and metadata in a protected file.
Section 8	8.6.1	**Q22.** Are expectations clear in regard to recording sequential manufacturing steps at the time of operation?	PIC/S might consider whether the manufacturing steps are more clearly defined in section 8.8 than in section 8.6.1.
Section 8	8.10.2	**Q23.** Is the description of metadata clear?	Metadata is defined in the definitions section, but PIC/S might consider expanding this discussion to add clarity. We believe this to be an area that is frequently misunderstood within industry. In section 8.10 (or in section 9), PIC/S may also want to elaborate on such topics as when is it not necessary to save electronic raw data, and how to handle data that were generated on old versions of software and therefore are no longer readable.
Section 8	8.10.2	**Q24.** Would examples be helpful to aid understanding?	Yes, definitely.
Section 9		**Q25.** Are the expectations for control of electronic systems clear?	We suggest a few items that PIC/S could consider clarifying: •In section 9.2.2, it could be argued that validation of a computerized system does include ensuring apppropriate administrative and physical controls. As worded now, it appears that these items are "in addition" to validation. Many companies have addressed these items post-validation but that is generally because they were missed during the initial validation •In section 9.2.2, we are uncertain whether the “Data Transfer between Systems” table is intended to apply to dynamic data storage/data backup or to data transfer between two systems for further downstream operation/analysis. If it is meant to apply to data storage/backup, we suggest adding discussion in the appropriate sections •In the table in section 9.5, item #2 states that "manual integrations and reprocessing of laboratory results must be performed in an approved and controlled manner.” PIC/S might consider including discussion of exceptions for complex sample analysis for manual integration. •In addressing system administrators for small organizations, PIC/S may want to suggest, based on the increased risk when production personnel have system admin rights, that permissible duties should be documented ahead of time and that audit trail review is specific and perhaps enhanced in this scenario. The same could apply in any scenario in which the system admin is also responsible for GXP data.
Section 9		**Q26.** Do the requirements place an unreasonable burden on industry?	No comment

Section 9		**Q27.** Is any difficulty foreseen in applying data integrity principles for computerised systems to a range of in-use electronic systems in different GMP activities (quality system, production QC, warehousing)? - For example: Are requirements for audit trails clearly described, including their purpose and role in data verification? - Is the difference between GMP audit trails and other audit trails sufficiently explained?	We believe that the distinctions between audit trail types (e.g., GMP vs other, system vs. server vs. injection level) could be more clear.
Section 9		**Q28.** Is the concept of the 'business process' clear with respect to computerised systems, and computer system validation?	Yes
Section 9		**Q29.** Are there technical difficulties in retaining electronic data throughout the required retention period?	Yes, technical difficulties often occur if an electronic record must maintain its dynamic nature, particularly when the record is created using a licensed platform. Companies may find it necessary to export and store such data in a static file format. While the text in 8.10.3 specifies that risk management principles can be applied to decisions about storage in a dynamic format, it would be helpful to include this information in section 9 (electronic records) as well, to ensure understanding by inspectors and regulated entities alike.
Section 9		**Q30.** If 'yes', do the technical challenges differ between legacy equipment and modern equipment?	Yes, as noted above.
Section 9		**Q31.** Are expectations for hybrid systems clear regarding what should be achieved in practice?	We believe that this could be made more clear. For instance, hybrid systems include simple systems that are not connected to computers (e.g., balance and pH meter) so their qualification, date and time restrictions, and duplicate print restrictions should be discussed. In addition, we suggest clarifying and expanding the definition of "hybrid system." We understand that computerized systems are not considered as hybrid systems, and standalone systems are different from hybrid systems. The definition of "hybrid system" might be overly broad and inadvertently incorporate some standalone systems.
Section 9	9.2.2, table item 1 (system validation and maintenance)	**Q32.** Are the expectations for legacy computerized systems clear in terms of need for gap analysis, risk assessment and remediation plans to address good data management and integrity practices?	Yes
Section 10		**Q33.** Are there any items in this section that appear ambiguous or unclear?	PIC/S might consider providing practical examples of what an inspector should look when gauging organizational behavior.
Section 10		**Q34.** Are there any practical restrictions/considerations relating to the review of data from contract providers that have been overlooked?	In general, PDA is concerned that this section may assume a level of transparency between purchaser and supplier that can be difficult to achieve in reality. For example, suppliers generally will not notify customers about data integrity risks or deviations. We recommend elaborating on this point and setting realistic expectations. In addition, we suggest that PIC/S clarify any distinctions between in-house vs supplier checking. Furthermore, as with the general discussion above, care should be given to distinguish best practices from regulatory requirements to avoid confusion. For example, the United States has no requirement for quality agreements, although they are strongly recommended by FDA, PDA, and others. Notwithstanding this fact, inspectors are begining to cite the lack of a quality agreement as a regulatory violation.
Section 12		**Q35.** Are there any elements of a data integrity remediation plan that require further explanation?	Please refer to our comments above in Q12 - Q14 regarding root cause and quality/performance metrics.
Section 12		**Q36.** Are the expectations for remediation sufficient?	As a potential best practice, we suggest that this discussion could highlight root cause analysis and discuss how the organization's remediation efforts might be measured for effectiveness. In addition, we suggest that PIC/S consider discussing who is evaluating the data. FDA Warning Letters have language relating to the use of a third party in this situation. At a minimum, the third party should be independent and qualified.
Section 12		**Q37.** Are any expectations onerous or unrealistic?	No, subject to our response to Q2.