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Observations on the latest revision to EU GMP for Computerised Systems

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Introduction

A personal review from a retired MHRA Senior Inspector.

Comments

New Annex 11 is more detailed than its predecessor. Now structured into a Principle, General, Project and Operational Phases and seventeen detailed sections (1. Risk Management, 2. Personnel, 3. Suppliers and Service Providers, 4. Validation, 5. Data, 6. Accuracy Checks, 7. Data Storage, 8. Printouts, 9. Audit Trails, 10. Change and Configuration Management 11. Periodic evaluation, 12. Security, 13. Incident Management, 14. Electronic Signature, 15. Batch Release, 16. Business Continuity, 17. Archiving) followed by a brief glossary. It offers a new benchmark to GxP disciplines beyond GMP.

Significant content includes: risk management, suppliers and service providers (substantial new sections 3.1 to 3.4 replacing old 18), validation (previous dispersed sections (2, 4 and 7) have been deleted and replaced with weighty clauses 4.1 to 4.8), periodic evaluation, (new section 11 replacing lightweight clause 17), security, (previous clause 8 on 'data-entry' replaced with sections 12.1 to 12.40), incident management (new section 13), electronic signature (brief new section 14), batch release (new section 15 covering identity of QP, certification and electronic signature replaces previous outdated clause 19).

The substantive requirements of current GMP Chapter 4 'Documentation' section '4.9' (concerning electronic data records) are now updated and incorporated in the 'Principle' to revised Chapter 4 (also implemented on 30th June 2011) and the revised Annex 11 (9. Audit Trails, 7. Data Storage, 12. Security etc.). New Chapter 4 specifies a broader range of GMP documentation, linking at last to an electronic age!

Risk management applies to patient safety, data integrity and product quality. A11 (1) makes it clear that this concern applies throughout the lifecycle of the computerised system. Where a regulated user has trust and confidence in suppliers following a justified and documented risk assessment then duplication of effort can be minimised.

A11 (2) requires all relevant personnel have appropriate qualifications, defined access levels and responsibilities to carry out their assigned duties. Project records should address this.

Compliance requirements for third parties who install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service, or for data processing, are found in A11 (3). Internal IT departments are regarded as 'analogous' in this context. Evidence of compliance and cooperation could include: formal agreements, (A11 3.1) and a demonstration of competence and reliability, as per A11 (3.2); if necessary a risk assessed audit or assessment report, (available for an Inspector to study if requested), as in A11 3.2/3.4; URS compliant documentation (reviewed and sourced from assessed suppliers) in support of commercial off the shelf products, as per A11 (3.3).

Annex 11 (4) (Validation) enables the optimising of effort between all parties. The validation documentation set A11 (4.1) requires 'manufacturers', (suppliers and possibly users) to justify their standards, protocols, acceptance criteria, procedures and records via risk assessment. Foundation sets of project standards and procedures may assist. Lists of relevant documents linked in the formal agreement, or VMP (and possibly audit report, for complex systems).

Requirements for change control records and reports of deviations during the project validation phase A11 (4.2) may (for complex projects) require a high level of cooperation by third parties involved to enable review of such records. This also supports the assessment of fitness for purpose

A11 (4.3) requires up to date GMP system inventories with additional requirements for critical systems in respect of data, processes, interfaces, system issues and security. Note: whilst 'applications' have to be validated, IT infrastructure can be 'qualified' (A11 - Principle). The

complexity of projects and degree of third party involvement will determine the need for ongoing access to updated information for evolving systems from third parties.

A11 (4.4), User Requirements Specifications based on documented risk assessment and GMP impact are required and should be traceable throughout the life-cycle.

Annex 11 (4.5) refers to the formal assessment of suppliers by a regulated user to demonstrate that system elements are developed in accord with an appropriate QMS. Confidence in the developers will support an end project goal of fitness for purpose.

Section A11 (4.6) refers specifically to custom or bespoke computerised systems and requires the formal assessment and reporting of quality and performance measures for all the lifecycle stages of such systems. Where such complex projects involve not only the supplier/developer, but also integrators and other contract staff, then control, coordination and cooperation are essential. The Validation Master Plan (VMP) and formal agreements between the parties should cover data and knowledge sharing to ensure optimal cooperation to achieve a product that will be fit for purpose.

Section A11 (4.7) provides opportunities to share supplier and customer knowledge and methodologies with evidence of appropriate test methods and scenarios, including system process parameter limits, data limits and error handling. Automated testing tools and test environments need to have documented assessments for their adequacy. Where suppliers hold relevant original information this may need to be made accessible to the regulated user (and possibly to an Inspector) as evidence in support of the specific compliance requirement. Responsibilities should be clearly defined in the formal agreement and VMP, as before.

Data integrity issues are addressed specifically in 'validation' section A11 (4.8) and extensively in the subsequent 'operational phase': Sections 5 to 17. Section A11 (4.8) (new) - concerns validation of the migration or transfer of data.

Comments re: new 'Operational Phase' Annex 11 sections 5 to 17:

5 (new) - concerns 'data' and the electronic exchange of data with other systems.

6 (revised text) – concerns 'accuracy checks' whilst linking accuracy and the potential consequences of errors to risk management.

7 'Data Storage' 7.1 (revised text) concerns physical and electronic security, readability and on-going access during retention. 7.2 (new, replacing old section 14) requires regular validated back-ups of relevant data and monitoring to ensure data integrity and accuracy during processing and restoration.

8 'Printouts' 8.1, essentially an edited old section 12, requiring the ability to print out copies of electronically stored data. 8.2 (new) requires that printouts supporting batch release should indicate any changes since original data entries.

9 'Audit Trails' (a revised and extended old section 10). Links the need for a system generated, intelligible, GMP data relevant audit trail, to a risk assessment; important in the context of GMP relevant changes and deletions supporting batch release.

10 'Change and Configuration Management' (simplifies and replaces old section 11). Any changes to computerised systems, including system configurations to be conducted in a controlled manner to a defined procedure.

11 'Periodic Evaluation' (enhanced text replacing old section 17), specific evaluations are called for to consider changes to system functionality, history, performance, reliability and security - inter-alia.

12 'Security' (enhanced text replacing old section 8). 12.1 specifying physical and/or logical controls to ensure only authorised access and use (including keys, pass cards, personal codes with passwords, biometrics, and restricted access).

12.2 Links security context to the criticality of the computerised system. 12.3 Changes to access authorisations to be recorded. 12.4 A 'management system' to record data processing entries and changes by operator/user with links to time and date.

13 'Incident Management' (new). For critical incidents this requires all system failures and data errors to be reported and assessed to determine root cause - as part of the firm's QMS for corrective and preventive actions (CAPA).

14 'Electronic Signature' (new). A brief set of statements specifying their relevance and context, linkage to relevant records and time and date when applied.

15 'Batch Release' (revised old section 19) links certification of batch release, qualified persons and the need for electronic signatures where certification and release are based on computerised systems.

16 'Business Continuity' (revised text replacing old sections 15 and 16). Robust alternative arrangements are required to support critical processes in the event of primary system failures. Appropriate responsive measures, adequately documented and tested, are required, dependent on risks and business consequences.

17 'Archiving' (new) permits electronic archiving subject to validated accessibility, readability and integrity, when first created and following any changes to the system or software.

Conclusions

Pharma-industry and suppliers/ developers

The revised GMP requirements essentially reflect current industry best practice and it is surprising that it has taken so many years for regulators to achieve some degree of 'catch-up'!

Leading industry guidance may be found in ISPE GAMP (Good Automated Manufacturing Practice) publications, including the 352 page GAMP-5, (A risk-based approach to compliant GxP computerised systems) ISBN-1-931879-61-3; also associated GAMP good practice guides (GPGs), (including: Testing and Validation for specific applications and notably: GPGs for 'IT Infrastructure, compliance and control' and 'A risk-based approach to compliant electronic records and signatures', 'Electronic archiving'). Visit www.ispe.org for more details.

Project validation strategies and planning documents, life-cycle elements and risk assessment records, all underpinned by robust quality management systems (implemented by all parties) will be key to deriving maximum collaborative benefit between project partners to ensure the fitness for purpose of the computerised system and its GMP compliance. In order to comply with Annex 11 (in particular, sections 1, 2, 3 and 4) suppliers and regulated users should define responsibilities for the provision of relevant documentation and records in support of validated project applications or services. A good starting point for agreeing and publishing intended deliverables and showing respective responsibilities, would be the VMP (and resulting reports). These, together with other key records such as supplier audit reports, formal agreements, life-cycle specifications, risk assessments, various testing reports, traceability matrices and other documents may need to be made available to Inspectors, depending on the nature of the computerised system.

Post implementation system compliance with 'Operational phase' GMP requirements (Annex 11 sections 5 to 17) will be determined largely by the regulated user's QMS, IT support and data processing controls. Further compliance information will be found in the PIC/S PI011 document (see below).

Inspection

The international inspectorate recommendation document: PIC/S PI011-3 (Good Practices for Computerised Systems in Regulated 'GxP' Environments, Pharmaceutical Inspection Convention, Geneva) is still current. This 50+ page document presaged the changes now made to EU GMP Annex 11. Readers may care to download the document from www.picscheme.org and carry out key word or phrase searches for terms used in relevant sections of Annex 11. Searches under 'risk management', 'data integrity', 'system security', 'back-up', audit trail', 'validation', 'GAMP guidance', 'electronic signature', 'inspection' yield prolific results for consideration. The PIC/S document has italicised text to highlight links to potential evidence to compliance for an inspector. Other relevant international consensus standards are ICH documents: Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) see www.ich.org; the TickIT Guide version 5.5, see www.tickit.org and ISO 9001 for software quality.

EU GMP references:

1. Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use:

Annex 11: Computerised Systems – revision 1, to be implemented 30th June 2011. Brussels: SANCO/C8/AM/sl/ares(2010)1064599.

2. Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use:

Chapter 4: Documentation – revision 1, to be implemented 30th June 2011.

Brussels: SANCO/C8/AM/sl/ares(2010)1064587.

Brief background to author:

Anthony Trill graduated with an honours degree in Pharmacy from the University of Aston. He also holds a Masters degree in Pharmaceutical Technology (London). Tony is registered as MRPharmS and listed as eligible to be a QP. He worked for 18+ years in the pharmaceutical industry for 3 multinationals and for 24+ years with the Medicines Inspectorate (MCA then MHRA). He retired from MHRA in 2008-09 where he had held the position of Senior Medicines Inspector responsible for a range of challenging GMP inspection requirements, standards and guidance matters. He was a founding member of GAMP Forum, worked as part of the original TickIT review panel and led the international specialist PIC/S team that drafted the PI011 document. Tony was also the Inspectorate liaison with RPS (Pharmaceutical Press) for the most recent revision to the 'Orange Guide'.

EDITOR'S NOTE: This article has been posted on PJ Online at the request of Mr Trill. It has not been edited by Journal staff.
