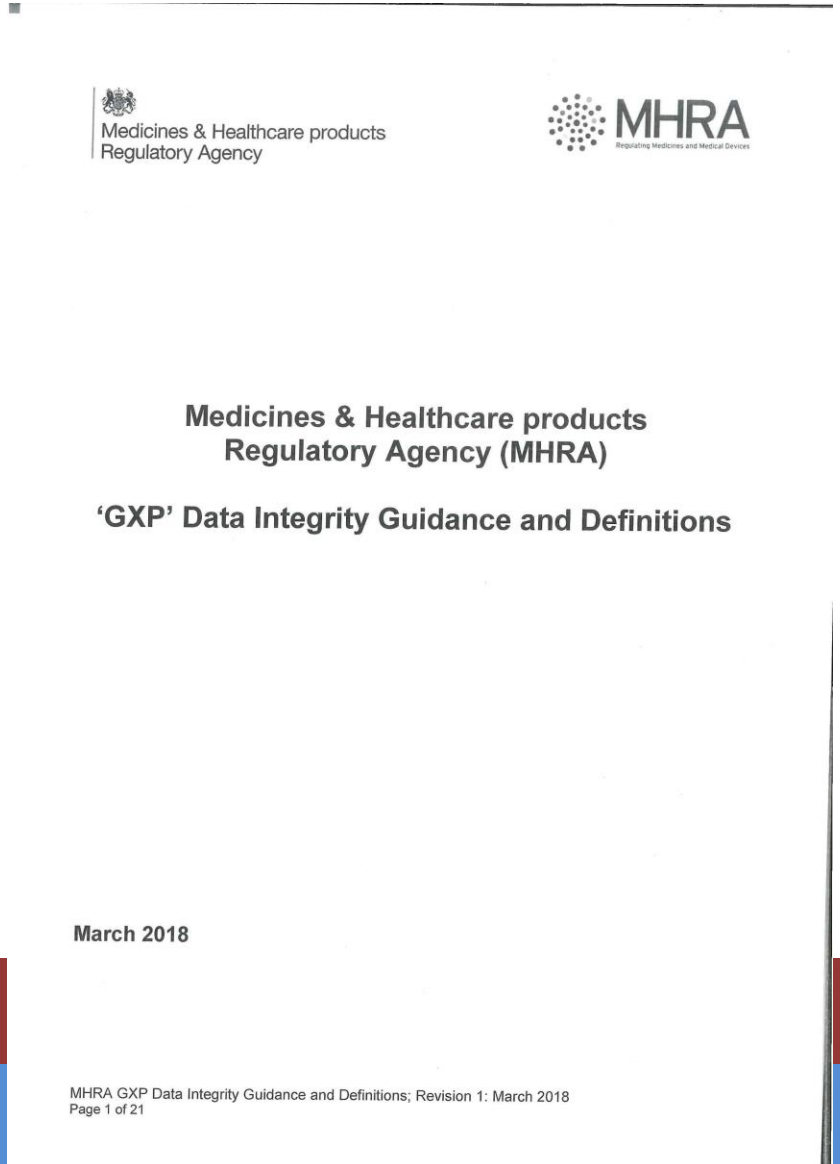
MHRA GxP Data Integrity Guideline, Mar-2018


Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

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
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MHRA Data Integrity Guidance, March 2018

Presented by Philip Butson, 15-Nov-2018

RQA

Disclaimer and Acknowledgements

- This presentation is intended for educational purposes only and does not replace independent professional judgement.
- Statements of facts and opinions expressed are those of the presenter and not those of RQA, GSK or any other organisation that I am associated with.

- Thanks to my GSK colleagues Jon Bartlett and Greg Webber, and RQA cross-GxP Data Integrity Team leader, Louise Mawer, for commenting on my draft.

Outline

- Background
  - Data integrity requirements in the GxPs
  - Increasing regulatory focus
  - New guidelines
- The MHRA 2018 guidance document
  - Outline
  - Changes from the 2015 guideline
- Challenges
- MHRA Blogs
- Conclusion

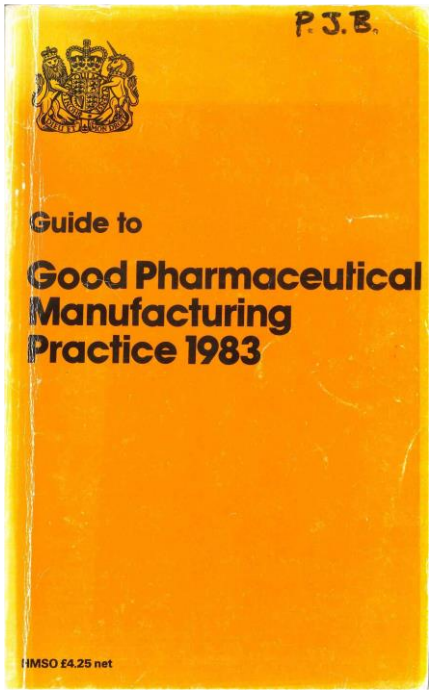
DATA INTEGRITY IS NOT NEW…

GLP – Regulations arose from data fraud

- Industrial Bio-Test 1976/77:
  - 618 of 867 (71%) of studies audited by the FDA were invalidated for having "numerous discrepancies between the study conduct and data
  - Three senior staff convicted of fabricating key product safety test data
  - Safety of a number of drugs and chemicals called into question
- US FDA Final Rule, Dec 1978 (21 CFR 58)
- 58.33 Study Director shall assure:
  All experimental data … are accurately recorded and verified
  Corrective action is taken and documented [if any circumstances impact quality and integrity of study]
- 58.35 (Independent) Quality assurance unit shall:
  - Assure management that … records … are in conformance with regulations
- 58.190 All raw data, documentation… shall be retained [in controlled archive]

GMP – ALCOA+ already evident in 1983!

3.1 (f) Persons making entries should do so in clear legible writing, and should confirm the entry by adding their initials or signatures. [Legible, Attributable]
(g) Entries should be made in ink or other indelible medium [Enduring]



3.3 If an error is made … it should be corrected in such a manner that the original entry is not lost and the correction initialled and dated. [Accurate, Original, Legible, Attributable, Contemporaneous]

3.6 An out-dated or superseded document should be removed from active use, and a copy retained for reference. [Accurate, Enduring/Available]

3.33 During manufacture the following should be entered onto the … Record, at the time that each action is taken: [Contemporaneous]

3.48 Original documents should be retained for at least six months after the batch to which they relate is first sold or supplied. They should not be destroyed until any copies made from them have been checked against them for completeness and legibility. [Original/True Copy, Legible, Enduring/Available]

GCP – Can see in the original ICH E6, 1995

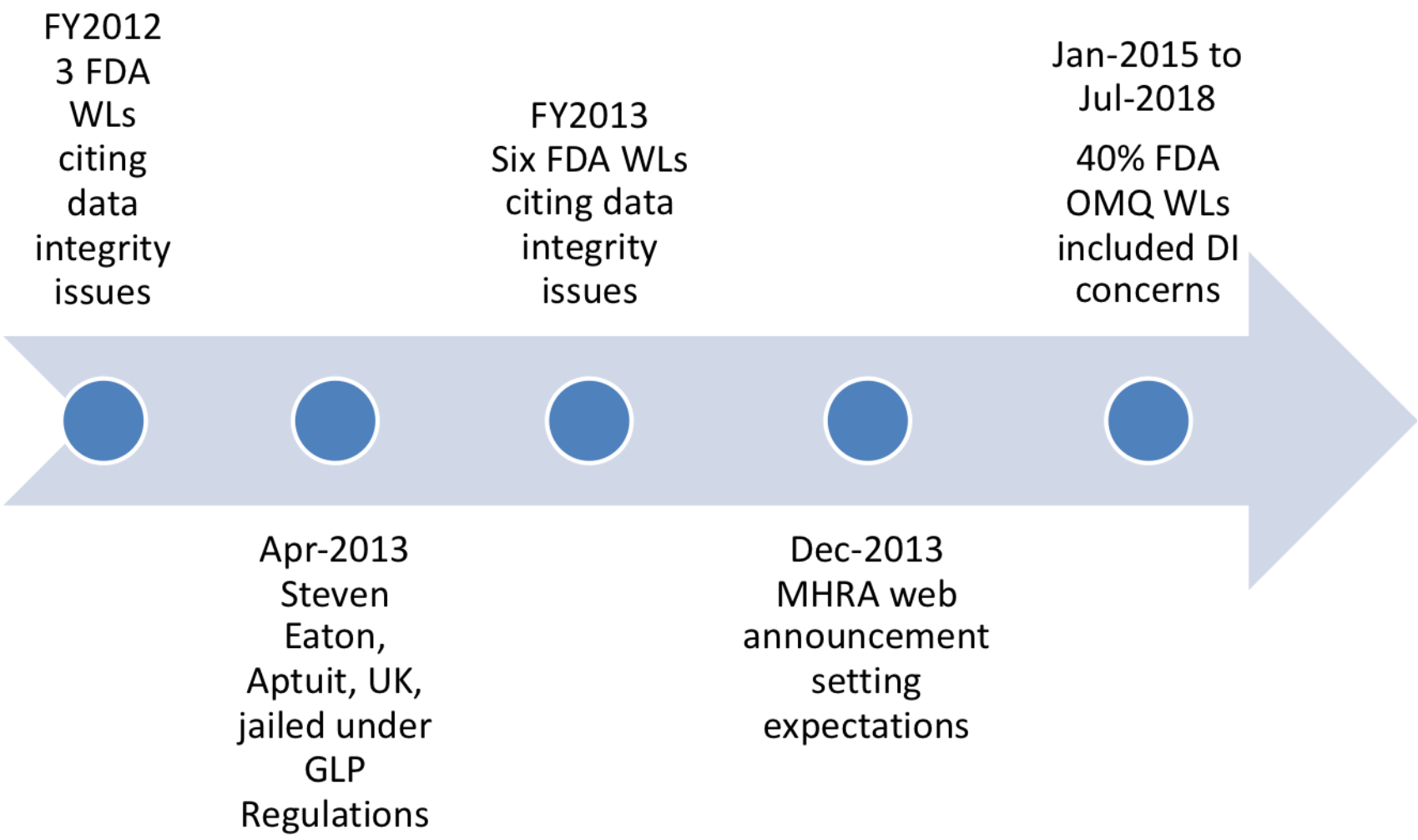
- **1.24 Good Clinical Practice (GCP)**
- A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
- **1.51 Source Data**
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- 4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- 4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- 5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
- 5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:
- a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

GxP computerised systems

- Regulators also recognised the shift from paper to electronic records and started to issue specific guidance relating to these:
  - OECD '*The Application of the Principles of GLP to Computerised Systems*' (1995) **Revised 2016**
  - EU GMP Annex 11 '*Computerised Systems*' (pre-1993) **Rev 2011**
  - FDA 21 CFR Part 11 '*Electronic Records; Electronic Signatures; Final Rule*' (1997)
  - FDA '*General Principles of Software Validation; Final Guidance for Industry and FDA Staff*' (2002, following 1997 draft)
  - FDA Guidance for Industry '*Part 11, Electronic Records; Electronic Signatures – Scope and Application*' (2003)
  - FDA 'Guidance for Industry Computerized Systems Used in Clinical Investigations' (1999) **Revised 2007**
  - PIC/S '*Good Practices for Computerised Systems in Regulated 'GXP' Environments*' (2007)

BUT THERE HAS BEEN A LOT OF FOCUS OVER THE PAST 6 YEARS OR SO…

Regulatory action



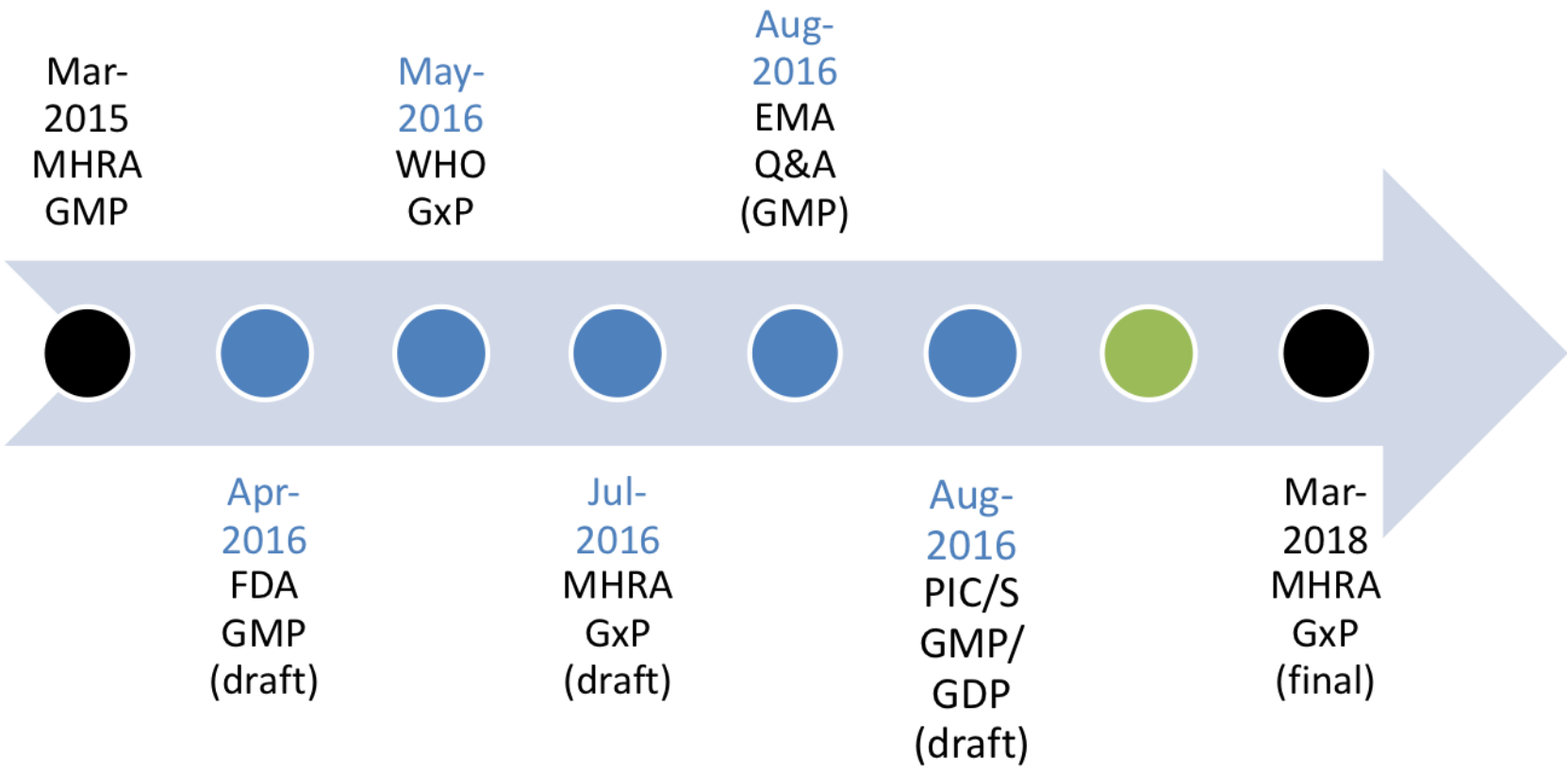
Further information on Regulatory actions

- 40% FDA OMQ WL issued to drug manufacturers between Jan-2015 and Jul-2018 cited data integrity issues
- 111 WLs containing data integrity deficiencies were issued between Oct-2012 and Jul-2018
  - 50% to manufacturers of finished products
  - 43% to API manufacturers
  - 7% to firms manufacturing both API and finished products
- 156 EU Non-compliance notices issued by EU health authorities between 01-Jan-2012 and 16-Aug-2018; 49% cited data integrity issues
  - 43% from manufacturing areas
  - 12% from laboratories
  - 35% from both

Source: Pink Sheet, 11 and 17-Oct-2018, based on presentation by Carmelo Rosa, division director in FDA's drug Office of Compliance

WHICH HAS LED TO A LOT OF NEW GUIDANCE…

New guidelines



Alignment of the guidelines

- Approaches – quite varied
- Level of detail – also varied
- Underlying principles – well aligned
  - ALCOA in all ['+' too, though not so visible]
- MHRA have been active in seeking to ensure alignment
  - PIC/S
  - EMA IWG
  - WHO
  - Bi-lateral agreement with US FDA – joint event in 2018
  - OECD – GLP – expected in 2019

ON TO THE LATEST MHRA GUIDELINE

Outline

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. Definition of terms and interpretation of requirements (20 subs)
7. Glossary
8. References

Definitions of terms and interpretations

1. Data
2. Raw data (source data)
3. Metadata
4. Data integrity
5. Data governance
6. Data lifecycle
7. Recording and collection of data
8. Data transfer / migration
9. Data processing
10. Excluding data
11. Original record and true copy
12. Computerised system transactions
13. Audit trail
14. Electronic signatures
15. Data review and approval
16. Computerised system user access / system administrator roles
17. Data retention (archive / backup)
18. File structure
19. Validation for intended purpose
20. IT suppliers and service providers (including cloud, SaaS, PaaS, IaaS)

What has changed?

- Format-wise – almost everything!
- Scope – of course! – now GxP, not just GMP
- Details – a lot of minor points; a few that are more significant – see following
- Principles – only the wording; the underlying principles have not changed at all

Principles

- Starting point = organisational culture
  - Key role of senior management behaviour
  - Policy from highest level in organisation
- ALCOA(+)
- Applies to both paper-based manual systems and automated or computerised systems
- Build quality in
  - Design and implement systems supporting data integrity
  - NOT expected to implement a forensic approach to data checking on a routine basis

Principles

- Risk-based approach
  - DIRA: Data integrity risk assessment – map processes
  - Identify: data criticality and inherent risks
  - Effort and resource commensurate with risk – impact of a data integrity failure on the patient or environment
- Where weaknesses identified – CAPA – think holistically across activities and systems, not in isolation
- Appropriate notification to regulatory authorities if significant data integrity incidents are identified

Additions

- The following sections have no equivalent in the 2015 guideline:
  - 6.7: Recording and collection of data
  - 6.8: Data transfer / migration
  - 6.9: Data processing
  - 6.10: Excluding data
  - 6.14: Electronic signatures
  - 6.20: IT suppliers and service providers, including ‘cloud’

Deletions

- ‘Primary record’

“The record which takes primacy in cases where data that are collected and retained concurrently by more than one method fail to concur.”

- “… by the end of 2017”
  - 6.13 and 6.16: Replaced by general statements about compliance with current regulatory expectations
- “at least 2 years of data … for … inspection”
  - 6.5: More general “data are readily available… on request”
- Spectrum of complexity & Details around computer system transactions
  - Reduced detail as part of revision, but principles remain part of risk assessing data lifecycle and in 6.12

Other points

- 6.15: Data review and approval - Much of the text here is new and significantly expands the text on 'Data review' in the 2015 guideline.
  - Risk-based – data, metadata, relevant audit trails
  - Routine reviews and periodic audits
  - Procedure – review; approval; action if error/omission
  - Documented, including "a positive statement regarding whether issues were found or not"
  - Third party reviews and summary data reports
  - Use of computer system custom reports

Challenges?

- Demonstrating compliance
- Taking a risk-based approach
- Understanding data risk, criticality and lifecycle
- The complexity of our systems and processes
- Hybrid systems
- Evolving technologies
- Frame of mind

Organisational culture

MHRA Blogs on data integrity

https://mhrainspectorate.blog.gov.uk/ and search for 'data integrity'

- Three-part series on 'Good Manufacturing Practice (GMP) data integrity: a new look at an old topic'
  - 2015/06/25 2015/07/14 2015/08/27
- ePRO – An Inspector's Perspective 2016/07/07
- MHRA data integrity guidance: 18 months on 2016/07/21
- Two-part series on 'a behavioural approach to data integrity'
  - 2017/03/10 2017/03/30
- I don't believe it! 2018/05/25
  - As an inspector, when reviewing data I ask myself ''does this data matter (i.e. is it critical) and if so, can I trust what I see?''

Conclusion

- Data integrity is not a new requirement, but…
- … Issues have led to more regulatory action and the issue of new guidance for industry
- Revised MHRA guidance
  - Recognises importance across all GxPs
  - Is well aligned with other guidance documents
  - Is helpful!
- Strong Principles and Risk-Based Approach are key
- Details worth working through
- Use resources such as the MHRA Blogs to help you