Confused by Data Integrity Guidance ?

(Data Integrity Guidance: "Pick and Mix" !)

Paul Smith

Agilent Technologies

paul_smith@agilent.com

Agenda

- **Background / Introduction**
- **Data Integrity Guidance Documents:**
  - **FDA**
  - **MHRA**
  - **WHO**
  - **PIC/S**
- ***Additional Information (Appendix)***

(Including GAMP DI Guidance)….

External Hyperlink ☜

More Detailed Analysis……..

High Level Comparison…..

Key:

FDA	**Food and Drug Administration** ☜
MHRA	**Medicine and Healthcare Products Regulatory Agency** ☜
WHO	**World Health Organization** ☜
PIC/S	**Pharmaceutical Inspection Co-operation Schema** ☜

It's Only Paper! – A Dark Industry Background

Paper is a commodity, purchased by procurement…..

[and they change suppliers – different quality / aging properties……]

- Paper = Commodity
- Quality Varies
- It Ages…… Differently
- Historically……
- Store Paper – *to Re-Print*…...

Visible / known…… ***(4 % of DI Problems Known to Senior Mgt.)***

More not visible / unknown…..

DATA INTEGRITY - BACKGROUND

Where is the Quotation From ?

'GXP' Data Integrity Guidance and Definitions

Title: MHRA 2018 Data Integrity Final Guidance ☜

"When is it permissible to invalidate a cGMP result and exclude it from the determination of batch conformance ?"

Q 2 - FDA Dec. 2018 Data Integrity Guidance for Industry

https://www.fda.gov/media/97005/download

"Equally important are the procedure to audit data and programs and the process for correcting errors."

FDA 1993 Laboratory Inspection Guide ☜

"Data integrity in computer-based information systems is a concern because of damages that can be done by unauthorized manipulation or modification of data."

Does Anyone Disagree With these Statements ?

"The emphasis on controlling access to data has served to mask the issue of data integrity."

Thomas R Ivan, 1991 MSc Thesis, Comparison of Data Integrity Models

https://apps.dtic.mil/dtic/tr/fulltext/u2/a243770.pdf

[Note: may need to cut and paste the above link into your browser]

Print Out = Raw Data ?

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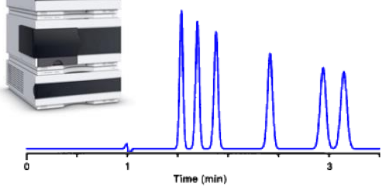
Balance

Simple

Complex

HPLC

Data Complexity



Data
(e.g. Balance Print Out)
Simple Meta Data

Data
(e.g. Chromatograms)
Complex Meta Data

Print Out ✓

Raw Data = Print Out

Print Out ✘

See Appendix

FDA Level 2 Guidance

✓

Raw Data = Electronic Copy

ALCOA+ – Foundation of Data Integrity….

People need to be able to understand / remember and "relate" to Data Integrity requirements……

***A**ttributable*	**A**	- **Who Did The Work** *(work attribution and passwords)* *(Sharing passwords is like sharing your toothbrush !)*
***L**egible*	**L**	- **Can You Read It** *(Electronic or Paper)*
***C**ontemporaneous*	**C**	- **Was it Recorded at The Time** *(No Writing on Hand / Lab. Coat / Post it Note…Etc.)*
***O**riginal*	**O**	- **Is it Original or "*True Copy*"** *(Original Data or Certified Copy)*
***A**ccurate*	**A**	- **No Errors or Undocumented Changes** (represents what was done) *(Is it Representative of The Work)*

\+
- Complete
- Consistent
- Enduring
- Available

MHRA Labs. Symposium

PDF Copy: Courtesy of the Medicines and Healthcare products Regulatory Agency, © Crown 2019

13th March 2019

Medicines & Healthcare products Regulatory Agency

MHRA

Practical Applications of Data Integrity for Laboratories

Jason Wakelin-Smith, Lead GCP & GLP Inspector

The Importance of Dialogue:

Added value in maintaining a dialogue:

Jason is interested in feedback from this meeting….

"…. What else can the Regulator do… ?"

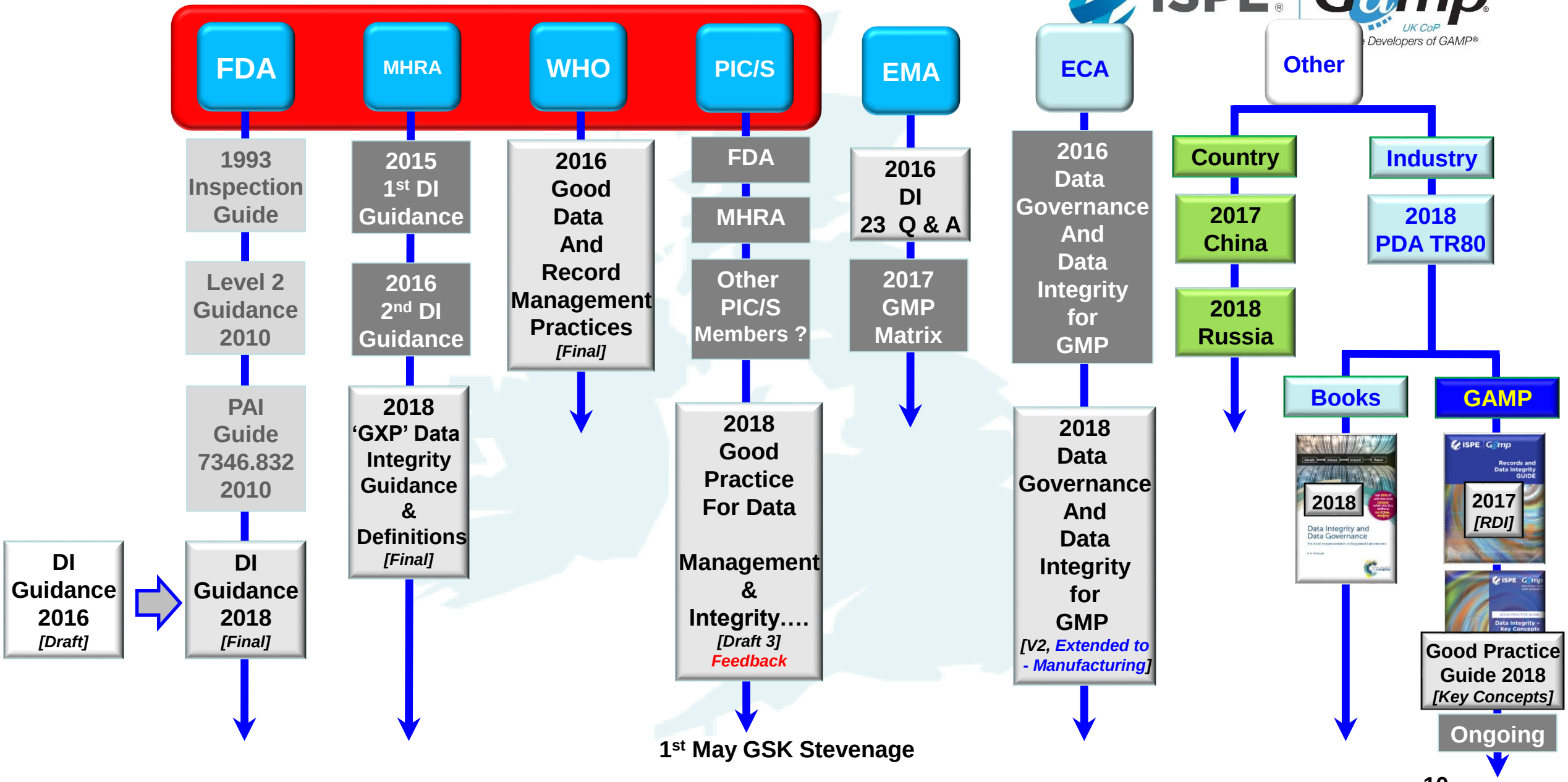
(paraphrase of e-mail)

Opportunity to provide feedback……

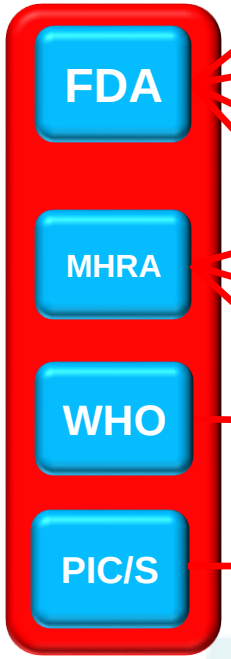
Presentations from the MHRA event are normally only for delegates *(crown copyright).* However, following a request / e-mail exchange with Jason, a PDF of this presentations has been made available to this GAMP meeting.

DATA INTEGRITY GUIDANCE

Guidance Documents…… A Lot of Guidance



Links to Guidance Documents



- 1993 Inspection Guide — 12 pages
- Level 2 Guidance — 8 pages
- PAI Guidance — 53 pages
- Data Integrity Guidance — 13 pages
- 2015 DI Guidance *(V1.1)* — 16 pages
- 2016 DI Guidance — 14 pages
- 2018 DI Guidance (Final) — 21 pages
- 2016 Good Data & Record Management — 46 pages
- 2018 Good Practice for Data Management & Integrity — *(Select PI 041-1)* — 52 pages

- 2016 Q & A — 9 pages
- 2017 DI GMP Matrix *(see slide 7)* — Presentation, 22 pages

- 2016 Data Governance and Data Integrity for GMP — *Contact Bob McDowall or Margarita Sabater* — 71 pages
- 2018 Data Governance and Data Integrity for GMP — 89 pages
  [extended to include manufacturing]

External Hyperlink

- 2017 China — *Translation Available from Barbra Unger (Rx – 360 Working Group)* — 12 pages
- 2018 PDA TR80 — https://store.pda.org/TableOfContents/TR80_TOC.pdf *(PDA - € 325 – PDA Book Store)* — 63 pages
- 2018 Russia — 37 pages
- 2016 OECD Application of GLP Principles to Computerized Systems — 33 pages
- 2017 GAMP RDI / 2018 Key Concepts — *(Purchase from ISPE - € 185 – ISPE Member)* — 152 pages / 196 pages
- 2018 Book – Data Integrity & Data Governance *(Purchased from RSC)* — 600 pages

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ISPE, the Developers of GAMP®

Excluding *"publications"*
1,400 Pages of Guidance
(Google: "Data Integrity Guidance" - ~100,000,000 Hits)

- Not Harmonized, but Common Principles *(GMQA)*
- Different Content / Formats
- Different Perspectives

Guidance Documents…… A Lot of Guidance

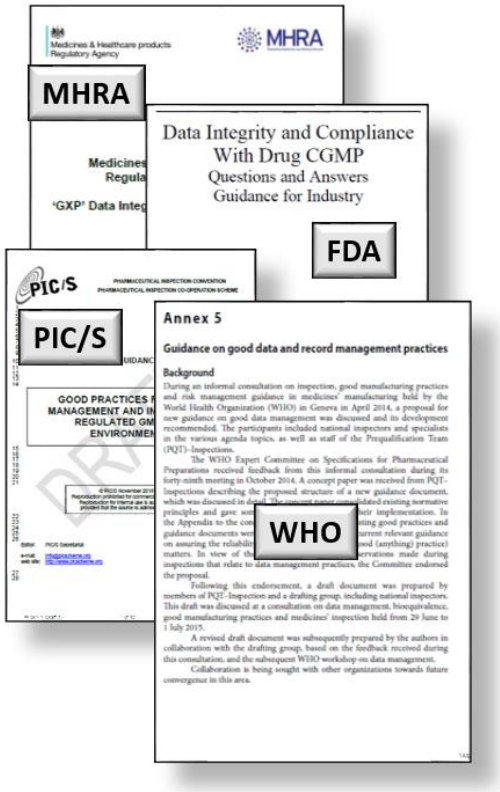
	FDA	MHRA	WHO	PIC/S
Pages:	17	21	46	52
Word Count:	5,805	7,836	15,486	19,321

50,000 words is a small book…
(the average size of a Mills & Boon Book !)

- **FDA** → DI Guidance 2018 *[Final]*
- **MHRA** → 2018 'GXP' Data Integrity Guidance & Definitions *[Final]*
- **WHO** → 2016 Good Data And Record Management Practices *[Final]*
- **PIC/S** → 2018 Good Practice For Data Management & Integrity…. *[Draft 3]* ***Feedback***

Different Guidance Interpretation

Data Integrity Guidance



Guidance Documents Need to be Interpreted !

("what, but not how")

If a Guidance Document Includes the word "*must*"

- Do you need to comply with the requirement ?

Manufacturing / R&D May Interpret These Questions Differently ?

If a Guidance Document Only Includes the word "*should*"

- Do you need to comply with the requirement ?

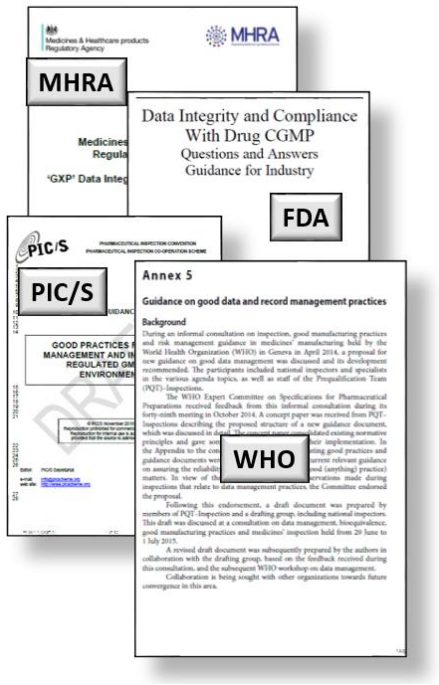
Language of Compliance:

- **Company SOP – *Must* / *Should***

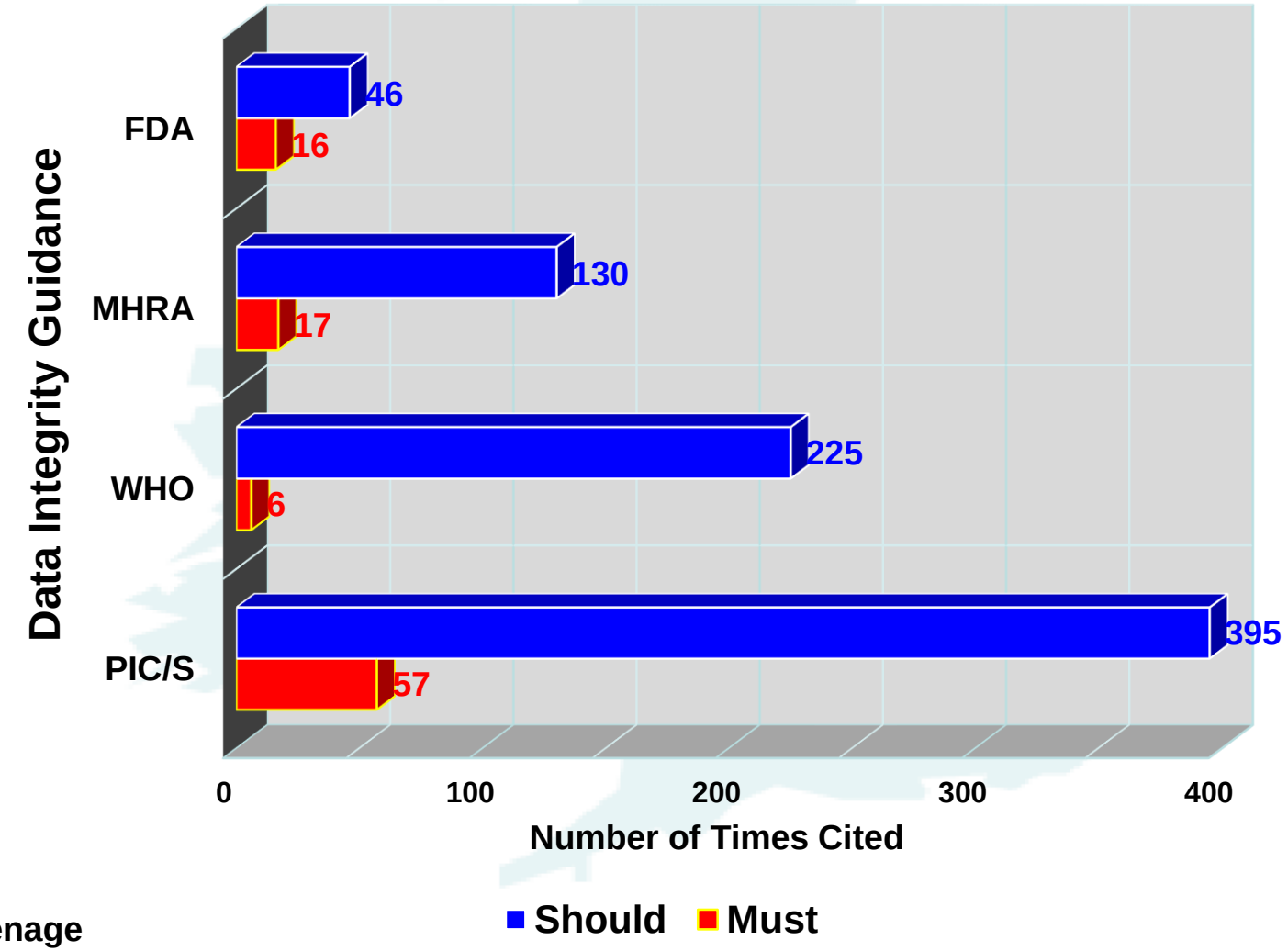
Does the same thinking apply to:

- **Regulatory Guidance – *Must* / *Should* ?**

Must / Should - Comparison



Wording of Data Integrity Guidance

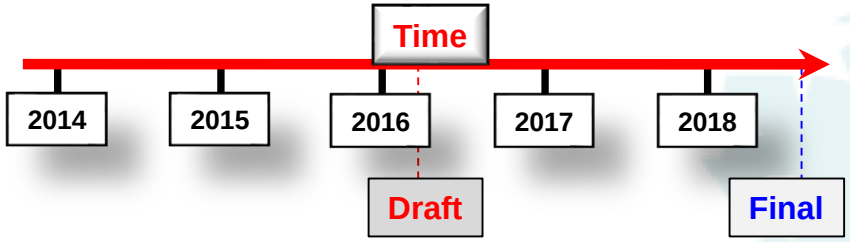


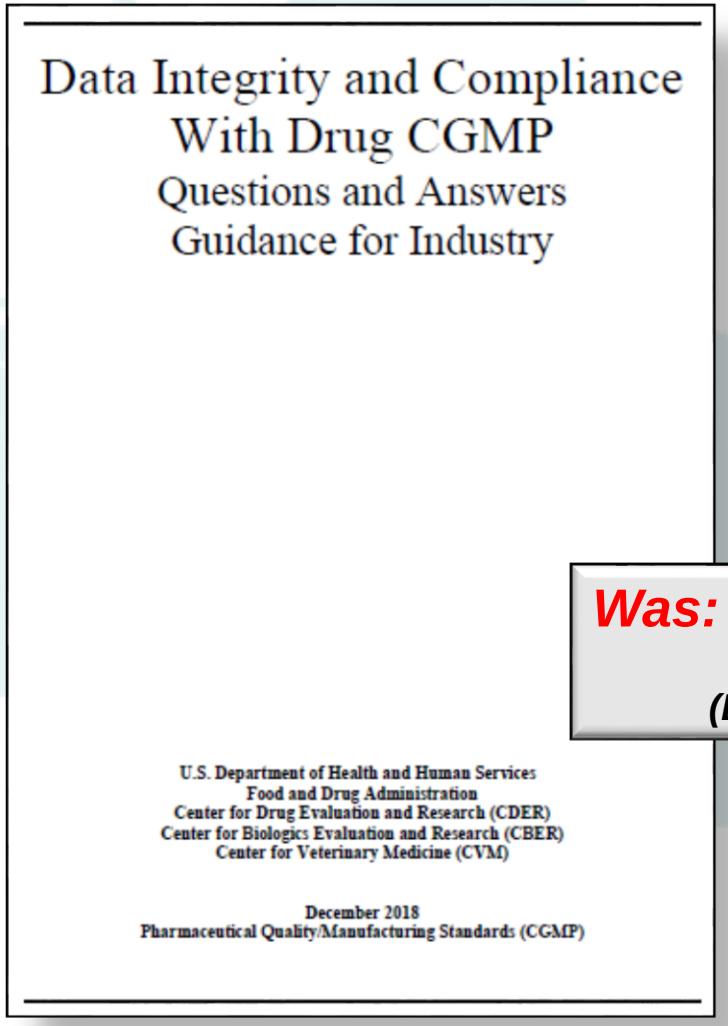
Which Guidance Includes:

SMALLEST number of MUST statements ?

LARGEST number of SHOULD statements ?

FDA DATA INTEGRITY GUIDANCE




Data Integrity and Compliance
With Drug CGMP
Questions and Answers
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

December 2018
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Was: **ucm495891**
(Final)
(Dec. 2018)

Press Statement (Data Integrity Guidance)

December 12th 2018

FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's efforts to improve drug quality through vigilant oversight of data integrity and good manufacturing practice

For Immediate Release

December 12, 2018

"The guidance covers the design, operation, and monitoring of systems and controls to maintain data integrity."

17 Pages, 5,805 Words

- **I Introduction**
- **II Background**
- **III Clarification of Terms**
- **Question & Answer 2 – 18**

III Clarification of Terms

b. What is "metadata"?

Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it

Question & Answer 2 – 18

3. Does each CGMP workflow on a computer system need to be validated?

Yes, a CGMP 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)). The extent of validation studies should be commensurate with the risk posed by the automated system. When the same system is used to perform both CGMP and non-CGMP functions, the potential for non-CGMP functions to affect CGMP operations should be assessed and mitigated appropriately.[10]

FDA Data Integrity Guidance

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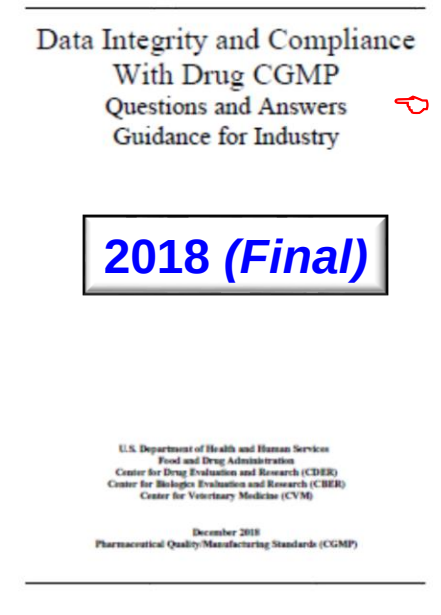
Q & A Format – *18 Questions*….

- **Changes to Questions**
- **Changes to Content**
- **Changes to References**

13 Pages	17 Pages
DI Guidance 2016 *[Draft]*	DI Guidance 2018 *[Final]*
4,669 Words	*5,805 Words*

1. Clarify Terms…..
2. When is it permissible to invalidate a cGMP result and exclude it from the determination of batch conformance?
3. Does each CGMP workflow on a *(previously "our")* computer system need to be validated ?
4. How should access to CGMP computer systems be restricted ?
5. Why is FDA concerned with the use of shared login accounts for computer systems ?
6. Who should blank forms be controlled ?
7. Who should review audit trails ? *(Questions 8 in Draft Guidance)*
8. How often should audit trails be reviewed ? *(Question 7 in Draft Guidance)*
9. Can electronic copies be used as an accurate reproduction of a paper record ?
10. Is it acceptable to retain paper printouts or static records…., such as FT-IR instrument ?
11. Can electronic signatures be used…… ?
12. When does electronic data become a cGMP record ?
13. Why has the FDA cited use of actual samples during system suitability..?
14. Is it acceptable to only save the final result….. ?
15. Can an internal tip regarding a quality issue….. DI…. Outside of quality ?
16. Should personnel be trained in data integrity…. ?
17. Is the FDA investigator allowed to look at my electronic records ?
18. How does FDA recommend data integrity problems….. be addressed ?


Data Integrity and Compliance
With Drug CGMP
Questions and Answers
Guidance for Industry

2018 *(Final)*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

December 2018
Pharmaceutical Quality/Manufacturing Standards (CGMP)

FDA – Question 2 Changes

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	2018 *(final new wording)*	2016 *(draft deleted words)*
2	When is it permissible to invalidate a CGMP result and exclude it from the determination of batch conformance?	When is it permissible to exclude cGMP data from decision making ?

Implies that it is permissible under some contexts !

Stronger alignment with Out of Specification *(OOS)* requirements….. (limits *"testing into compliance"*)

2018 – Part of Q2 Answer **1 of the 16 *(must)***

Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180).[9]

2018 – Part of the Answer to question b "What is "*metadata*" ?

Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194). The relationships between data and their metadata should be preserved in a secure and traceable manner.

2 of the 46 *(should)*

1st May GSK Stevenage

21 CFR…. Ref.

FDA – Wordcount

Q & A Format – 18 Questions….

- Changes to Questions
- Changes to Content
- Changes to References

Overall Increase = + 24 %
(pages & words)

Word Count Example

Q17 Answers

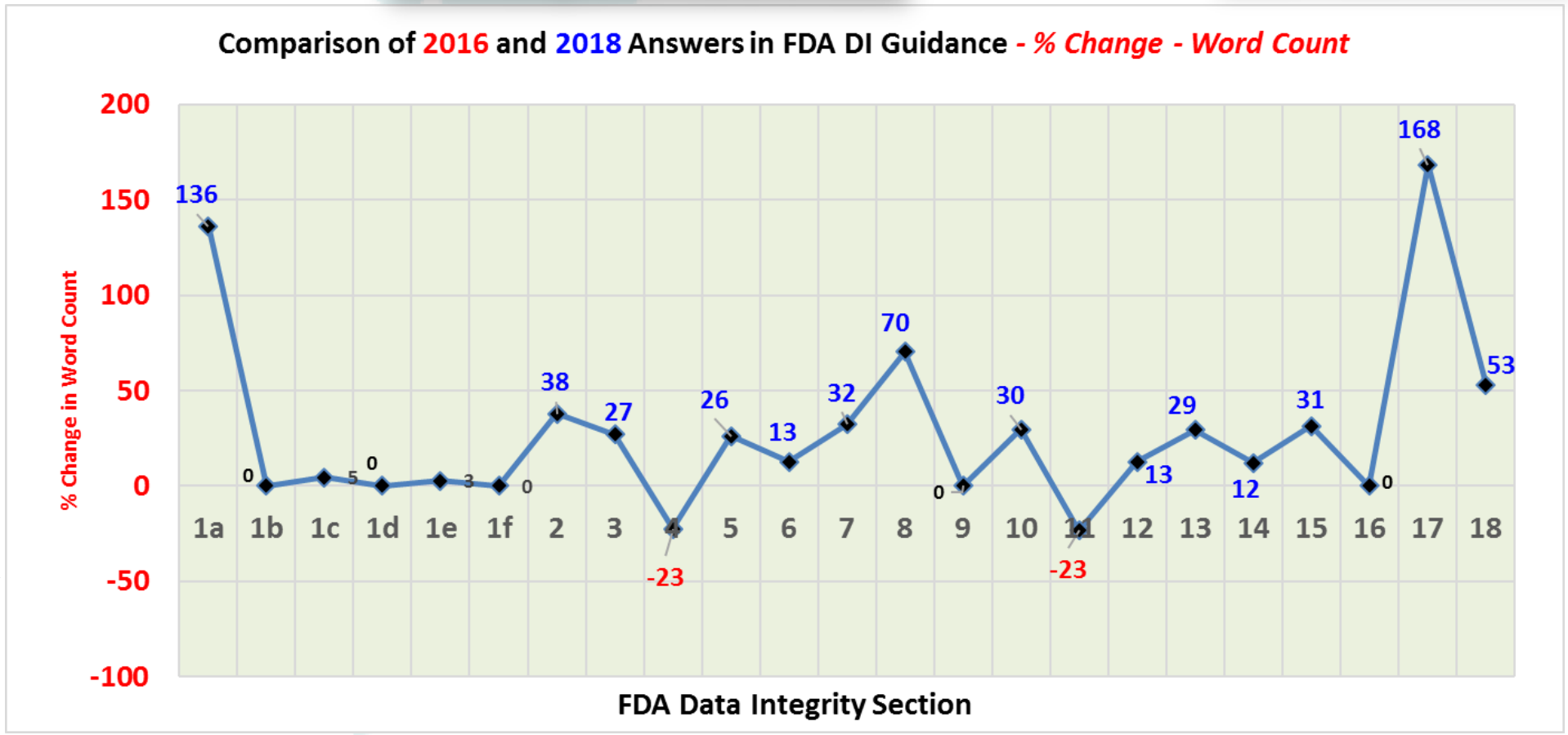
Q17 - 41 words *(2016)*

Q17 - 110 words *(2018)*

% Change =

$$\left(\frac{110 - 41}{41}\right) \times 100 = 168\ \%$$

% Change Across The Guidance



FDA – Wordcount

Q & A Format – 18 Questions….

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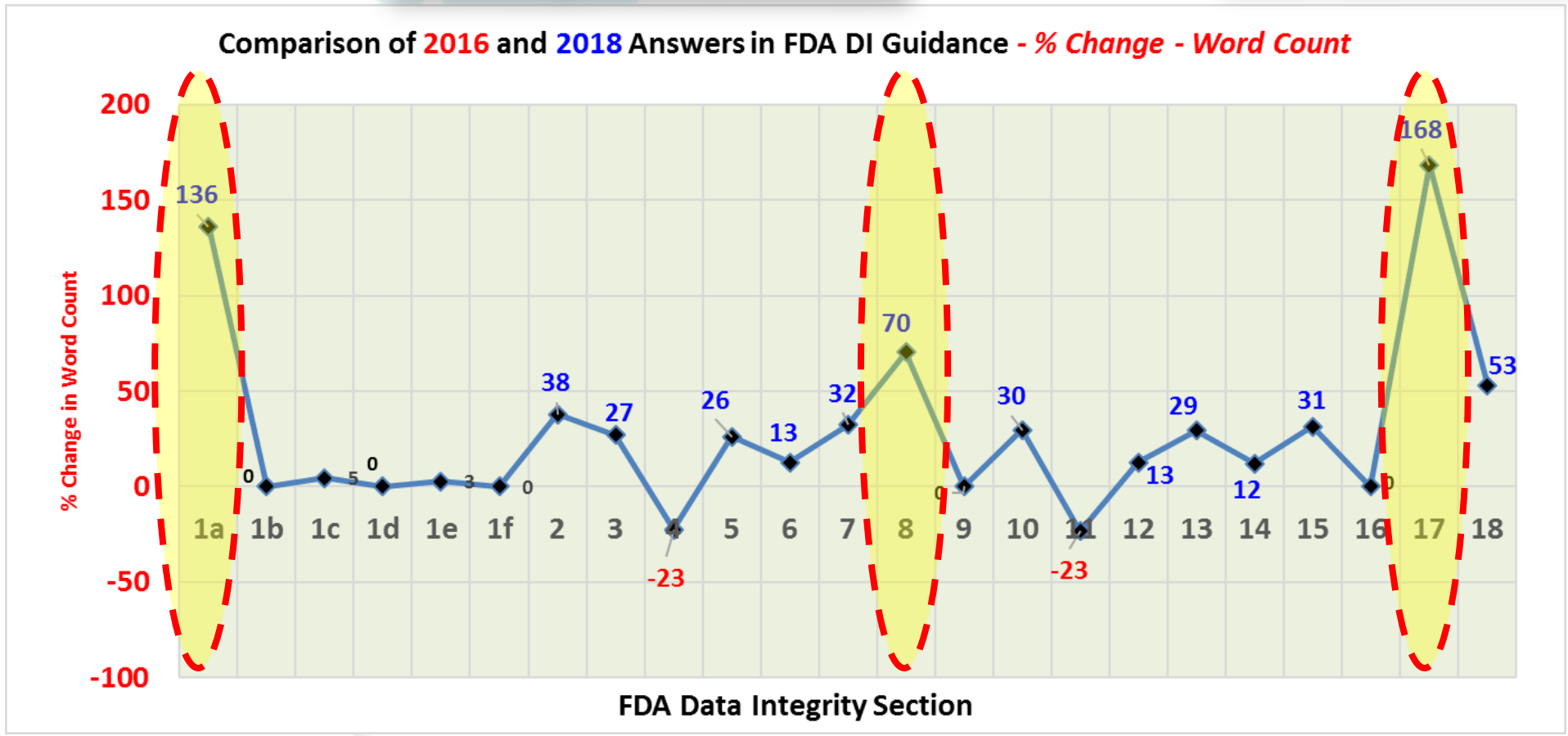
Sections with the Largest % Change



FDA – Wordcount

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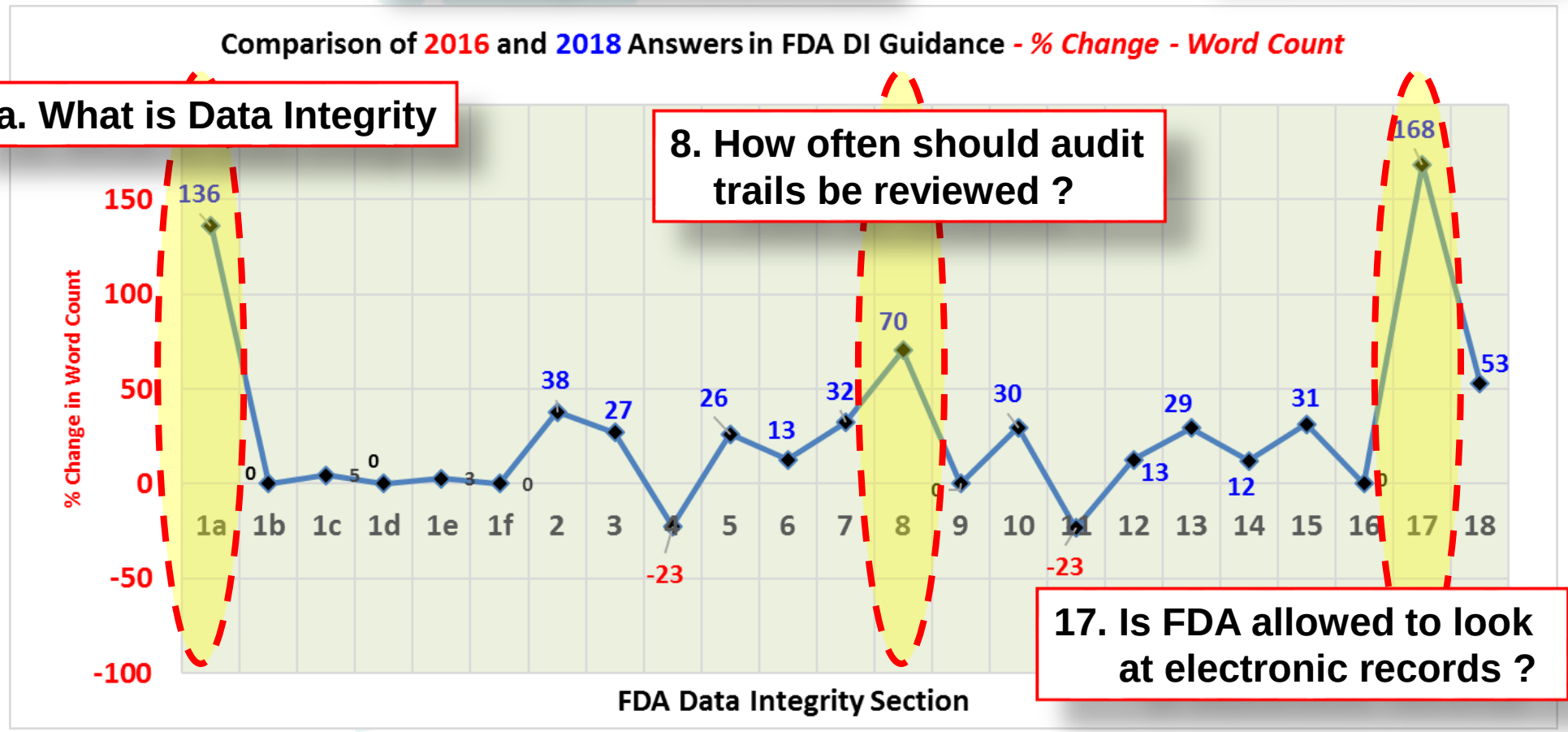

FDA – CFR *(Code of Federal Regulations)……*

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Q & A Format – 18 Questions….

- Changes to Questions
- Changes to Content
- Changes to References

CFR *(Keyword Search)*

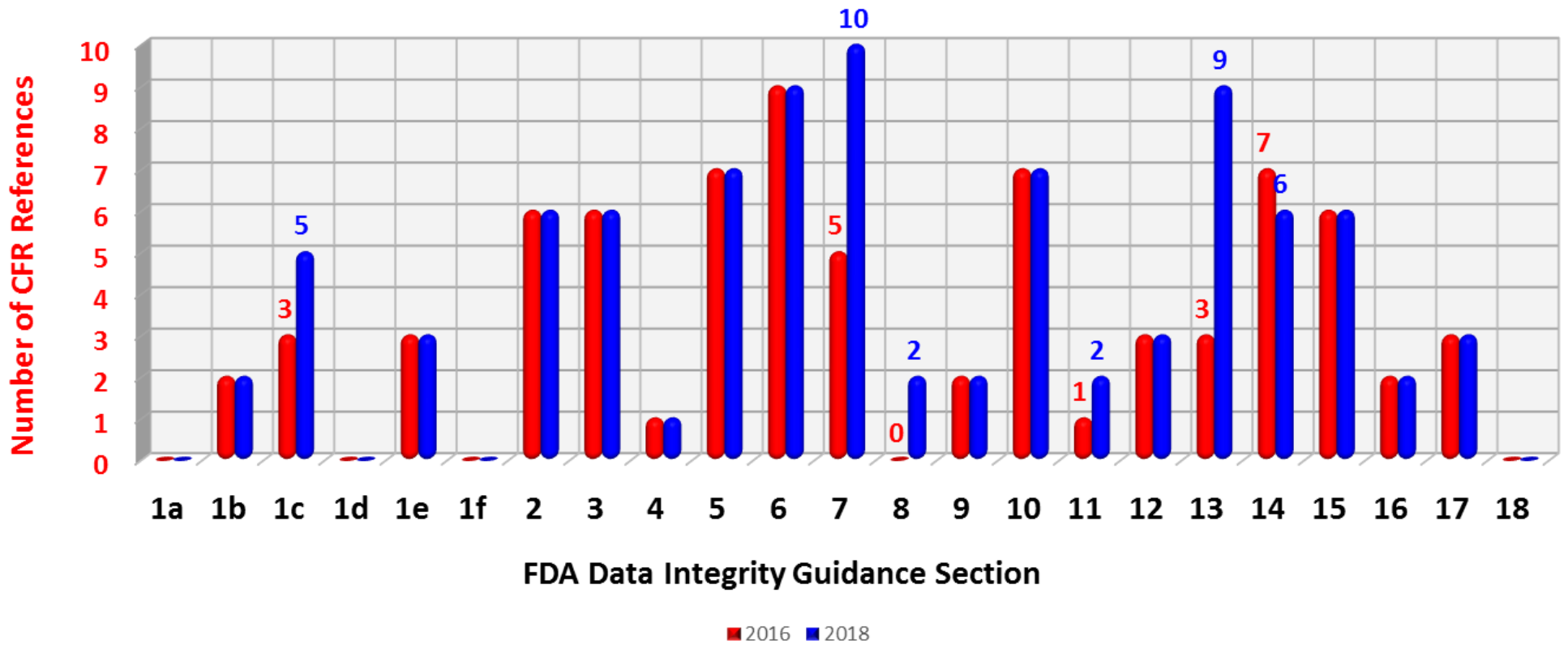
Q13 Answers

2016 *(3)* **2018** *(9 new)*

	211.68(b)
	211.160
	211.165
211.160	211.186(a)
211.165	211.188
212.60	211.192
	211.194
	211.194(a)(8)
	212.60

CFR References….

Change in CFR References Across The Guidance



FDA – CFR *(Code of Federal Regulations)……*

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Q & A Format – 18 Questions….

- Changes to Questions
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- Changes to References

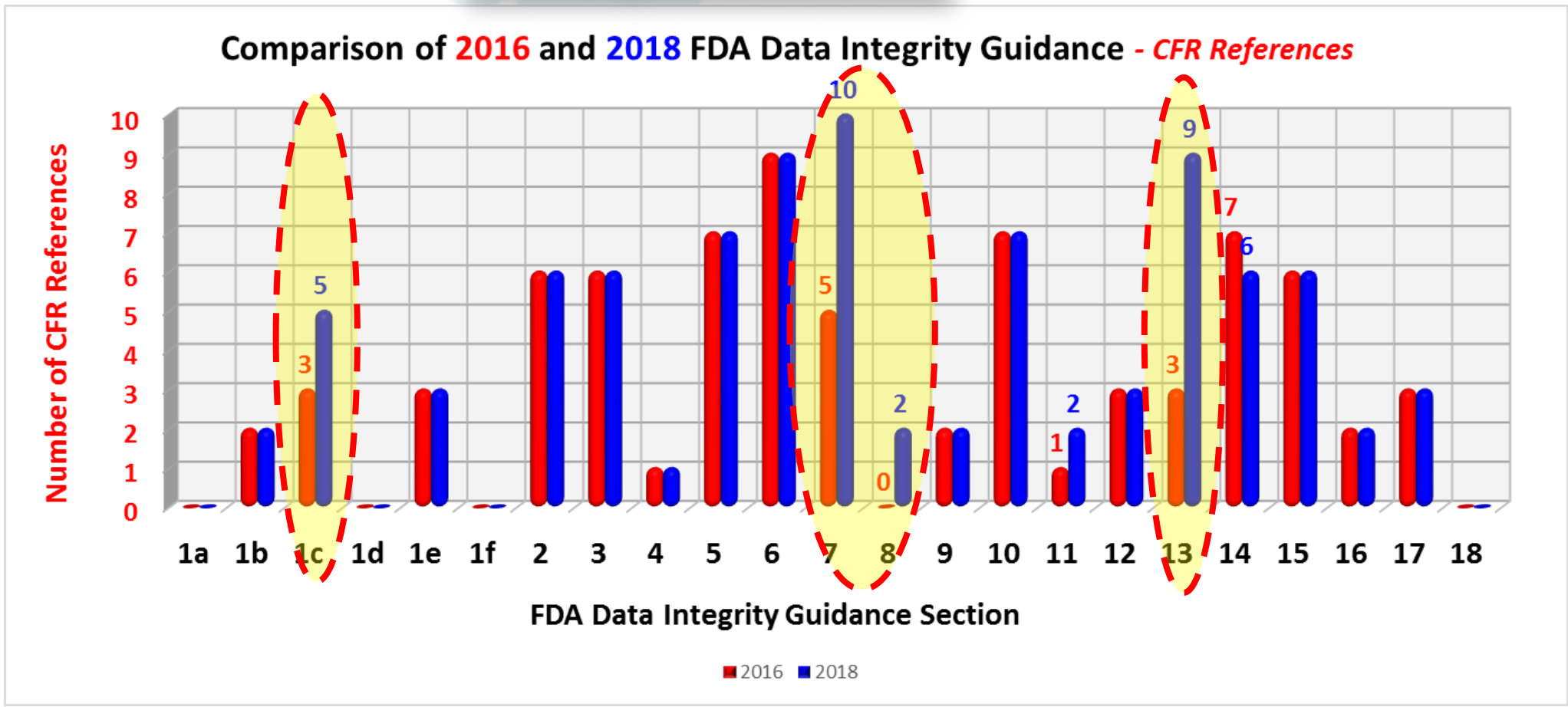
CFR *(Keyword Search)*

Q13 Answers

2016 *(3)*	2018 *(9 new)*
	211.68(b)
	211.160
	211.165
211.160	211.186(a)
211.165	211.188
212.60	211.192
	211.194
	211.194(a)(8)
	212.60

CFR References….

Sections with the Largest No of CFR Changes



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FDA – CFR *(Code of Federal Regulations)……*

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Q & A Format – 18 Questions….

- Changes to Questions
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CFR *(Keyword Search)*

Q13 Answers

2016 *(3)* **2018** *(9 new)*

2016	2018
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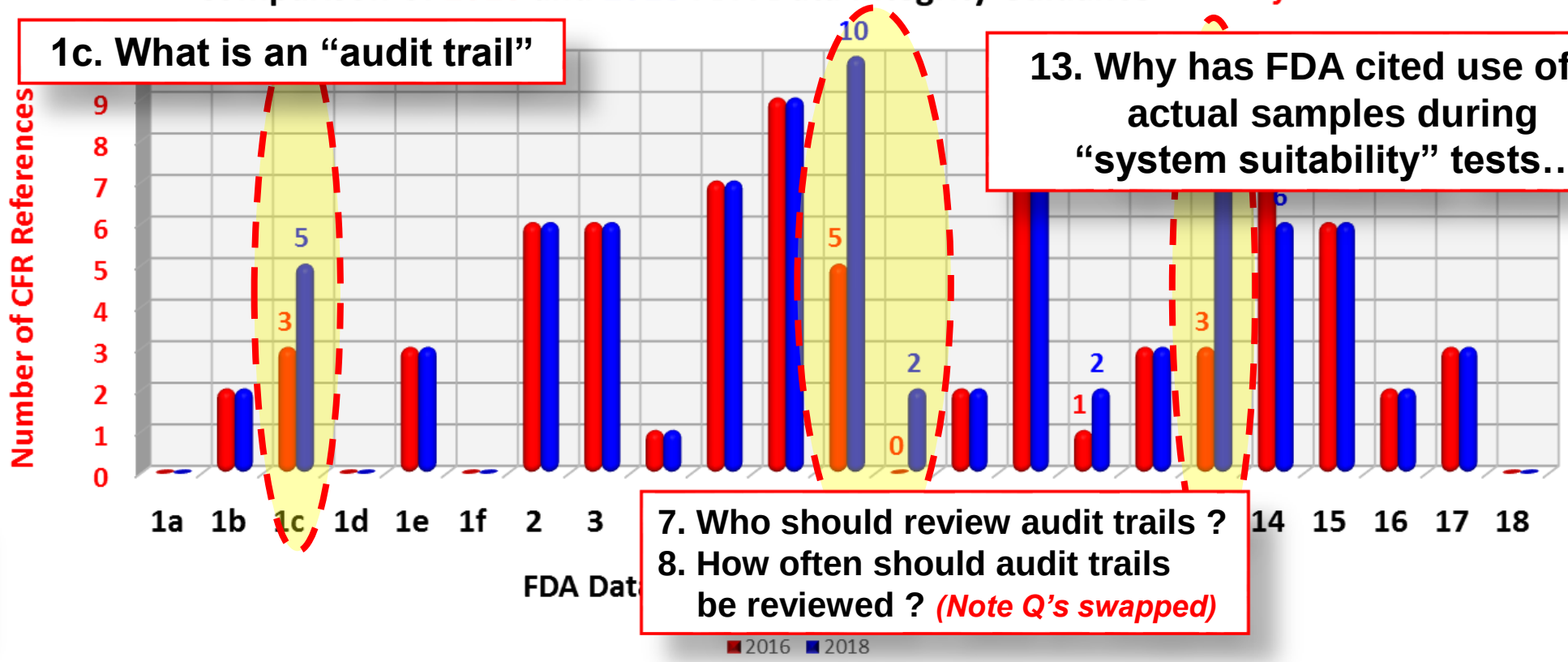
	211.165
211.160	211.186(a)
211.165	211.188
212.60	211.192
	211.194
	211.194(a)(8)
	212.60

CFR References….

Sections With the Greatest Change

Comparison of 2016 and 2018 FDA Data Integrity Guidance *- CFR References*



1c. What is an "audit trail"

13. Why has FDA cited use of actual samples during "system suitability" tests….

7. Who should review audit trails ?
8. How often should audit trails be reviewed ? *(Note Q's swapped)*

FDA – CFR *(Code of Federal Regulations)……*

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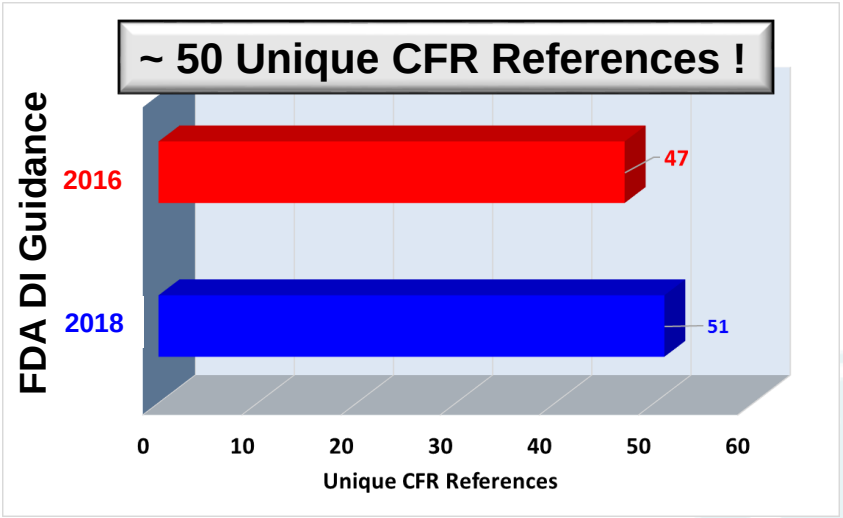
Q & A Format – 18 Questions….

- Changes to Questions
- Changes to Content
- Changes to References

~ 50 Unique CFR References !



Unique to 2018:

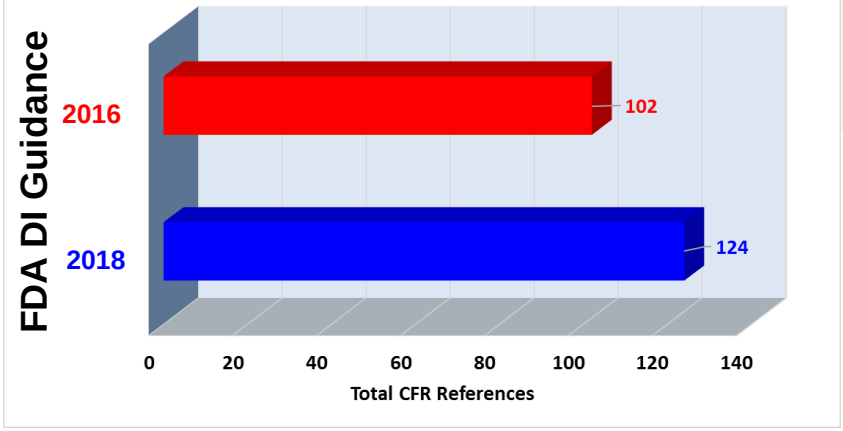
11.2a
211.103
211.182
211.188(b)

11. Can electronic signatures be used instead of handwritten signatures for……

7. Who should review audit trails ?

8. How often should audit trails be reviewed ?

Total CFR References ***(includes repeat ref's.)***



Q 2

2. When is it permissible to invalidate…..etc.

2016 *(Draft)*		2018 *(Final)*	
6	211.22 211.180 211.188 211.192 212.70 212.71(b)	211.63 211.68(b) 211.100 211.110(a) 211.186 212.50(b)	6

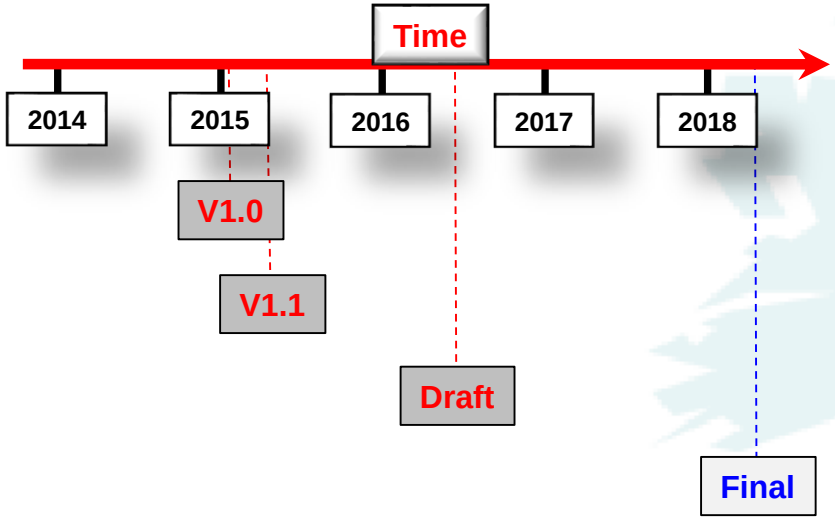
Different CFR References ***(in the "Answer")***

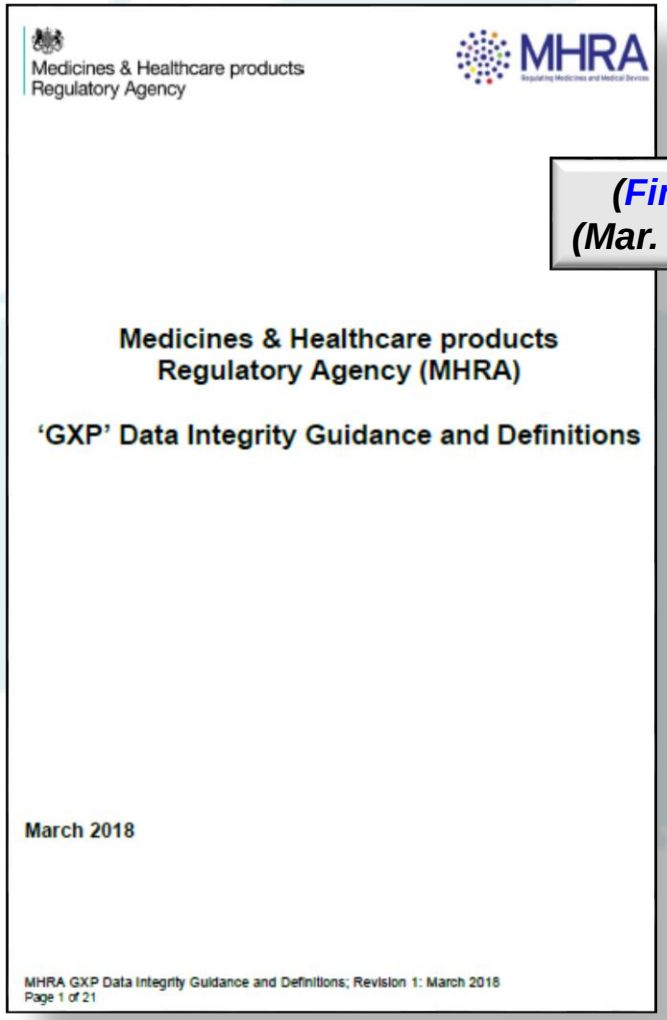
1st May GSK Stevenage

Summary of FDA DI Changes

- **Increased References to the CFR…** *(Audit Trails **Q7 & 8**, and Trial Injections / System Suitability **Q13**)*
- **Expanded Wording….** *(What is Data Integrity ? **Q1a**, How often should audit trails be reviewed **Q8**, and Is the FDA Allowed to Look at Electronic Records ? **Q17**)*
- **Potential Expansion – Inspection Authority** *(e.g. "including electronic communications that support CGMP activities", e-mail **Q17** +168 %)*
- **Invalid Data Criteria Clarified (OOS)** *("Exclude data…" all data must be evaluated, even invalidated data **Q2**)*
- **Enhanced Audit Train Review** *(audit train **must** be reviewed.. Etc, **Q7**, **Q8** ("Review" mentioned 38 times, 19 for Q7&8. Ctrl F of guidance – See footnote p8….)*
- **Stricter Access Control** *("PET Drug Guidance" ref. removed, system admin **should** be independent of record content)*
- **Appendix – Robert Wherry (GAMP DI SIG)** *(permission to share his annotated copies of FDA DI Guide)*

MHRA DATA INTEGRITY GUIDANCE




Medicines & Healthcare products Regulatory Agency

MHRA

Medicines & Healthcare products Regulatory Agency (MHRA)

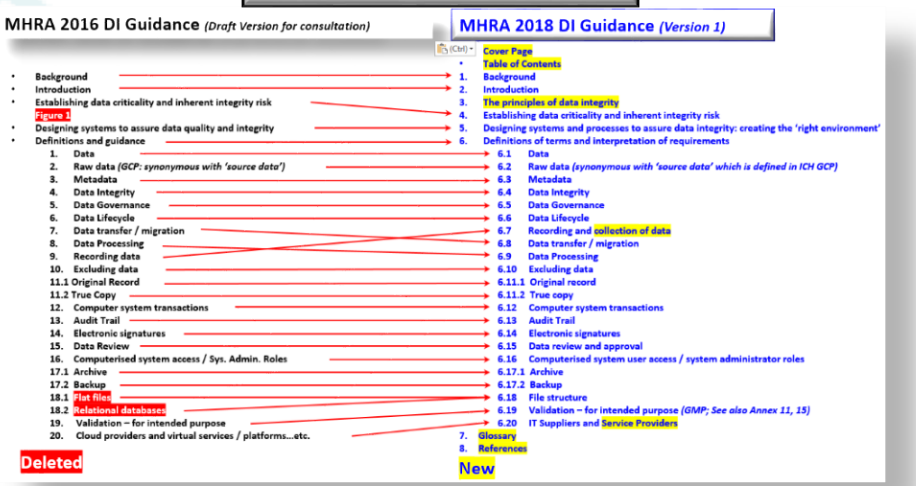
'GXP' Data Integrity Guidance and Definitions

March 2018

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018
Page 1 of 21

(Final)
(Mar. 2018)

Mapping (2016 to 2018)
See Appendix



MHRA Data Integrity Guidance

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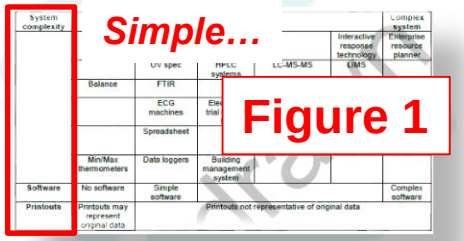
Changes

- Deletions
- Revisions
- Additions



- Concept of "*Primary Record*" *(was in 2015)*
- Line Numbers !
- End of the World ! *– 2017 Audit "Deadline" !*
- Introduction *– opening sentence !*

21 This document provides guidance on the data integrity expectations that should be considered by
22 organisations involved in all aspects of the chemical[1] and pharmaceutical development lifecycle.

Analysis by Barbra Unger 👈
(permission to share)


PHARMACEUTICAL ONLINE

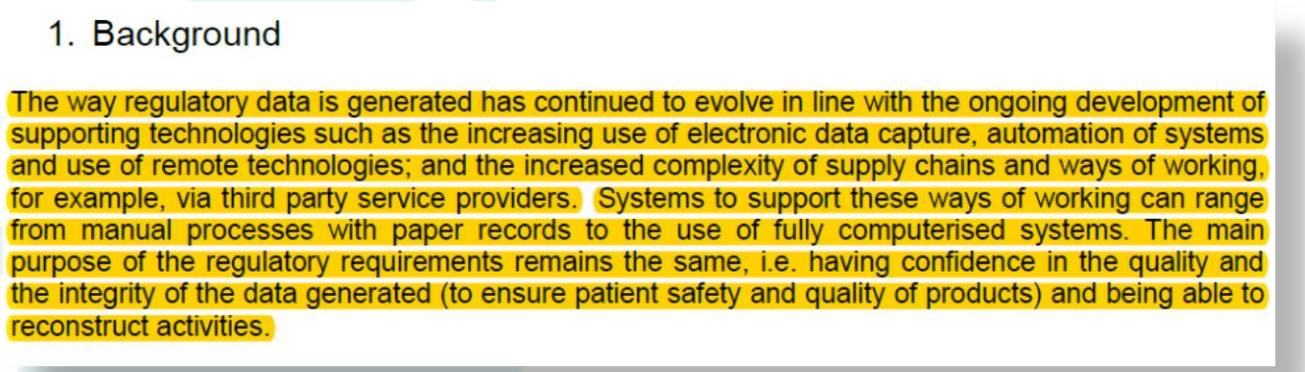
Development & Mfg | Packaging & Protection | Quality | Pharma Logistics

Guest Column | March 19, 2018

What's New In MHRA's Revised Data Integrity Guidance – A Detailed Analysis

By Barbara Unger, Unger Consulting Inc.

Highlighted Copy of 2018 MHRA Guidance by Barbra Unger


1. Background

The way regulatory data is generated has continued to evolve in line with the ongoing development of supporting technologies such as the increasing use of electronic data capture, automation of systems and use of remote technologies; and the increased complexity of supply chains and ways of working, for example, via third party service providers. Systems to support these ways of working can range from manual processes with paper records to the use of fully computerised systems. The main purpose of the regulatory requirements remains the same, i.e. having confidence in the quality and the integrity of the data generated (to ensure patient safety and quality of products) and being able to reconstruct activities.

Click here to view a version of the revised guidance with all new text highlighted. 👈

+ Barbra Unger Blog – DI Guidance Changes 👈

1st May GSK Stevenage

MHRA Data Integrity Guidance

ISPE | GAMP UK CoP
ISPE, the Developers of GAMP®

15 Pages
3,567 Words

16 Pages
3,963 Words

14 Pages
5,407 Words

21 Pages
7,836 Words

Time

Jan. 2015

Mar. 2015

Jan. 2016

1,300 Comments

Mar. 2018

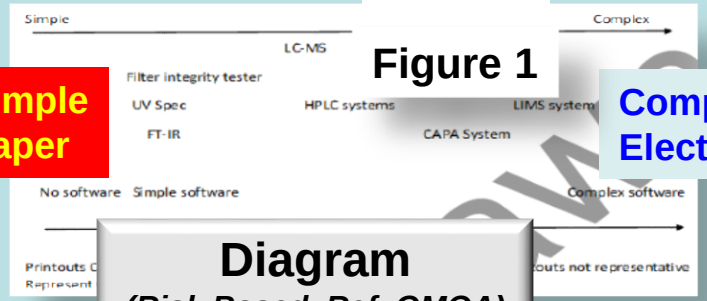
Ver. 1.0

Ver. 1.1

Draft For Consultation

Final Version

Figure 1



Simple Paper

Complex Electronic

Diagram
(Risk Based. Ref. GMQA)

Reads like a set of PPT training slides
(e.g. "MOSTLY Definitions")

Figure 1

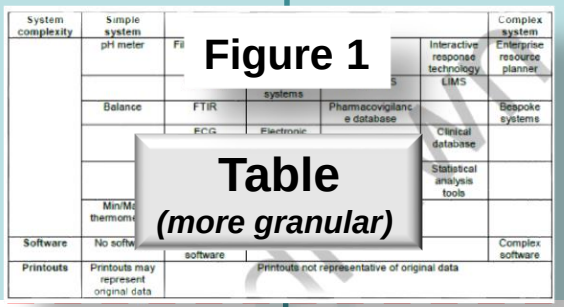


Table
(more granular)

Structure

Introduction / Positioning

+

Definitions +
Some Guidance
(Evolving…)

Data Integrity Principles

Integrated / Mature Data Integrity Guidance

No Figure 1

"GXP"
[more overtly GXP]

1st May GSK Stevenage

MHRA Data Integrity Guidance

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ISPE, the Developers of GAMP®

21 Pages, 7,836 Words

Table of Contents - New

Draft Versions

Introduction / Positioning

+

Definitions + *Some Guidance (Evolving)*

Final Version – Mar. 2018

Background / Introduction

↓

Principles of DI (10)

↓

Establishing Data Criticality / Risk

↓

Designing Systems…..

↓

Definitions / INTERPRETATION

↓

Glossary / References

MHRA Data Integrity Guidance

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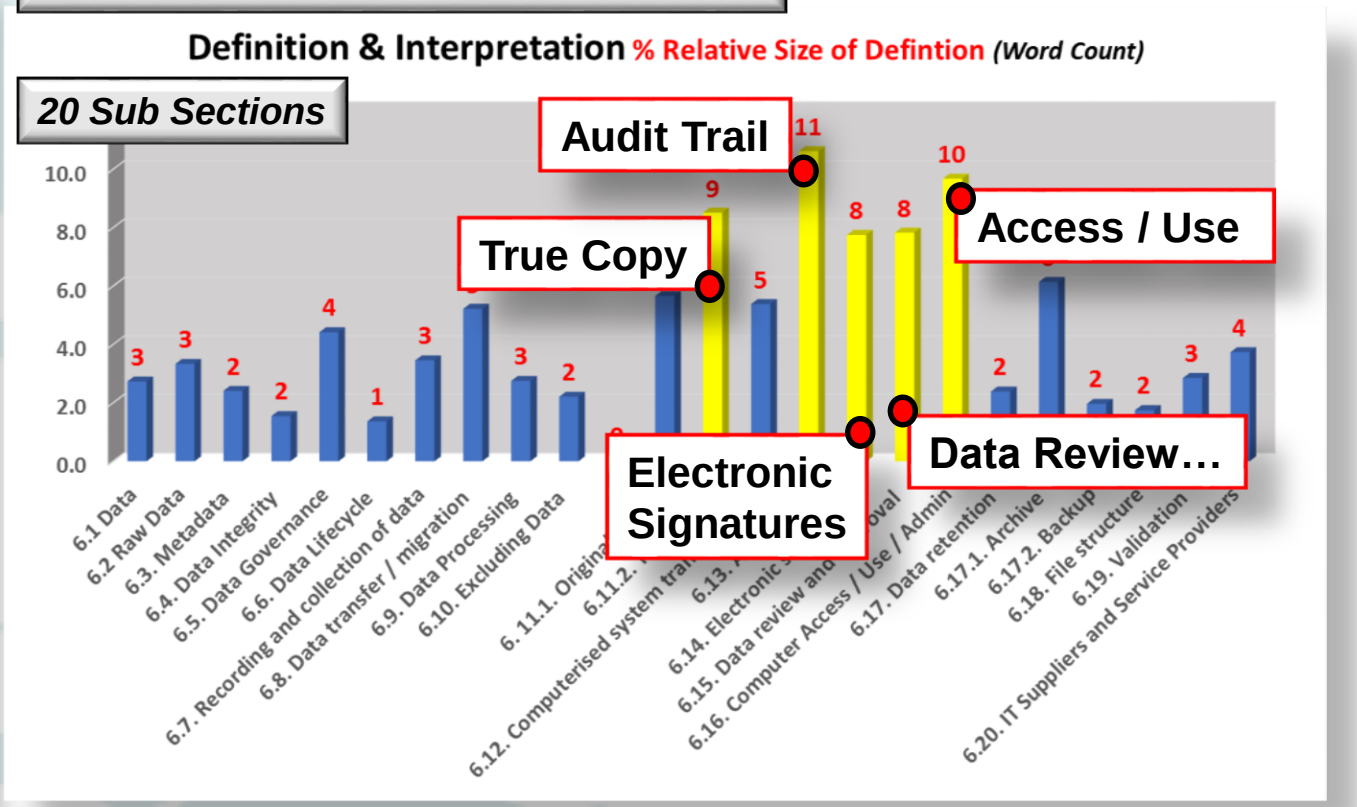
21 Pages, 7,836 Words

67 % of Word Count – Section 6



5 Largest Sub-Sections of Section 6

Revisions to Guidance	Comments *(Abbreviated – See Guidance)*
Establishing Data Criticality and Inherent Integrity Risk *(Section 4, p 5)*	**Substantial expansion, structure and new text / detail**
	Sections 4.5 & 4.6 – *Risk Assessment & Remediation*
Designing Systems and Processes… *(Section 5, p 7)*	**Substantial expansion, use of "*Scribes*"** *(e.g. GLP example, for contemporaneous recording sterile operations by observations now included).*
Data *Definition* *(Section 6.1, p 8)*	**Now includes the + of ALCOA+** *(e.g. Complete, Consistent…. Etc.)*
Raw Data *(Section 6.2, p 8)*	**No electronic storage, print out = Raw Data** *(e.g. balance).*
Data Integrity *Definition* *(Section 6.4, p 9)*	**Substantial expansion** *(e.g. now incorporates requirement for quality risk management systems, sound scientific principles and good document practice).*
Original Record *Definition* *(Section 11.1, p 11)*	**Rewording of static and dynamic record format**
Original Record *Definition* *(Section 11.1, p 11)*	**Manual observation – *risk assessed*** *(2nd check, depending on criticality)*
Audit Trail *(Section 6.13, page 13)*	**Substantial changes.** *(e.g. Definition, justify legacy systems (evidence of compliant solution being sought), risk assess – for data review, use of exception report. Deficiency may be cited – if remediation not implemented in a timely manner).*
Electronic Signatures *(Section 14, p 14)*	**Substantial expansion – related to use** *(e.g. aspects to consider)*
Data Review & Approval *(Section 6.15, p15)*	**Periodic Audit** *– might verify effectiveness of existing control measures*
Computerised System Access *(Section 16, p 16)*	**User Access** *– must be used* **Sys. Admin….** *…should not …interest in the data..*
Data Retention *(Section 6.17, p 17)*	**Destruction of Data** *– procedures should consider data criticality & legislation…*
File Structure *Definition* *(Section 6.18, p 19)*	**Simplified and shortened** *– different structures require different controls*
Section 6.20 Title change *(p 19)*	**IT Suppliers and Service Providers.**

MHRA DI Guidance - *Additions*

Regulating Medicines and Medical Devices

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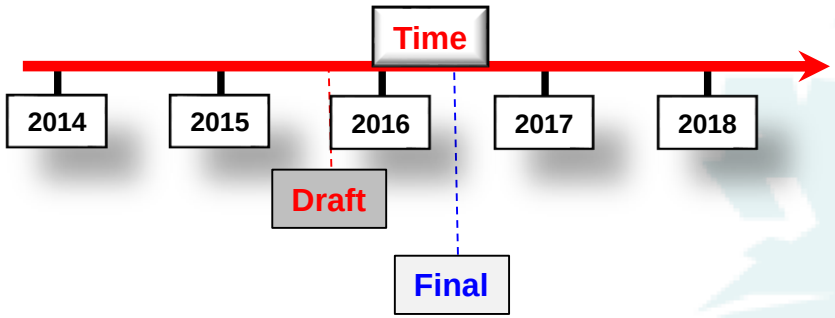
Additions to the Guidance	Comments *(Abbreviated - See Guidance, 2016, 2018)*
Table of Contents *(p 2)*	And associated numbering. Not present in 2016 version
Scope….	More *"overtly GXP"* *(e.g. Ref. GMP:4-7, GLP: 1-5, GCP: 1-6, GDP: 0-2, GXP:6-20)*
Principles of Data Integrity *(p 4)*	Consolidation – of *10 principles* *(3.1 to 3.10, previously throughout 2016 draft)*
Raw Data *(p 8)*	Synonymous with '*source data*' *– ICH GCP Ref.*
Recording *and Collecting of* Data *(p 10)*	Justify *– "resolution (detail)" of Data*, Blank Forms *– Should be controlled*
Data Transfer / Migration *(p 10)*	Substantial Expansion *– There should be an audit trail, procedures should include rationale, transfer should be validated, software should be managed through QMS, Electronic Worksheets should be version controlled… etc.*
Data Processing *(p 11)*	Now includes: *"attribution of who performed the activity".*
Excluding Data *(p 11)*	Not Applicable to GPvP
Electronic Signatures *(p 14)*	References MHRA draft – *informed consent for GCP*
Data Review *and Approval* *(p 15)*	Substantial Expansion - *…Should meet all applicable regulatory requirements and be risk-based.*
Archive *(p 18)*	Hybrid Systems – *"…references between physical and electronic records must be maintained…"*
Glossary *(p 20)*	eCFR, ECG, data quality, DIRA.... etc.

DATA INTEGRITY GUIDANCE



Annex 5

Guidance on good data and record management practices

Background

During an informal consultation on inspection, good manufacturing practices and risk management guidance in medicines' manufacturing held by the World Health Organization (WHO) in Geneva in April 2014, a proposal for new guidance on good data management was discussed and its development recommended. The participants included national inspectors and specialists in the various agenda topics, as well as staff of the Prequalification Team (PQT)–Inspections.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations received feedback from this informal consultation during its forty-ninth meeting in October 2014. A concept paper was received from PQT–Inspections describing the proposed structure of a new guidance document, which was discussed in detail. The concept paper consolidated existing normative principles and gave some illustrative examples of their implementation. In the Appendix to the concept paper, extracts from existing good practices and guidance documents were combined to illustrate the current relevant guidance on assuring the reliability of data and related GXP (good (anything) matters. In view of the increasing number of observations mad inspections that relate to data management practices, the Committee the proposal.

Following this endorsement, a draft document was pre members of PQT–Inspection and a drafting group, including national i This draft was discussed at a consultation on data management, bioequivalence, good manufacturing practices and medicines' inspection held from 29 June to 1 July 2015.

A revised draft document was subsequently prepared by the authors in collaboration with the drafting group, based on the feedback received during this consultation, and the subsequent WHO workshop on data management.

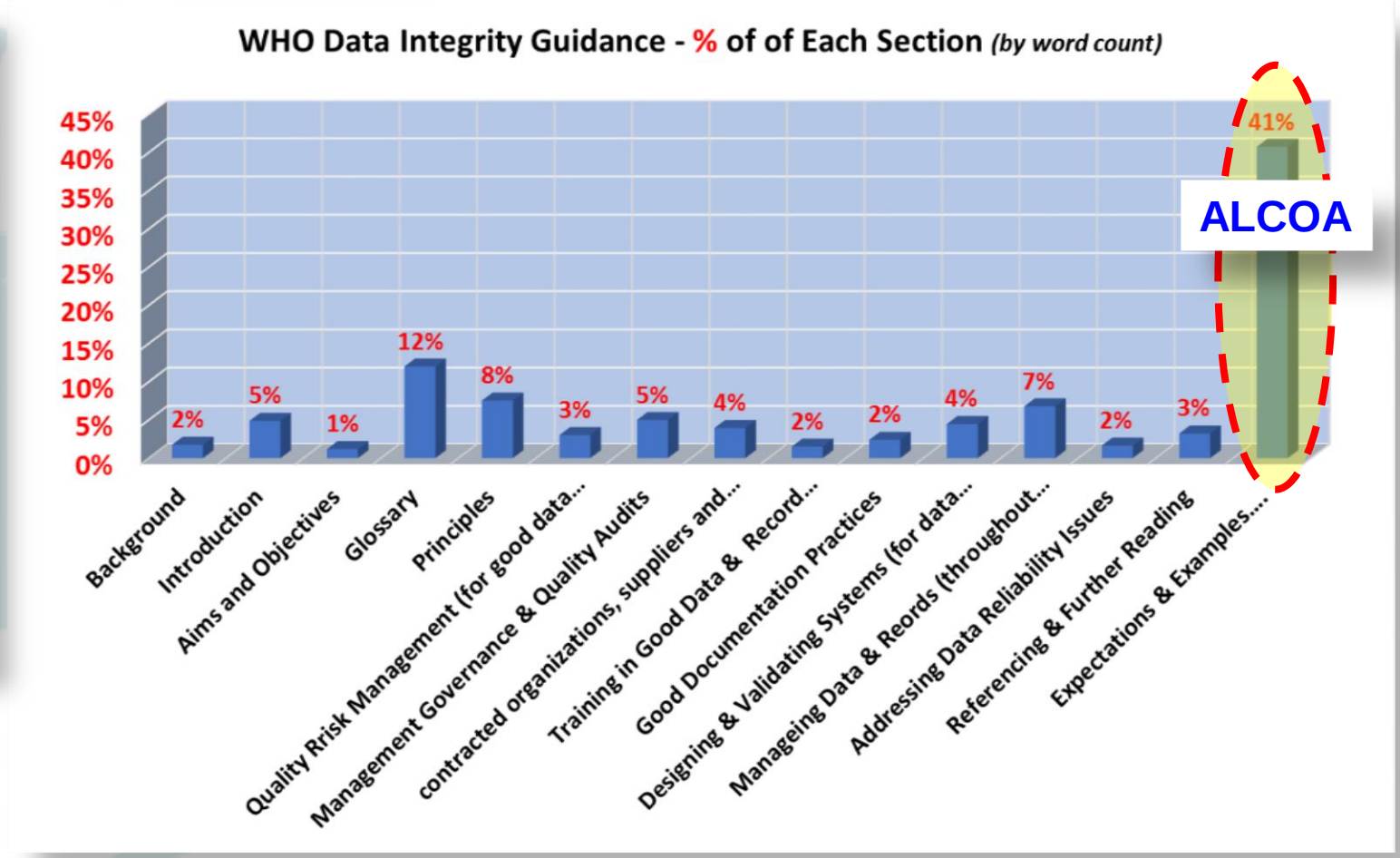
Collaboration is being sought with other organizations towards future convergence in this area.

Technical Report 996
(Final)
(2016)

Data Integrity Guidance

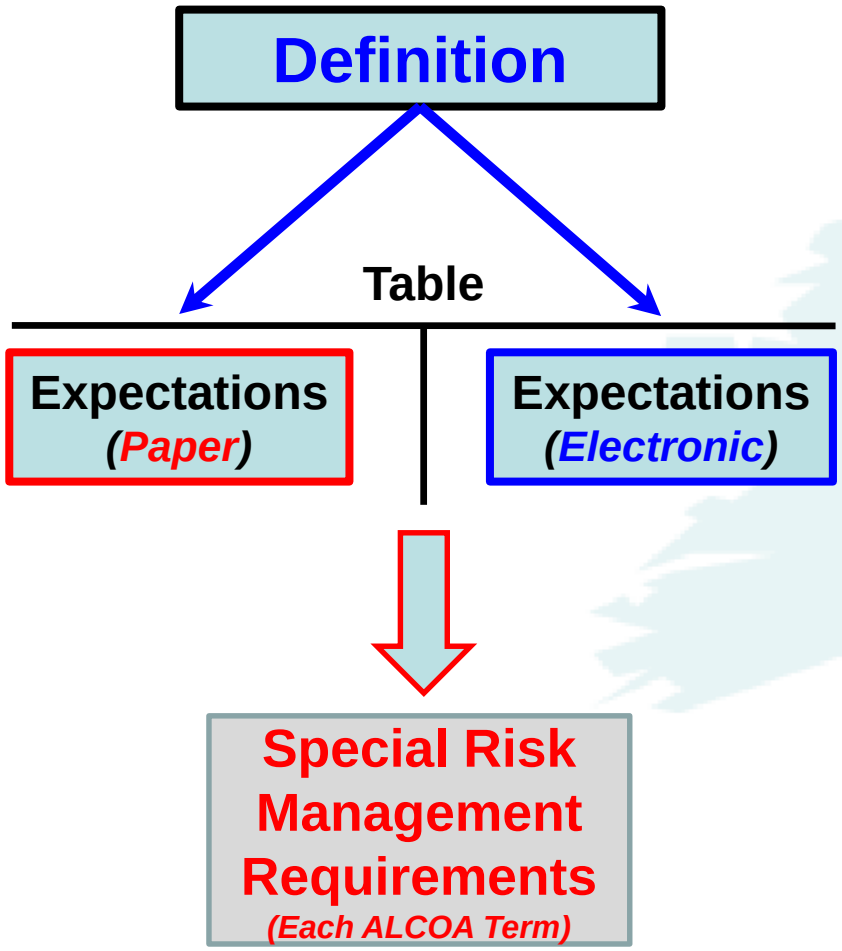
Primary Focus: *Education and Understanding*

46 Pages, 15,486 Words



Guidance – ALCOA Structure

For Each section of ALCOA



Contemporaneous

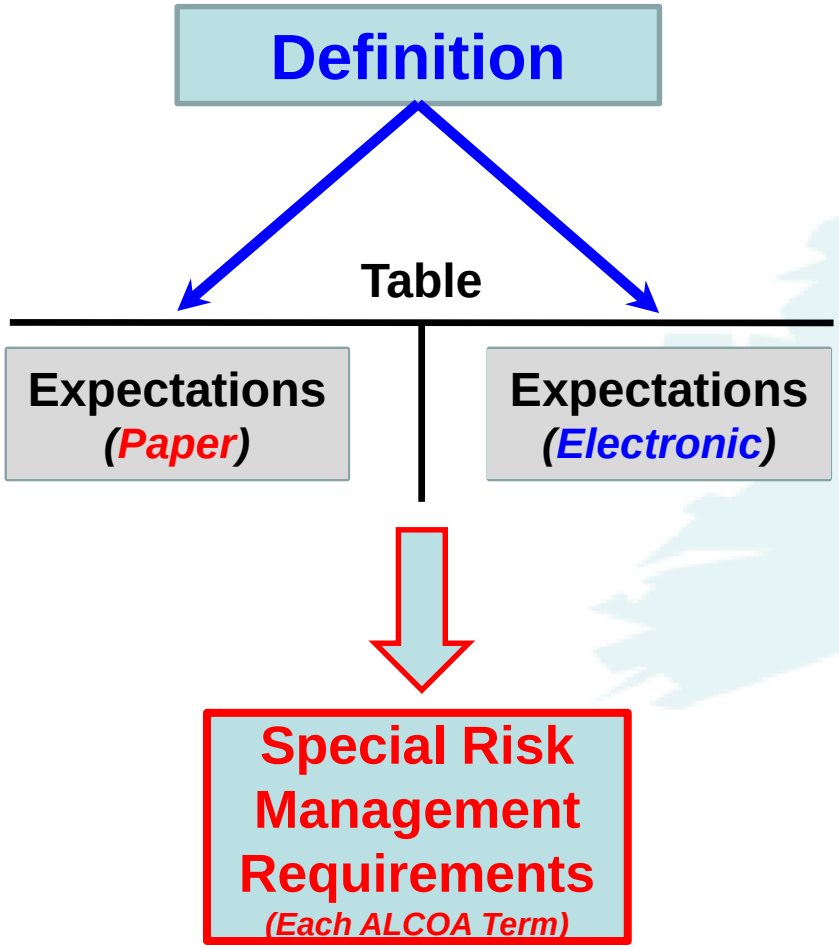
Contemporaneous

Contemporaneous data are data recorded at the time they are generated or observed.

Contemporaneous	
Expectations for paper records	**Expectations for electronic records**
Contemporaneous recording of actions in paper records should occur, as appropriate, through use of: • written procedures, and training and review and audit and self-inspection controls that ensure personnel record data entries and information *at the time of the activity directly in official controlled documents* (e.g. laboratory notebooks, batch records, case report forms);	Contemporaneous recording of actions in electronic records should occur, as appropriate, through use of: • configuration settings, SOPs and controls that ensure that data recorded in temporary memory are committed to durable media upon completion of the step or event and before proceeding to the next step or event in order to ensure the permanent recording of the step or event at the time it is conducted;

Guidance – ALCOA Structure

For Each section of ALCOA

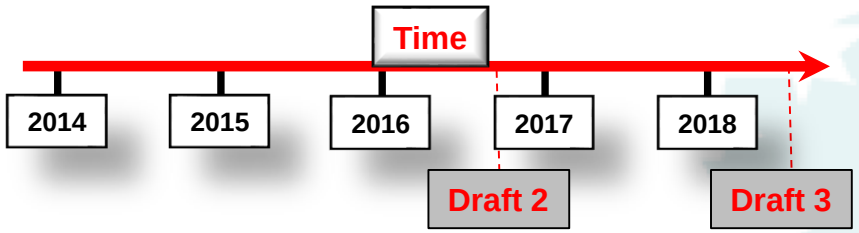


Special risk management considerations for contemporaneous recording of GXP data

Contemporaneous

- Training programmes in GDocP should emphasize that it is unacceptable to record data first in unofficial documentation (e.g. on a scrap of paper) and later transfer the data to official documentation (e.g. the laboratory notebook). Instead, original data should be recorded directly in official records, such as approved analytical worksheets, immediately at the time of the GXP activity.
- Training programmes should emphasize that it is unacceptable to backdate or forward date a record. Instead the date recorded should be the actual date of the data entry. Late entries should be indicated as such with both the date of the activity and the date of the entry being recorded. If a person makes mistakes on a paper document he or she should make single-line corrections, sign and date them, provide reasons for the changes and retain this record in the record set.

PIC/S DATA INTEGRITY GUIDANCE



PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 3)
30 November 2018

PIC/S GUIDANCE

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

Editor: PIC/S Secretariat

e-mail: info@picscheme.org
web site: http://www.picscheme.org

P1041-1
(Draft 3)
(Nov. 2018)

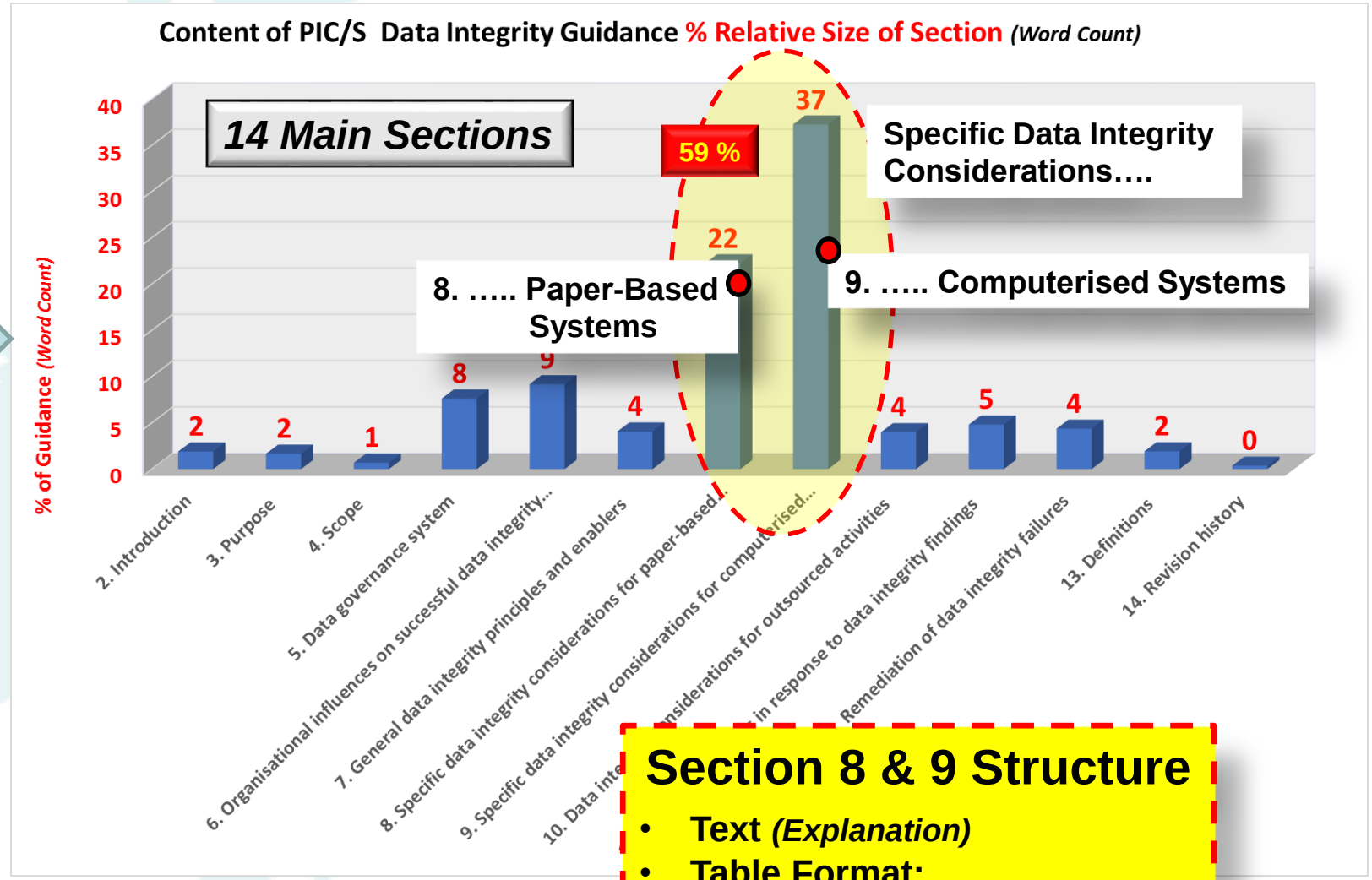
Data Integrity Guidance

ISPE, the Developers of GAMP®

Most Granular Table of Contents

TABLE OF CONTENTS

52 Pages, 19,321 Words

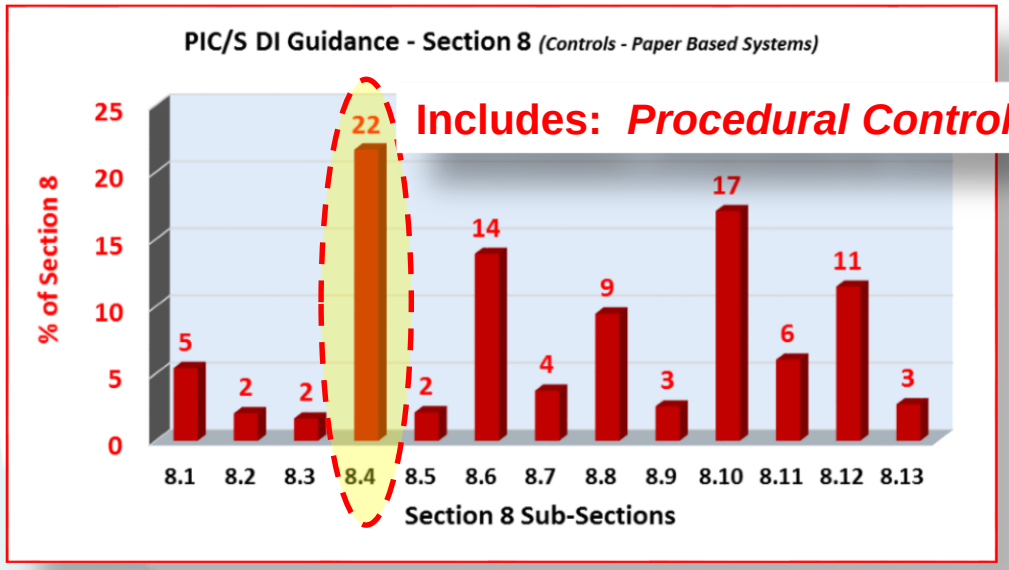


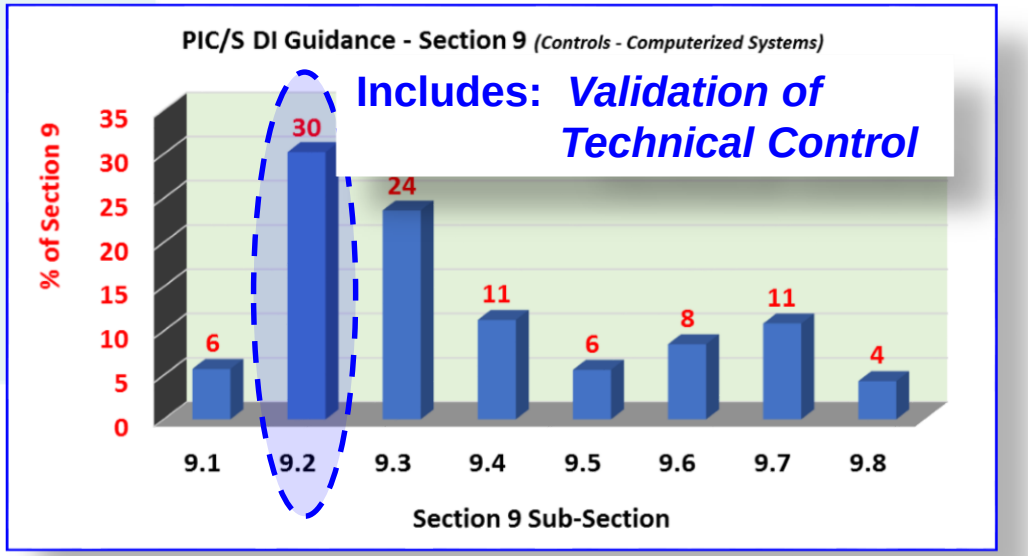
Section 8 & 9 Structure

- Text *(Explanation)*
- Table Format:
  - *Expectations*
  - *"Instructions"*

Data Integrity Guidance

8	Specific data integrity considerations for paper-based systems
8.1	Structure of the QMS and control of blank forms/templates/records
8.2	Importance of controlling records
8.3	Generation, distribution and control of template records
8.4	Expectations for the generation, distribution and control of records
8.5	Use and control of records located at the point of use
8.6	Filling out records
8.7	Making corrections on records
8.8	Verification of records (secondary checks)
8.9	Direct print-outs from electronic systems
8.10	True copies
8.11	Limitations of remote review of summary reports
8.12	Document retention
8.13	Disposal of original records
9	**Specific data integrity considerations for computerised systems**
9.1	Structure of QMS and control of computerised systems
9.2	Qualification and validation of computerised systems
9.3	System security for computerised systems
9.4	Audit trails for computerised systems
9.5	Data capture/entry for computerised systems
9.6	Review of data within computerised systems
9.7	Storage, archival and disposal of electronic data
9.8	Management of Hybrid Systems





Data Integrity Guidance

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9.6	Review of data within computerised systems
9.7	Storage, archival and disposal of electronic data
9.8	Management of Hybrid Systems

Expectations Table

Table Format Applies to Sub-Sections:
8.4, 8.6,
9.2 – 9.8

Instructions Table

Table Format Applies to Sub-Sections:
8.7, 8.8, 8.10, 8.12

DI Guidance – *Expectations Table*

Table

Section *(e.g. 8.4)*	Expectations	Specific elements that should be checked / Potential risk of not meeting expectations
	Details…	*Details….*

Life Cycle Stages (8.4):
- *Generation*
- *Distribution & Control*

Very Structured Content

Table Format Applies to Sub-Sections:
8.4, 8.6,
9.2 – 9.8

Example 8.4 – Expectations for generation, distribution….

	Expectations	Potential risk of not meeting expectations/items to be checked
Item:	**Generation**	
1	All documents should have a unique identification number (including the version number) and should be checked, approved, signed and dated. The use of uncontrolled documents should be prohibited by local procedures. The use of temporary recording practices, e.g. scraps of paper should be prohibited.	Uncontrolled documents increase the potential for omission or loss of critical data as these documents may be discarded or destroyed without traceability. In addition, uncontrolled records may not be designed to correctly record critical data. It may be easier to falsify uncontrolled records.

DI Guidance – *"Instructions" Table*

What to Do
How, When, Where….
(e.g. 8.10)

Table

How should records be corrected?	Specific elements that should be checked when reviewing records:
Details…	*Details….*

What to Check….

Very Structured Content
– "*Instructional*" / *Directional* in nature

Table Format Applies to Sub-Sections:
8.7, 8.8, 8.10, 8.12

Example 8.10 – True copies….

Item	How should the "true copy" be issued and controlled?	Specific elements that should be checked when reviewing records:
1.	Creating a "true copy" of a paper document. At the company who issues the true copy: - Obtain the original of the document to be copied - Photocopy the original document ensuring that no information from the original copy is lost;	Verify the procedure for the generation of true copies, and ensure that the generation method is controlled appropriately. Check that true copies issued are identical (complete and accurate) to original records. Copied records

High Level DI Comparison

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Source	Title	Pages / Words	Scope / Format	Comments and Recommendations (*Pick*, *Concern*, *Useful*) *(2 sets of complementary guidance documents…)*
FDA	Data Integrity and Compliance With Drug CGMP	17 5,805 *(2018)*	cGMP Q & A	• Easiest to understand the - *"WHY"* - of FDA Focus *(Q&A format).* • CFR *Complexity (e.g. "Legal" wording & FDA "Cite ID") – hard to deeply understand CFR requirements (if "new" to Data Integrity).*
MHRA Regulating Medicines and Medical Devices	"GXP" Data Integrity Guidance and Definitions	21 7,836 *(2018)*	GXP Principles	• Wide GXP scope, strength: definition of terms / EXPLANATION of DI principles and interpretation of requirements. • Understand Data Integrity Principles *– APPLY to all situations.* • Harmonized to incorporate industry feedback.
WHO	Guidance on good data and record management practices	46 15,486 *(2016)*	GXP *More Granular*	• Holistically, greater scope than the other 3. • Best structure and description of ALCOA. • Document Practice *(Section 9)*. • Governance is Key.
PIC/S	Good Practices for Data Management and Integrity in Regulated GMP.GDP Environments	52 19,321 *(2018)*	GMP/ GDP *More Granular*	• Sections 8 (*paper*) and 9 (*computer*) based systems…, particularly the *"Expectation"* and *"Instructional"* Tables • Good for understanding Data Integrity Risks. • Mapping of ALCOA against EU and PIC/S GMP. • Most "*instructional*" / *"Directional"* of all the guidance.

Change = Clarity of Requirements / "Continued Focus" !

- *"Pick and Mix" !*

"Houston (Regulator) We Have a Problem"

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What does the guidance say about *"Show and Tell"* ?

Notify Regulator Vs *"Whistle Blower"…….*
(Case Studies in Bob's Presentation)

Key Guidance Areas

FDA

Q 15 — *"Can an internal tip or information regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?"*

- No….. *Must* be fully investigated under cGMP
- *"FDA Invites individuals to report"…* DrugInfo@fda.hhs.gov

Q 18 — *Refers to Application Integrity Policy……*

MHRA

3.9 — *"Appropriate notification to regulatory authorities should be made where significant data integrity incidents have been identified".*

WHO

4.7 — Quality Culture – *transparent and open reporting…*

5.1 — QMS Requirement – *mechanism for staff to report….*

12.1 — Investigation - Notify Health Authorities – *material impact*

PIC/S

5.2.3 — Data Governance – *…communication of expectations…. empowerment to report failures…*

6.1.2 — Quality Culture *– control measures cover open / closed…*

6.2.5 — Ethics/Policies – *…confidential escalation program*

Additional Reference Information

MHRA Labs. Symposium

13th March 2019

Symposium Highlights…..

- Agenda
  - Practical Applications of DI
  - QC / QA
  - Method Validation
  - "*Live*" Inspection Interviews
  - Electronic "*Polling*" tool / Q
- MHRA - High DI "*Expectations*"
  - Workflow Mapping…..
  - Risk Assessment
- Data Integrity "*Weaknesses*":
  - *Don't Publicise* (*e.g. restrict to people who "need to know" – to correct*)
  - *Corrective Action* (*"fix"*)…..

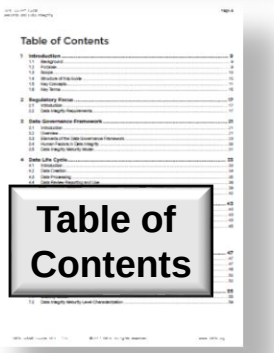
"*GXP*" Range of MHRA Guidance……

GAMP DATA INTEGRITY GUIDANCE

GAMP - RDI

Contents *(35 pages)*

1. **Introduction** *(6 pages)*
2. **Regulatory Focus** *(4 pages)*
3. **Data Governance Framework** *(11 pages)*
4. **Data Life Cycle** *(10 pages)*
5. **Quality Risk Management** *(4 pages)*



Appendices *(107 pages)*

Management *(46 Pages)*

- 6. *Corporate Data Integrity*
- 7. *Data Integrity Maturity Model (11 pages)*
- 8. *Human Factors*
- 9. *Data Audit Trail and Audit Trail Review*
- 10. *Data Auditing and Periodic Review*
- 11. *Inspection Readiness*
- 12. *Integrating DI Into Records Mgt…..*

Development *(28 Pages)*

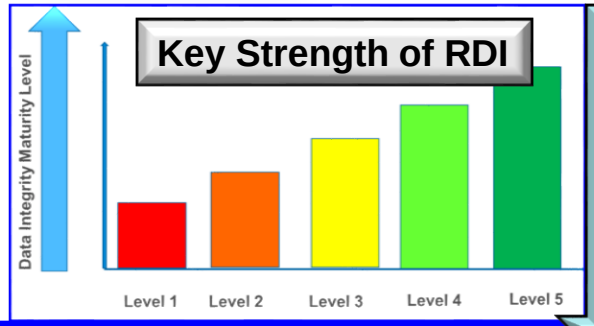
- 13. *User Requirements*
  - 19 Technical Requirements
  - 26 Procedural Requirements
- 14. *Process Mapping and Interfaces*
- 15. *Risk Control Measures…..*
- 16. *Data Integrity Concerns – Architecture....*
- 17. *Data Integrity for End-User Applications*

Operational *(15 Pages)*

- 18. *Retention, Archiving, and Migration*
- 19. *Paper Records and Hybrid Systems*

General *(11 Pages)*

- 20. *References*
- 21. *Glossary*



1st May GSK Stevenage

GAMP - Key Concepts

RDI

Good Practice Guide

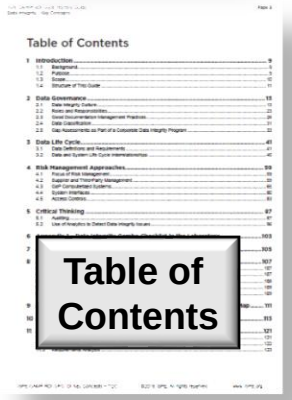


Table of Contents

Contents *(93 pages)*

1. Introduction *(3 pages)*
2. Data Governance *(27 pages)*
3. Data Life Cycle *(18 pages)*
4. Risk Management Approaches *(27 pages)*
5. Critical Thinking *(16 pages)*

23 Appendices *(89 pages)*

1. *Data Integrity Gemba Checklist in the Lab.*
2. *IMPACT Tool Applied to Data Integrity*
3. *Corporate Data Integrity Program Case Study*
4. *Culture and Continuous Improvement Capability Road Map*
5. *Regulatory Definitions of Data Terminology*
6. *Requirements Planning*
7. *Requirements Specification and Data Integrity Risk for Interfaces*
8. *Example of a Four-Tier Classification System of a Life Science Company*
9. *Security Controls*
10. *Case Study: DBA and Security Controls for an RTSM System in a GCP*
11. *Case Study: DBA and Security Controls for an ERP System in a Medical Device Manufacturing Environment*
12. *Case Study: Laboratory Computerized System*
13. *Case Study: Uncontrolled Spreadsheet*
14. *Case Study: Process Control System*
15. *Case Study: Business Application System*
16. *Reviewing Laboratory Systems*
17. *Reviewing IT Systems*
18. *Reviewing Supporting Data*
19. *Auditing Access Controls*
20. *Regulatory Guidance Regarding Classification of Deficiencies*
21. *Detecting Aberrant Results*
22. *References (65)*
23. *Glossary*

Data Integrity Risks/ Issues

What to Audit

DI Guidance – ALCOA CFR References

1st May GSK Stevenage

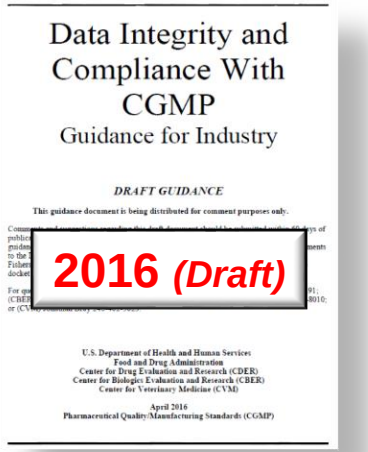
***A**ttributable*	**A**	211.101(d), 211.122, 211.188(b)(11), 212.50(c)(10)
***L**egible*	**L**	211.180(c), 212.110(b)
***C**ontemporaneous*	**C**	211.100(b), 211.160(a)
***O**riginal*	**O**	211.180, 211.194(a)
***A**ccurate*	**A**	211.22(a), 211.68, 211.188, 212.60(g)

[4] For attributable, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for legible see §§ 211.180(e) and 212.110(b); for contemporaneously recorded (at the time of performance) see §§ 211.100(b) and 211.160(a); for original or a true copy see §§ 211.180 and 211.194(a); and for accurate see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

No Changes Between 2016 (Draft) and 2018 (Final Guidance) – Above is from 2016 (Draft)

Changes to FDA Guidance:

Permission to share Annotated Files From - Robert Wherry - Takeda

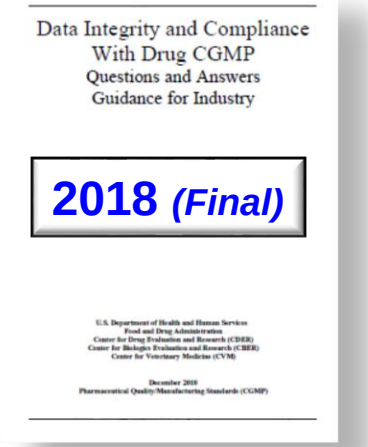


Deletions from the 2016 draft guidance:

Example – *Question 4 Answer*

How should access to CGMP computer systems be restricted ?

If these independent security role assignments are not practical for small operations or facilities with few employees, such as PET or medical gas facilities, FDA recommends alternate control strategies be implemented.[7] For example, in the rare instance that the same person is required to hold the system administrator role and to be responsible for the content of the records, FDA suggests having a second person review settings and content. If second-person review is not possible, the Agency recommends that the person recheck settings and his or her own work.



Changes highlighted with annotation:

Example – *Question 4 Answer*

Change in wording and annotation (see example below):

3. Does each CGMP workflow on a computer system need to be validated?

Yes, a CGMP 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)). The extent of validation studies should be commensurate with the risk posed by the automated system. When the same system is used to perform both CGMP and non-CGMP functions, the potential for non-CGMP functions to affect CGMP operations should be assessed and mitigated appropriately.[10]

Risk-based validation

DI Guidance – Index Map

MHRA 2016 DI Guidance *(Draft Version for consultation)*

- Background
- Introduction
- Establishing data criticality and inherent integrity risk
  Figure 1
- Designing systems to assure data quality and integrity
- Definitions and guidance
  1. Data
  2. Raw data *(GCP: synonymous with 'source data')*
  3. Metadata
  4. Data Integrity
  5. Data Governance
  6. Data Lifecycle
  7. Data transfer / migration
  8. Data Processing
  9. Recording data
  10. Excluding data
  11.1 Original Record
  11.2 True Copy
  12. Computer system transactions
  13. Audit Trail
  14. Electronic signatures
  15. Data Review
  16. Computerised system access / Sys. Admin. Roles
  17.1 Archive
  17.2 Backup
  18.1 Flat files
  18.2 Relational databases
  19. Validation – for intended purpose
  20. Cloud providers and virtual services / platforms…etc.

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MHRA 2018 DI Guidance *(Version 1)*

- Cover Page
- Table of Contents

1. Background
2. Introduction
3. The principles of data integrity
4. Establishing data criticality and inherent integrity risk
5. Designing systems and processes to assure data integrity: creating the 'right environment'
6. Definitions of terms and interpretation of requirements
   - 6.1 Data
   - 6.2 Raw data *(synonymous with 'source data' which is defined in ICH GCP)*
   - 6.3 Metadata
   - 6.4 Data Integrity
   - 6.5 Data Governance
   - 6.6 Data Lifecycle
   - 6.7 Recording and collection of data
   - 6.8 Data transfer / migration
   - 6.9 Data Processing
   - 6.10 Excluding data
   - 6.11.1 Original record
   - 6.11.2 True copy
   - 6.12 Computer system transactions
   - 6.13 Audit Trail
   - 6.14 Electronic signatures
   - 6.15 Data review and approval
   - 6.16 Computerised system user access / system administrator roles
   - 6.17.1 Archive
   - 6.17.2 Backup
   - 6.18 File structure
   - 6.19 Validation – for intended purpose *(GMP; See also Annex 11, 15)*
   - 6.20 IT Suppliers and Service Providers
7. Glossary
8. References

New

– A Key Component in Regulatory Collaboration

Dr. Margret Hamburg
(Former FDA Commissioner)

Mr Tor Graberg
(Former PIC/S Chair)

Keynote address to the PIC/S 40th Anniversary Symposium
(Dr. Margaret Hamburg):

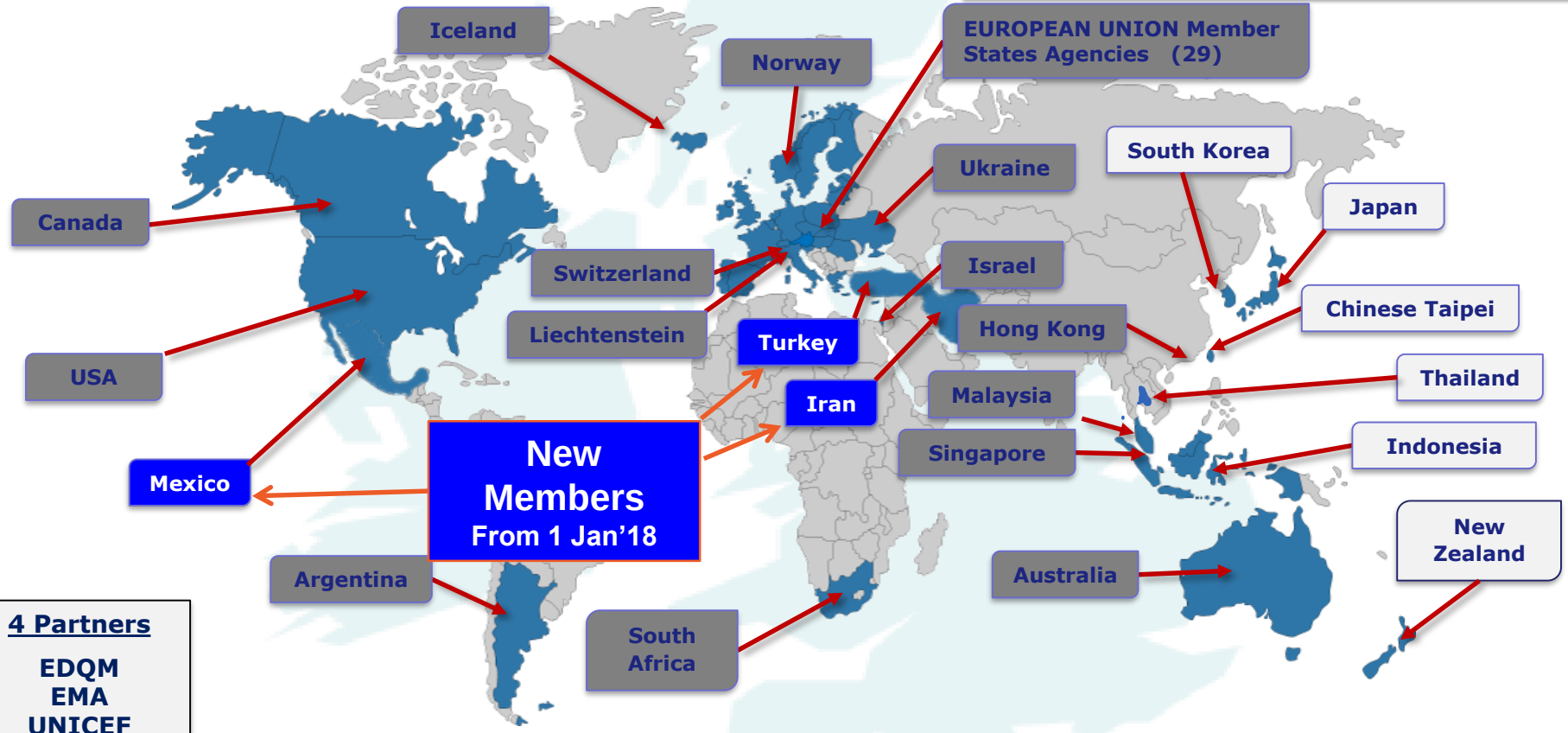
"PIC/S' main advantage over a Mutual Recognition Agreement is that it is not legally binding…." ***Dr. Margaret Hamburg***

52 PIC/S Member Authorities

(1 January 2018)

EUROPEAN UNION Member States Agencies (29)

Austria	Belgium	Croatia	Czech Rep(H&V)	Cyprus (H)
Denmark	Estonia	Finland	France (H&V)	Germany
Greece	Hungary (H)	Ireland	Italy	Latvia
Lithuania	Malta	Netherlands	Poland	Portugal
Romania	Slovak Rep.	Slovenia	Spain	Sweden
UK (H&V)				



4 Partners

EDQM
EMA
UNICEF
WHO

Candidates for PIC/S Membership

(on 1st June 2018)

Applicants *(Up to 6 years)*	Pre–Applicants *(Gap Analysis by PIC/S)*	Interested
• Italy (vet)	• Russia	• Bulgaria
• Brazil	• Pakistan	• Hungary (vet)
• Armenia	• Saudi Arabia	• Nigeria
		• China (CFDA)
		• India (CDSCO)
		• Vietnam
		• Philippines

Colour coding for different regions

Americas Asia
Europe Africa

Update Provided by – Bob Tribe
(Retired Chief GMP Inspector - TGA)

1st May GSK Stevenage

What Triggered - the Data Integrity Focus ?

ISPE | GAMP UK CoP
ISPE, the Developers of GAMP®

Examples of Influential Data Integrity Events

Differences Between Computer Records and *Paper Print Outs*:

"Those who forget the past are condemned to repeat it" (Joanna Gallant):

1993 – Barr Ruling – *Testing into compliance* – *Sued the FDA, "OOS"*

2005 – Able Laboratories – Fraud case – "*Let's go straight to Consent Decree*"

- FDA Page
- Legal

2006 – 2009 – Repeat Violations - FDA Warning Letters – *Ignored FDA Actions*

2012 – Consent Decree – Application Integrity Policy (AIP)…… *"Telephone System"*

- Consent Decree *(see Page 11, X for Telephone Requirement)*
- FDA Page

Difference

1st May GSK Stevenage

FDA Remediation……

ISPE | GAMP UK CoP
ISPE, the Developers of GAMP®

MARCS-CMS 487471 — 06/09/2016

FDA Recommendations…..

- **A** *Investigate Extent*
- **B** *Risk Assessment*
- **C** *Management Strategy*

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified evaluate all data integrity lapses.

FDA Remediation

A *Investigate Extent*

- Investigation Protocol / Methodology…… *Scope*
- Interview: Current / Former Employees….. *Root Cause*
- Extent…. *Report All Deficiencies*
- Deeper Investigation of Breaches…… *3rd Party*

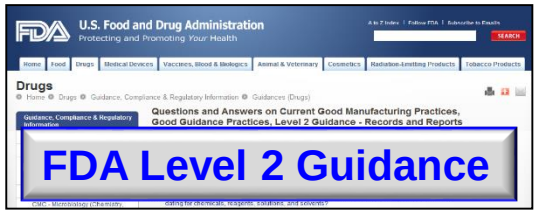
B *Risk Assessment*

- Impact of Data Integrity Lapses…… *On Drug Quality*

C *Management Strategy*

- Detailed Corrective Action…… *to Ensure* *Reliability* / *Completeness*
- Comprehensive Description…… *Root Cause*
- Interim Measures …… *Actions*
- Long Term Measures…… *Actions*
- Report…… *Status*

FDA - Level 2 Guidance



Technical Explanation…….

Some in industry misinterpret the following text

August 2003 Scope and Applications:

164 Under the narrow interpretation of the scope of part 11, with respect to records required to be
165 maintained under predicate rules or submitted to FDA, when persons choose to use records in
166 electronic format in place of paper format, part 11 would apply. On the other hand, when
167 persons use computers to generate paper printouts of electronic records, and those paper records
168 meet all the requirements of the applicable predicate rules and persons rely on the paper records
169 to perform their regulated activities, FDA would generally not consider persons to be "using
170 electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the
171 use of computer systems in the generation of paper records would not trigger part 11.

From Level 2 Guidance

"For High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) systems…."

21 CFR 211.68 ……. ***"Exact and Complete"***

21 CFR 211.180 (d) …… ***"Original Records or True Copies"***

"Electronic records themselves to be retained and maintained…."

"Printed chromatograms do not satisfy the predicate rules….."

ISO 17025

Data Integrity and ISO 17025

***A**ttributable*	**A**	-	*Clause:* **7.5.1**	*("…technical records shall include the data and identity of personnel responsible for each activity and for checking data and results")*
***L**egible*	**L**	-	*Clause:* **7.5.2**	*("…ensure that amendments to technical records can be traced to previous versions or to original observations")*
***C**ontemporaneous*	**C**	-	*Clause:* **7.5.1**	*("Original observations, date and calculations should be recorded at the time they are made…")*
***O**riginal*	**O**	-	*Clause:* **7.5.2**	*("…original and amended data shall be retained")*
***A**ccurate*	**A**	-	*Clause:* **7.11.3 c)**	*("….provides conditions which safeguard the accuracy of manual recording and transcriptions")*

\+

- **Complete -** **7.11.3 e)**
- **Consistent -** **7.11.6**
- **Enduring -** **7.11.3 b)**
- **Available -** **8.4.2**