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October 31, 2016

MHRA
151 Buckingham Palace Road,
London, SW1W 9SZ, UK
inspectorate@mhra.gsi.gov.uk

RE: MHRA GxP Data Integrity Definitions and Guidance for Industry
Draft Version for Consultation July 2016

Dear Sir/Madam:

PDA appreciates the opportunity to provide feedback on this draft and proposes that the document should be clearly stated as being applicable to all GxP operations, and as the replacement of any earlier MHRA document on data integrity, to avoid any confusion.

PDA also notes that in the current format for this draft, definitions are interspersed with guidance information. For clarity and to avoid redundant information in different parts of the document, PDA recommends amending the document to have separate sections for "definitions" and "guidance". PDA recommends the definitions themselves be pulled out into a glossary section that is moved to the end for convenient reference in the future. In addition the guidance gives no reference information for the other cited guidelines, such as GAMP5. A reference section would be helpful.

The comments indicated as "critical" in the attachment were determined by the task force to be the most important aspects of this document with potential to have a major impact on patient safety or product quality.

Finally, in its *Elements of a Code of Conduct for Data Integrity in the Pharmaceutical Industry*, PDA notes that every employee at each company is responsible for his/her own conduct to maintain a bond of trust between the company and its stakeholders, namely the patients, health care providers, and regulators (i.e., to prevent a broken bond due to data integrity issues). Employees have a duty to perform their GXP functions in an ethical manner that meets company requirements and industry standards as articulated in company requirements, and in accordance with all relevant laws, regulations or legislative directives of regulatory authorities. PDA recommends that this guide be written with the presumption of professionalism and innocence with allowance for the

various checks and audits to be done if there is evidence or suspicion that data may lack integrity.

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 with experience in pharmaceutical manufacturing and quality including members representing our Data Integrity Task Force, Regulatory and Quality Advisory Board and Board of Directors.

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

Sincerely,

Georg Roessling
Vice President, PDA Europe

CC: Richard Johnson, PDA; Denyse Baker, PDA

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Comment sheet for MHRA draft document:

MHRA GxP Data Integrity Definitions and Guidance for Industry

Deadline for comments: 31 October 2016

Send comments in Word format to: inspectorate@mhra.gsi.gov.uk

Comments from:

Name of organisation or individual
Parenteral Drug Association

Please be aware that information submitted may be made public under a Freedom of Information Act request. Please highlight any information considered commercially sensitive.

1. General comments:

Please include rationale / background to any general comments.

PDA notes that in the current format for this draft, definitions are interspersed with guidance information. For clarity and to avoid redundant information in different parts of the document, PDA recommends amending the document to have separate sections for "definitions" and "guidance". PDA recommends the definitions themselves be pulled out into a glossary section that is moved to the end for convenient reference in the future. In addition the guidance gives no reference information for the other cited guidelines, such as GAMP5. A reference section would be helpful.

PDA proposes that the document should be clearly stated as being applicable to all GxP operations, and as replacement of any earlier MHRA document on data integrity, to avoid any confusion.

In our recently published Elements of a Code of Conduct for Data Integrity in the Pharmaceutical Industry, PDA notes that every employee at each company is responsible for his/her own conduct to maintain a bond of trust between the company and its stakeholders, namely the patients, health care providers, and regulators (i.e., to prevent a broken bond due to data integrity issues). Employees have a duty to perform their GXP functions in an ethical manner that meets company requirements and industry standards as articulated in company requirements, and in accordance with all relevant laws, regulations or legislative directives of regulatory authorities. PDA recommends that this guide be written with the presumption of professionalism and innocence with allowance for the various checks and audits to be done if there is evidence or suspicion that data may lack integrity.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

2. Specific comments on text:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Comment and rationale**	**Proposed Change (if any)** *(If changes to the wording are suggested, please highlight using 'track changes')*	**Critical Comments**
31 - 32	All characteristics of data cited in the previous sentence refer to data integrity. Since the concept of data validity appears in this half-sentence only and is neither necessary nor part of the definition of Data Governance in lines 220ff in this document, it should be deleted, regulatory filing should be added as an impact area for clarity, and for the same reason "environment"should be replace by "product" (GxP, not environmental regulation).	Replace sentence with: The effort and resource applied to assure the ~~validity and~~ integrity of the data should be commensurate with the risk and impact of a data integrity failure to the patient, **regulatory filing** or ~~environment~~ **product**.	
35-37	Mentioning of forensic approach first gives wrong connotation. Important to emphasize the correct approach first.	Organisations are expected to implement design and operate a fully documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. Organisations are not expected to implement a forensic approach on a routine basis.	Y
43-44	Electronic data are describing the format of data while manual data are describing the mode of data creation. PDA recommends paper and electronic are the only definitions that should be used throughout the document for clarity.	… that data integrity requirements apply equally to ~~manual~~ paper and electronic data.	

56-57	Why only “impact to quality attributes”? It appears the the impact to patient safety been excluded here. In order to be applicable across GXP, there may be situations where product quality attributes are not yet defined but patient safety is always important.	The degree of effort and resource applied to the organisational and technical control of data lifecycle elements should be commensurate with its criticality in terms of **impact to patient safety** and product **critical** quality attributes.	
67-69	Differentiating between equipment and computerized system is enormous as many equipments may be highly computerized or supported by PLCs. Data itself cannot be configured. Only the system generating or providing data may be configurable.	The inherent risks to data integrity ~~relating to equipment and computerized systems~~ may differ **between different equipment and computerized systems and their relative complexity** depending upon the degree to which the system can be configured and the data generated therefore potentially manipulated.	Y
81	The figure is very generic and there may be systems in the middle section that might rely solely on printouts and still are in line with data integrity requirements. The system examples shown do not reflect the complexity of systems, e.g. the calculation of an FT-IR is more complex than the workflow software of a Trackwise CAPA system. Some examples are very detailed and some are very general (“spreadsheet” vs. ECG machines”).	Please remove the figure.	Y
84-89	This is a guidance document for data integrity, not for instrument qualification/validation. For example, calibration is not part of data integrity per se.	PDA recommends deleting this paragraph and replacing with: **Any computerized system generating GxP data must be validated for its intended purpose as part of a data governance program.**	Y
96-98	You may have multiple individuals with advanced skill sets in relation to a type of software but may not have the appropriate user role/access to make amendments. A risk based approach should be used.	Reduced effort and/or frequency of control measures may be justified for data that has a lesser impact to product and patient, if those data are obtained from a process that does not provide the opportunity for amendment without specialist software/knowledge **or access. Areas with data most critical to patient and product should be first evaluated for risk to integrity.**	
100 - 101	The original sentence infers that certain processes with a risk for inconsistency are used without appropriate risk reduction. Complex processes may lead to inconsistent practices.The proposed wording puts emphasis on the importance to mitigate such	Replace sentence with: Data risk **may be** ~~is typically~~ increased by complex ~~inconsistent~~ processes **which can have a higher risk of inconsistency unless appropriately mitigated**, with open ended and subjective outcomes compared to simple tasks that are **inherently** consistent, well defined and objective.	

	risk, in line with the overall intention of the document.		
107	The comparison of data risk with other quality and compliance priority seems to indicate that data risk can be low priority for a company to address.	Delete the line ~~Companies should balance data risk with other quality and compliance priorities.~~	
113	Data integrity is a subset of data quality. The current phrasing suggests these are different and independent things. Data quality is important but not discussed in this document.	Recommend changing heading to read: Designing systems to assure data ~~quality~~ integrity	
115	"Compliance" should not be "encouraged", but "ensured". Some of the following controls factually help "ensuring", not only "encouraging".	Systems should be designed in a way that ~~encourages~~ **ensures** compliance with the principles of data integrity	
119	To make it clear that separate and system based clocks are a potential source or inaccuracy and can be subject to manipulation.	Access to appropriately controlled / synchronised clocks for **manual or automatic** recording timed events	
120 - 121	The original sentence infers that the true original data set is not kept, whereas the issue at hand is the need of transcription and the possibility of error inherent in such transcription. PDA also recommends alignment with predicate GMP phrasing.	Replace sentence with: Accessibility of records at locations where activities take place so that ad hoc data recording **is enabled** and later transcription **from the raw data record** to official records is not necessary**.**	
124	The original wording may interpreted to say that an audit trail remediates the lack of authorization for data amendments, this should be avoided. Separate user access from audit trails.	Replace sentence with: User access rights that prevent ~~(or audit trail)~~ unauthorised data amendments **and audit trails that make all relevant changes traceable.**	
125	These seem to be only two examples for a much wider field of possibly attached devices. There are more possibilities such as card readers for user authentication or technical interfacing of system components to eliminate manual data entries where possible. Furthermore, it remains unclear what exactly is	**Use of external devices or system interfacing eliminating manual data entries and human interaction with the computerized system, such as bar code scanners, ID card readers, or printers.).**~~Automated data capture or printers attached to equipment such as balances~~	Y

	expected from such attached devices in terms of the requirement to ensure data integrity compliance through adequate system design. PDA suggests considering re-phrasing in a more general way and then providing specific examples of devices for illustration purposes.		
128	Ensuring access to raw data and audit trail is an additional measure to ensure data integrity and therefore more appropriate as a concluding paragraph.	Delete bullet in line 128, and add this statement as a concluding paragraph: **To mitigate previous risks, staff performing data checking activities should have ready access to all raw data and to the audit trail.**	
167	Recommending clarifying reference to definition of GCP in the body of the section.	Add to the text: **Raw data is synonymous with "source data" which is defined in ICH GCPs.**	
173-174, 176-178	The statements in these lines are contradictory. Lines 173-174 state "paper copies of raw data generated electronically cannot be considered as 'raw data'." Lines 176-178 state "In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes the raw data."	Suggest revising the statements to clarify.e g.: state "**In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes the raw data. If there is no printed data output, the contemporaneous manual recording of the datum constitutes the raw datum.**	
216	The definition integrity should be consistent with other sections and refer to ALCOA or ALCOA – plus rather than relisting characteristics differently.	Data integrity arrangements must ensure that the **ALCOA requirements are met**. ~~ensure that the accuracy, completeness, content and meaning of data is retained throughout the data lifecycle.~~	
220-248	This section on "data governance" covers aspects that are also part of a pharmaceutical quality system according to ICH Q10. e.g. continuous improvement, lifecycle management. These are not new rules but existing concepts	The sum total of arrangements to ensure …and accurate record throughout the data lifecycle. **These aspects are normally covered by a well developed pharmaceutical quality system according to ICH Q10.**	
247 - 248	The wording "directly accessible" seems redundant and should be deleted. Archived data can never be "directly accessible."	Replace sentence with: Data governance systems should also ensure that data are readily available ~~and directly accessible~~ on request from national competent authorities	
Line 311-340,	PDA recommends staying with the term True Copy throughout the document. Recommend deleting the	Make changes as per comment from Line 311 to line 340 also lines	

354,533,362	term “verified copy” and “certified copy” throughout.	354,533, 362.	
320-321	The analogy is old fashioned: currently photographs are no longer prints on photo paper, but electronic data which are dynamic.	A better example would be an Excel file (dynamic) including the calculations and a pdf copy (static) which has only the values.	
331 - 332	The text should not exclude the possibility to reconvert data from a static to a dynamic format with recovery of dynamic interaction options, allowing storage and archiving of the static format, where preferable.	Replace sentence with: Once printed or converted to static file format (e.g. .pdfs), chromatography records lose the interaction capability. **If static data can be reconverted to a dynamic format with recovery of dynamic interaction options, storage and archiving in such a static format is acceptable.**	Y
338 - 340	To be consistent with lines 331 – 332, the reversal between different format types should be included.	Replace sentence with: A true copy may be retained in a different electronic file format to the original record, if required, but must retain the equivalent static/dynamic nature of the original record, or it must allow reconversion to a format that gives the same dynamic interaction options as the original format.	Y
349 - 351	Align wording with previous sentence to avoid misunderstandings and have consistent use of terminology.	Replace sentence with: ~~Accurate and complete~~ **True** copies ~~for certification~~ should include the meaning of the data (e.g. date formats, context, layout, electronic signature and authorisations), as well as the full audit trail.	
354 - 356	Align wording with previous paragraphs to avoid misunderstandings.	Replace sentence with: Where **true** ~~certified~~ copies are made, the process for **making true copies** ~~certification~~ should be described, including the process for ensuring that the copy is complete and accurate and for identifying the **copying** ~~certifying~~ party and their authority for making that copy.	
362 - 365	Align wording with previous paragraphs to avoid misunderstandings.	Replace sentence with: However, the data retention process must be shown to include ~~verified~~ copies of all raw data, metadata, relevant audit trail and result files, any variable software/system configuration settings specific to each record, and all data processing runs (including methods and audit trails) necessary for reconstruction of a given raw data set **as part of the true copy.**	
421-423	The sentence indicates that the validation of legacy spreadsheets is not necessary. PDA recommends excluding the term “spreadsheets”. Spreadsheets	Where relevant audit trail functionality does not exist (e.g. within legacy systems ~~and spreadsheets~~) an equivalent level of control may be achieved for example by the use of log books, protecting	

	can be of various complexity. Simple spreadsheets, e.g. short lists or spreadsheets used only once that are printed out completely and with formula, if applicable, do not require an audit trail.	each version and change control.	
435-437	The language in lines 435-437 suggests that legacy systems should be replaced as soon as fully audit trailed systems become available. This is not always a viable option. Systems and processes using this type of data sources require lead time to be developed, validated and in many cases are filed with and approved by Health Authorities.	Suggest changing "as soon as fully audit trailed systems become available" to "**as soon as practical."**	Y
439 and 492-498	The amount of upgrades needed to be implemented and approved by health authorities by end of 2017 does not seem feasible, therefore PDA recommends allowance for risk-based evaluation on which upgrades are most necessary and which can be postponed.	… it is expected that GMP facilities should **evaluate a possible** upgrade to an audit trailed system by the end of 2017	Y
454	Some e-signature systems do not provide for "signature manifestations" such that the reader can immediately know that someone has signed, who it was, their title, and the date. One must 'click through' to see the underlying person. (Reference to Annex 11)	For clarity: Add, "**E-signature systems must provide for "signature manifestations" such that the reader can immediately know that someone has signed, who it was, their title, and the date (and time, if significant)**."	
532	Consistent with comments to line 311.	Proposed Text: to ensure that ~~the copy is certified~~ **that the outcome is a true copy**.	
539	The term "reconstruction" could be misunderstood as a requirement for recalculation. PDA recommends the term "Verification" for clarity.	*…purposes of ~~reconstruction~~* ***verification*** *of the process or activity.*	
550-551	PDA believes it may be misleading to equate virtual environments with cloud computing or SaaS. A VM does not necessarily have to be in a cloud but can also exist on a server within the premises of the company.	This may be achieved by maintaining software in a virtual environment (e.g. **Virtual Machine**, Cloud or SaaS).	

559-560	A shorter definition seems to be clearer. The added wording in brackets does not change the definition and could create confusion. The definition should be applicable to more than analytical operations.	Backup “A copy of current ~~(editable)~~ data, metadata and system configuration settings~~(variable settings which relate to an analytical run)~~ maintained for the purpose of disaster recovery.”	

Please add more rows if needed.