Data Management / Data Integrity Guidance

FDA, EMA, MHRA, WHO, PIC/S, China FDA

Major regulatory authorities published guidance addressing data management and data integrity in 2015 and 2016. A *previous entry* addressed two of these, the draft from FDA published in April 2016 and the guidance from EMA posted in August 2016. Here we continue with the guidance from MHRA (effective version *HERE* and new draft revision *HERE*), *PIC/S*, *WHO* and the recently published Drug Data Management Standard from the *China FDA*. The English translation herein of the document from China was graciously provided by the China Working Group of Rx-360. *Rx-360* is a not for profit consortium led by volunteers from the Pharmaceutical and Biotech industry including both manufacturers and suppliers.

Simply due to the comparable length of the documents, the comparison will first address the MHRA guidance (effective and draft revision). Separately we will look at the WHO and PIC/S guidance. And finally, we will evaluate how the China FDA guidance compares to this group.

EXECUTIVE SUMMARY:

The similarity among the MHRA, WHO, and PIC/S guidance is obvious and was facilitated by participation of many of the same teams, if not the same people, in their development. Similarly, the EMA and FDA Q&A's do not stand in isolation, and represent communication between and among the regulatory authorities. The draft document from China, the most recent to be published, reflects features found in the others. While the formal scope in several of the documents is identified to be GMP/GDP or GMP alone, the concepts are applicable to all GXP areas. Some highpoints from all the global regulatory agency documents:

- The FDA and EMA Q&A Guidances, and the PIC/S guidance provide detailed information on the **existing rules, Chapters / Annexes, and guidance** that govern data integrity. Thus, the focus on data integrity and data management does not represent new requirements, but rather an application of existing requirements.
- If ever there was a lingering thought that a printed chromatogram represents raw data, all authorities are clear that **raw data** are data in the format in which it was originally collected. So, for those firms who have laboratory equipment with associated computers and software, and who maintain they are a paper-based organization, that's just not correct. All the laboratory computer systems moved your firm into the world of electronic records. Recognizing this sooner rather than later, and implementing the necessary remediation, will save the grief and cost of having a regulatory authority point this out.
- It is important to consider the status of data governance and data integrity of **suppliers and contract manufacture / laboratory sites**. All guidance, excepting the one from FDA, explain responsibilities and expectations for these types of arrangements.
- All agencies focus on the expectation for a **risk based approach over the data lifecycle**, concepts that are fundamental to ICH Q guidance. In addition, the data governance activities are to be part of the firm's **Quality System**.
- Guidance from all agencies includes both **paper records and electronic records** within their scope.
- Regarding electronic signatures, the guidances which address this state that use of a **stored digital image of a person's handwritten signature** is not acceptable.

MHRA DATA INTEGRITY DEFINITIONS and GUIDANCE FOR INDUSTRY:

The effective version of the MHRA guidance published in March 2015, and a draft revision was published for consultation in July 2016. At a high level, the most significant difference between the two is that the proposed revision applies to GXP systems whereas the original applied to GMP. It makes logical sense to extend the scope of the guidance beyond GMP particularly considering data integrity problems in the GCP[i] areas in the past several years.

Along with the broadened scope, the revised draft is formatted differently and includes a few additional terms with definition and explanation, and in other cases terms have been reorganized or the definition and examples have been expanded. In one notable instance a term is no longer included in the revised draft. The important changes are identified below:

DELETED TERMS
PRIMARY RECORD is a term found in the existing guidance, but is not included in the revised guidance. This may have been eliminated to resolve confusion about what constitutes a primary record and the perhaps incorrect decision by some that original data records that were not designated as the primary record could be discarded.
NEW TERMS
DATA TRANSFER / MIGRATION is new to the draft revision.
ELECTRONIC SIGNATURE has been added to the revised draft with a definition, and identification of the governing Directive. The text here is important and states: '*An inserted image of a signature alone or a footnote indicating that the document has been electronically signed (where this has been entered by a means other than the validated electronic signature process) is not sufficient*.' It also states that '*Where a paper or pdf copy of an electronically signed document is produced the metadata associated with an electronic signature should be maintained together with the associated document.'*
CLOUD PROVIDERS and VIRTUAL SERVICE PLATFORMS section is new to the draft revision and reflects many of the common practices in the GXP area to move toward data storage in 'the Cloud.'
REVISIONS or ENHANCEMENTS
ORIGINAL RECORDS / TRUE COPY are treated as separate sections (11.1 and 11.2 respectively in the draft revision) in the revision though expectations do not seem markedly different. Both documents state that a process must be in place to ensure that the copy is verified to be complete. The revision adds the statement that the verified true copy '*maybe verified by dated signature or by a validated electronic signature.*'
DATA PROCESSING is expanded to its' own section (8) in the draft revision.
DATA LIFECYCLE definition and example in the effective version mentions that at least 2 years of data '*must be retrievable in a timely manner for the purposes of regulatory inspection.'* The draft revision is silent the specific time bounded data which must be available for inspection.
COMPUTER SYSTEM TRANSACTION addresses the concept of 'temporary memory' and that the time which data spends in this temporary memory should be minimize because data in this status are not subject to visibility in an audit train is they are changed or deleted. The page of examples in the effective guidance is not present in the draft revision.
DATA REVIEW section has been expanded in the revised draft to include data exchanged between companies. Before accepting summary report from the contract acceptor in lieu of exchange of original data or a true copy, the contract giver should perform an evaluation of '*the contract acceptors compliance with data integrity principles'*. When the contract acceptor

does not perform a data review these responsibilities must be '*documented and agreed' by the parties.*
COMPUTERIZED SYSTEM USER ACCESS / SYSTEM ADMINISTRATOR ROLES is expanded to state that '*Controls should be applied at both the operating system and application levels.'* Further, now that the draft revision includes GCP processes, an example is provided about the locking of clinical trial data at a specific point in the management process.
AUDIT TRAIL in the draft revision has been modified to remove the term *'full audit trail'* in describing all changes to the data. The draft revision has been refined to state that '*It is not necessary for audit trail review to include every system activity.'*
DATA RETENTION is modified in the draft revision so that the mention of contracted data and document retention to a 3rd party is eliminated.
ARCHIVE is modified in the revised draft to address what actions should be taken when legacy systems ae no longer supported.
BACKUP must be periodically tested as a new requirement in the revised draft.

We might expect to see a final version publish in early 2017 based on a 3-month consultation period for the draft revision.

Remember, the existing guidance includes **two requirements that are expected to be met by the end of 2017**:

- In the absence of an audit trailed computer system, a paper based audit trail maybe implemented if they '*achieve equivalence to integrated audit trail[s]…*'. If equivalence cannot be demonstrated, firms must '*upgrade to an audit trailed system by the end of 2017.'* The WHO guidance takes a bit more stringent approach and state that '*The use of hybrid systems is discouraged, but where legacy systems are awaiting replacement, mitigating controls should be in place.'*
- Regarding the lack of unique logins, '*It is expected that GMP facilities should upgrade to systems with individual login and audit rails by the end of 2017*.'

WHO and PIC/S Guidance

These two guidance documents provide more granularity and examples than either the FDA or EMA Q&A guidance or the guidance from China provided later in this article. Both documents are forty-plus pages long but are worth reading for the wealth of detail. The content and requirements are similar though the organization is different. Both PIC/S and WHO reflect the ALCOA-plus attributes for data requiring that it be: Attributable, Legible, Contemporaneous, Original, Accurate as well as Complete, Consistent, Enduring, and Available.

PIC/S draft guidance titled '*Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments'* is dated August 10, 2016. A previous blog entry provided a look at this guidance. It is intended to be used by inspectors in *'interpretation of GMP/GDP requirements in relation to data integrity and the conduct of inspections.*' It is not available for public consultation, instead feedback will be provided by the inspectors using the guidance. Consistent with FDA and EMA, PIC/S states that the guidance does not impose additional requirements but rather provides guidance on the interpretation of existing PIC/S requirements. Thus, predicate rules and existing requirements provide the framework for ensuring integrity of

data. It is written for GMP/GDP but the principles are applicable to GXP systems, and it would not be surprising to see the scope expanded in the future.

Th PIC/S Guidance is divided into fourteen sections, many of which have subsections. The eight sections that address specific topics include:

- Section 5: Data Governance System
- Section 6: Organizational influences on successful data integrity management
- Section 7: General Data Integrity principles and enablers
- Section 8: Specific data integrity considerations for Paper based systems
- Section 9: Specific Data Integrity Considerations for Computerized systems
- Section 10: Data Integrity Considerations for Outsourced Activities
- Section 11: Regulatory actions in response to data integrity findings
- Section 12: Remediation of data integrity failures

The WHO guidance, '*Guidance on Good Data and Record Management Practices'*, published in 2016, applies to GXP systems. A previous *blog entry* addressed changes between the draft and final versions of the document. This guidance progressed through public consultation prior to being finalized. This includes a single appendix titled '*Expectations and examples of special risk management considerations for the implementation of ALCOA (-plus) principles in paper-based and electronic systems'.* Appendix 1 is similar to the tabulated presentations in the effective MHRA guidance where expectations for paper records and electronic records are provided in detail.

The general sections of the WHO guidance are divided as follows:

- Section 5: Quality Risk Management to ensure good data management
- Section 6: Management governance and quality audits
- Section 7: Contracted organizations, suppliers and service providers
- Section 8: Training in Good Data and record Management
- Section 9: Good Documentation Practices
- Section 10: Designing and validating systems to assure data quality and reliability
- Section 11: Managing data and records throughout the data life cycle
- Section 12: Addressing Data Reliability Issues

CHINA FDA DRUG DATA MANAGEMENT STANDARD:

In October, 2016 the China FDA published a Draft Standard on Drug Data Management for consultation. This translation was graciously provided by the Rx-360 China Working Group. The standard seems to have relied on the previously published regulatory authority guidance in this area. Like the MHRA draft revision, this draft Standard applies across the GXP continuum and specifically includes mention of contract research organizations (CRO). Further, this standard applies during drug development.

The Standard is governed by the principles of Quality Risk Management and incorporation of the activities into the Quality Management System. The following table identifies selected, but by no means all, similarities with other regulatory authority guidance on this topic and new items not clearly addressed by other regulatory authorities.

SELECTED UNIQUE EXPECTATIONS or TERMS
Article 12 states that "Advanced techniques are encouraged to be adopted to control risks in data integrity…" It is not clear what constitutes 'advanced techniques'.
Article 15 makes specific mention that management should ensure that '*employees' work relating to data integrity is not affected by the pressure or motivation from commercial, political, financial and other organizations.'*
ALCOA is defined as a *'common acronym for 'trueness, accuracy, promptness and traceability".* The intent seems similar with other regulatory agency guidance, though the terms are different.
Definitions seem to be slightly different than in other regulatory agency guidance, the most obvious difference is 'filing' vs 'archive'; 'senior manager' vs senior management'. Again, while the intent seems similar with other regulatory agency guidance, the terms are different.
SELECTED ITEMS COMMON TO OTHER REGULALATORY AUTHORITY GUIDANCE
The standard states that industry should employ appropriate risk management for ensuring data integrity thru the data lifecycle and should be incorporated into the Quality System.
Self inspections should evaluate data integrity implementation and results should be reviewed by top managerial staff.
Data Integrity shortcomings should be investigated thru the deviation procedures and findings that impact patient safety and product quality should be reported to the 'drug administration' department.
Requirements and expectations regarding data integrity should be incorporated into the quality agreement with defined actions for each of the parties. The 'entrusting party' has final responsibility for data integrity and decisions made based on these data.
Data must be attributable to a single person, and computer system accounts shall not be shared.
Alternative to audit trails within computer systems are permissible if they can ensure that traceability of the data cannot be altered.
This Standard addresses the issue of 'Primary Records' as defined in the effective MHRA guidance. The draft revision no longer uses or defines this term, perhaps due to the confusion and misinterpretation it may cause.
Review of electronic data cannot be substituted by review of a printed paper record. Review of the electronic data should include review of appropriate meta-data.
True copies of both paper records and electronic records should be verified to ensure that the true copy '*…has all the contents and meanings of the original record*.'
Processes shall be put in place to *'prevent and/or help to discover the intentional or unintentional alteration, deletion, loss, deficit, replacement transcription or other nonconforming treatment of data.'* This is reminiscent of 21 CFR 11.10(a) regarding the ability to discern invalid or altered records.
Article 47 appears to represent a description of segments of computer system validation.
Article 49 that addresses 'system replacement' appears to be similar to data migration in other guidance where the accuracy of the migration is ensured as are the data in the system after migration

In conclusion, individuals who want to learn about the expectations for data management and data integrity would be well served to read the guidance documents published by all the regulatory authorities. The guidances from PIC/S and WHO provide more granularity than the others. Taken together, the collection of guidance documents are substantially harmonized with each other, likely based on the overlap of individuals and teams who contributed to their development. These guidance documents should be considered along with publicly available

enforcement actions taken by FDA, EMA and WHO in the areas of data management and data integrity. Taken together, they provide a sound basis for any firm that wants to evaluate their compliance status in this area.

[i] Including but not limited to: WHO Notice of Concern to Quest Life Sciences Private Limited issued in 2015 and Notice of Concern issued to *Svisera Labs Private Limited*.

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For assistance in GMP auditing or evaluation of data governance and data integrity concerns, please contact me at bwunger123@gmail.com or 805.217.9360