NEW ANNEX 11
EVOLUTION AND CONSEQUENCES

On 12 January 2011, after a 3-year long wait, the revised Annex 11 — Computerized Systems — to the European GMP Guide was released. This document, which is based on ICH Q9 principles and covers, more exhaustively than the first version, the life cycle of computerized systems, takes into account and focuses on a risk-based approach.

The genesis of the revised Annex 11 is likely to be found in the written work for the PIC/S Guide PI 011.[1] Indeed, the purpose of this Guide, released in 2003 (that is, around 10 years after the first version of Annex 11), is to provide recommendations to the inspectors — and consequently to the regulated user and its suppliers — for reviewing the implementation of Annex 11.[2] During 1992–2003, the use of computerized systems dramatically increased and the industry developed various approaches for fulfilling possible regulatory expectations.

Main Evolutions

The draft of Annex 11 released in 2008 specified too many details and needed some improvements regarding consistency. It received numerous comments (more than 1200 within 6 months) from the pharmaceutical industry and its suppliers. The revised 2011 version, although very similar to the initial version, is smaller than the draft and develops consistently, where necessary, the topics covered in the initial version:

- The necessity of mastering the life cycle — from requirement to retirement — is now an explicit requirement. This principle has been extended to the control of processes.
- IT infrastructures supporting regulated systems have to be "qualified" — they have to be kept under control throughout the life cycle of the supported systems. This requirement is not really new because it was widely implicit in the previous version of Annex 11, but explicit in PIC/S Guide PI 011, §17.3. It is also stipulated that internal IT departments, as well as external service providers, must be considered in the same way, particularly the need for formal service and operation level agreements (SLA, OLA) defining the operational conditions of supported applications and systems.
- The key principles of a science-based risk management derive directly from ICH Q9 focused on patient safety, product quality and data integrity.[3] Supplier management and service provider management rely on such consistent risk management as well. Although such requirements were not mentioned in the previous version of Annex 11, they were already part of PI 011.
- Different roles, such as system owner and process owner, are now clearly identified as major compliance players. Even though the definition of these roles is less detailed than described in GAMP 5, the stipulated responsibilities are essential.[4]
- Within the framework of risk-based compliance, supplier effort can be significantly leveraged provided they have been consistently assessed. It is expected, therefore, that "Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request."[5]
- The section concerning validation has been significantly improved and suggests the following:
  - The need to maintain an up-to-date system inventory — already mentioned in Annex 15

Industry Responses to the Revised Annex 11

Generally companies to which the revised Annex 11 applies fall into one of three categories:

- Mature companies that have to monitor computer system validation (CSV) activities and their results only a little more closely.
- Young companies that have experienced considerable trouble with the initial version of Annex 11 and continue to struggle with the new version. At the same time, FDA suggests that those companies that have noticeable CSV deficiencies also experience significant GMP deficiencies
- Companies that are unaware of the revised Annex 11, respectively ignoring European regulatory requirements and believing that only 21 CFR Part 11 is governing CSV. Surprisingly, such companies, including those in Europe, are common.

Specific areas of concern:

- applying a consistent risk-based approach
- improving supplier auditing practice
- managing suppliers efficiently
- performing efficiently periodic evaluation.

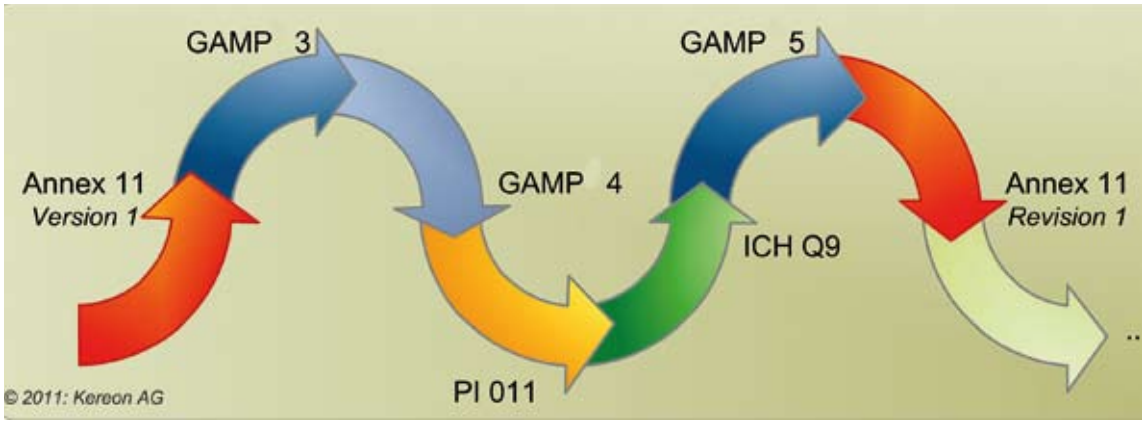

Figure 1: The revision of Annex 11 is the result of two decades' worth of iterative process.

and promoted in PI 011 — is now emphasized in Annex 11.[6]

- The necessity to ensure a systematic traceability throughout the life cycle of the computerized system is now required. Furthermore, it is expected that this traceability is based on a documented risk assessment and GxP impact.
- For critical systems, it is expected that a system description showing the system configuration, data flows and security measures is available.
- The regulated user can provide evidence of the pertinence of test methods and that test scenarios could be demonstrated. In addition, automated testing is acceptable so long as the adequacy of testing tools and test environments is documented. As automated testing tools can 'fit' into the GAMP Software Category 1, applying the recommendations and approaches promoted by the *GAMP Good Practice Guide: IT Infrastructure Control and Compliance* is one way for keeping such tools under control.
- For data that need to be converted to another format or transferred between two systems, it is necessary to validate such conversion or transfer and to include data verification in terms of value and meaning.
- The electronic signature is now officially recognized without becoming mandatory.
- The requirements regarding the operational phase are primarily based on good business and operation practices. Such requirements were widely mentioned in the previous version of Annex 11; some, however, have been developed in the new version.
- The operational requirements cover
  - data and accuracy checks
  - data storage
  - printouts
  - audit trails
  - change and configuration management
  - security
  - incident management
  - business continuity
  - archiving.
- In addition to Annex 15 clauses 23 and 45 (establishing since 2001 the need for a formal periodic evaluation), the new Annex 11 repeats explicitly this requirement for computerized systems.

Consequences

Although the new version of Annex 11 doesn't represent a revolution, it does have some implications, including

- Compliance decisions based on the results of risk management activities have to be justified. This expectation — already mentioned in PI 011 — is now mandatory, which implies that risk management activities must be conducted consistently and rigorously.
- The condition for leveraging supplier involvement is to put in place rigorous processes regarding supplier evaluation and selection, as well as supplier management. At the same time, the industry must make available audit information to inspectors, upon request (see clause 3.4).
- For critical systems, the need for a standalone, detailed description — in addition to the one embedded in the Validation Plan or in the User Requirements Specifications (URS) — as provided in the previous version of Annex 11 is reinforced. Such a document can be easily prepared based on the recommendations provided in *GAMP 5, Appendix D6 "System Descriptions."*
- The yearly revision of Validation Master Plans (VMP) offers an excellent opportunity for reviewing and maintaining an up-to-date system inventory.
- The supporting processes to the operational phase — already mentioned in the previous version of Annex 11 — are clearly stated. In addition, the requirement to evaluate periodically the systems' compliance enforces the importance of the operational supporting processes.


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THE REVISED ANNEX 11 REPRESENTS BOTH A RETURN TO THE ROOTS AND A SIGNIFICANT EVOLUTION IN COMPLIANCE MATURITY.

Annex 11 Versus 21 CFR Part 11

Annex 11 and 21 CFR Part 11 take different positions within their respective regulatory contexts. Whereas 21 CFR Part 11 discusses only the implementation of electronic records and electronic signatures within the GxP scope as defined in the predicate rules, Annex 11 focuses on the use of computerized systems in GMP environments. As such, the main requirements relating to system life cycle (until system retirement), supplier management, and qualification and validation activities as defined in Annex 11 can be summarized in 21 CFR Part 11 by paragraph 11.10(a), which stipulates that the validation of computerized systems is necessary and unavoidable for establishing electronic compliance. Furthermore, the revised Chapter 4 (concerning documentation) is much more detailed and prescriptive than 21 CFR Part 11.

The electronic signature manifestation is not explicitly identical in the both texts. 21 CFR Part 11 requires the signature meaning as part of the signature. Annex 11 does require it implicitly as signature meaning is in all cases a requirement for GxP documentation as stated in Chapters 1 and 4. Yet, except for batch release, which is specifically discussed in Annex 11, the impact of electronic signatures as equivalent handwritten signatures is limited to the boundary of the company.[7] Within a different legal context than in the EU (see 1999/93/EC and 2000/31/EC), 21 CFR Part 11 establishes electronic signatures as the "legally binding equivalent" to handwritten signatures. Nevertheless, both texts lay down the principle of an immutable link between the signature and the signed record as an essential compliance requirement.

Annex 11 does not stipulate that organizations must submit a declaration regarding the use of electronic signature for GxP activities to the EMA or other national Agencies. Similarly, those using an electronic signature do not have to provide a specific certification regarding its use.

Revised Chapter 4

Together with the revision of Annex 11, Chapter 4 of the European GMP Guide has been revised. This revision is limited as the enhancements concern mainly the use of electronic documents within the GMP context. Chapter 4, however, is an important document; yet regulated users are insufficiently familiar with it and fail to consistently apply it. Chapter 4 summarizes the requirements of GMP-related documentation activities, listing the various types of expected records and the corresponding retention periods, defining the processes for generating and controlling GMP documents, and reminding of the basic principles of Good Documentation Practices.

Convergence and Future Developments

The revision of Annex 11 — including Chapter 4 of the European GMP Guide — is the result of two decades'worth of iterative process (Figure 1). This process — based on a continuous sharing of experience between regulators and industry — has facilitated a demanding, but consistent, approach to electronic compliance commensurate to the criticality of the concerned processes to be defined. The convergence between regulatory requirements and industry recommendations, such as provided by GAMP, establishes a stable regulatory framework that enables the pharmaceutical industry and its suppliers to define a cost-effective and efficient approach to compliance.

The next version of the PIC/S Guide PI 011 should give regulators the opportunity to clarify the impact and the extent of some requirements, as well as details concernning the expected level of implementation. With regard to the draft for comment published in 2008, the revised Annex 11 represents both a return to the roots and a significant evolution in compliance maturity. **Pharma**

Notes

1. PIC/S, *Good Practices for Computerized Systems in Regulated GxP Environments* (September 2007).
2. PIC/S PI 011, footnote 1: "Throughout this document the 'users' (owners of the good practice computerized systems being inspected) are collectively referred to as 'regulated users' for clarity."
3. Within the European GMP, ICH Q9 has been initially established as Annex 20. Since February 2011, this document — as well as ICH Q10 — has been released as part of European GMP Part III.
4. ISPE, GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems (February 2008).
5. Annex 11:3.4.
6. Annex 15 to EU Guide to Good Manufacturing Practice (Volume 4) "Qualification and Validation" (2001).
7. The wording of this requirement is particularly important as it gives a more limited and pragmatic definition of the electronic signature than provided in the European Directives 1999/93/EC and 2000/31/EC.

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