What the Revised European Union’s Annex 11 Means to Life Science Companies
Introduction

When it comes to operations of life science companies, computerisation is inevitable. There is no turning back the clock of modernisation and globalisation. The recent revision of European Union's (EU) GMP Annex 11 on Computerised Systems was a response to this trend. It was meant to address problems stemming from an increasingly computerised GMP environment, in which computer programming can potentially replace human judgment.

What does this mean to life science companies and related suppliers currently in the EU market? First, Annex 11 is not a legal requirement but a guidance that applies to companies that manufacture or sell human and veterinary medicinal products in the 27 states belonging to the European Union.

While Annex 11 does not have the teeth of the U.S. FDA's 21 CFR Part 11 or similar regulations, it is key to compliance with GMP principles in these regulations: EU Directive 2003/94/EC covering human medicinal products and EU Directive 91/412/EEC covering veterinary medicines. Ignoring Annex 11, which interprets the directives, would be just as detrimental as ignoring the regulations.

Second, even though Annex 11 applies to pharmaceutical companies, it is also relevant to medical device and other life science companies. Martin Browning, president and co-founder of EduQuest and a former FDA investigator who helped in the drafting of Part 11, says medical device companies should align their activities with Annex 11. “Annex 11 represents the clearest thinking yet from the EU on the use of electronic record keeping and electronic signatures in a regulated environment. Complying now with Annex 11 will help medical device manufacturers go a long way toward meeting future European medical device expectations (especially from a notified body auditor’s viewpoint),” he said.

Key Changes in Annex 11

The revised Annex 11, which took effect in June 2011, provides that, “Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control, or quality assurance. There should be no increase in the overall risk of the process.” This is one of the three principles that appear up front. In this sense, Annex 11 shares the same goal as FDA’s 21 CFR Part 11: the use of safe computerised systems to ensure safe products.

The revised document covers more areas and provides more details than the old Annex 11. The following are some of the key changes.

Broader Scope: The revised Annex 11 applies to all computerised systems that are part of GMP-related activities, such as production, quality system, corrective and preventive action system, material supply, process controls, laboratory testing, clinical trials, records and documentation, and product release, storage, and distribution.
Emphasis on Validation: The second principle of Annex 11 states, “The application should be validated; IT infrastructure should be qualified.” The new document expounds on validation requirements, including documentation and process, under the “Project Phase” section. It requires periodic evaluation to confirm that computer systems are in a constant valid state. If data is transferred to another system, validation should be included during the migration process.

Inclusion of Electronic Signature and Archiving: Annex 11 now addresses electronic signatures and archiving. Electronic signatures should be permanently linked to the corresponding records and they should include the time and date they were applied. Data may be archived, but it should be checked for accessibility, readability, and integrity.

Risk Management: Regulated companies should apply risk management to computer systems. Annex 11 states, “As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.” Risk assessment is also recommended when deciding whether a supplier needs to be audited and in building audit trails.

Emphasis on Security: The revised document expands the section about security. Physical and/or logical controls should be in place to restrict access only to authorised people. Management systems should be designed to record the identity of persons entering, changing, confirming, or deleting data, including date and time.

Compliance Challenges in EU

Getting approval for a new drug or medical device is a costly and arduous process. In Europe, where there are numerous regulatory agencies, it can be even more challenging.

The European Medicines Agency (EMA) serves as a hub for regulatory agencies in European Union member states and in some countries that belong to the European Free Trade Association. However, each country maintains its own regulatory body that oversees pharmaceutical companies.

The EMA evaluates marketing authorisation applications (MAAs) for hundreds of human and veterinary drugs that fall under the scope of its centralised procedures (e.g., medicines derived from biotechnology and high-tech processes). The agency provides a single marketing authorisation that is valid throughout the EU. But manufacturers of thousands of medicines that don't fall under the centralised procedures must submit their applications to national regulatory agencies of individual countries or to a number of member states through mutual-recognition procedures.
As for medical devices, manufacturers have to obtain approval from the
decentralised regulatory bodies of each EU member state and individual European
country.

A life science company doing business in Europe is likely to have simultaneous
submissions in various agencies. These companies face many challenges,
especially if the documents for their MAA submissions are maintained through a
hybrid (partially electronic) system.

The following are some of the problems faced by life science companies using
hybrid systems that can be easily rectified by switching to a fully automated
system:

**Inefficiency:** When a company has overlapping MAAs in different European
regulatory agencies, or if it has simultaneous submissions to both the EMA and
the U.S. FDA, it is possible that similar information will be requested by the
agencies, but the information will be presented in different ways. With a hybrid
system, information is scattered in various places, requiring more time and effort
to generate the same or similar information.

**Lack of Document Control:** The revised Annex 11 puts emphasis on the
importance of controlling changes in documents. Similarly, the section about audit
trails reinforces the importance of document control; an audit trail is seen as a
tool for controlling any change or deletion in any GMP-relevant data, including
documenting the reason for the change. A hybrid system that relies partly on
paper may not reflect all the changes in a document or ensure that only the latest
version is in use.

**Lack of Security:** Annex 11 is concerned about protection of systems from
unauthorised access, loss, and damage. Section 12.1 specifies the importance of
“physical or logical controls” not only of computer systems but of storage areas. A
fully computerised system can be secured better than a hybrid system that relies
partly on paper copies stored in filing cabinets or rooms.

**Inspection Vulnerability:** Now that Annex 11 has been revised, companies can
expect more scrutiny of their computer systems. For example, Annex 11’s Section
3.4 provides that quality system and audit information relating to software
providers should be made “available to inspectors” on request. In other words,
inspectors want access to the information, not a report. A hybrid system is more
vulnerable to citation during inspection because access to information would not
be as easy.

**The MasterControl Solution**

With the revision of Annex 11, this may be the best time for life science companies
in the European market to switch from a paper-based or hybrid system to a fully
automated system.
The MasterControl quality and compliance system is an electronic, centralized, web-based platform for all processes critical to regulated companies, including document management, audit management, forms-based processes, quality management, change management, corrective and preventive action, training control, product lifecycle management, bill of materials, and submissions management.

MasterControl automates and streamlines the MAA document management process to improve efficiency and connects it to other compliance processes to accelerate getting to market. After obtaining a marketing authorisation and throughout the post-approval period, MasterControl will help ensure compliance.

Here are some of the features of MasterControl and their corresponding benefits:

**Centralized, Web-based System:** All MAA and compliance documents (protocols, study reports, safety/adverse event reports, quality SOPs, CTD, etc.) will reside securely in one place, making search and retrieval easy. Different MAA documents for different European regulatory agencies will be stored in one place, so comparing documents or repurposing data for different requirements will be easier and faster. MasterControl is web-based, so all users will be able to access the system anytime from virtually anywhere.

**Automated Routing, Escalation, and Approval:** All compliance documents can be routed, reviewed, and approved electronically, greatly increasing efficiency. Tasks will be transparent and easier to track. Tasks that are not completed within a certain period will be escalated automatically.

**Effective Change Control and Audit Trail:** Annex 11 puts emphasis on the importance of change control by stating in Section 6 that the “criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.” With MasterControl, revision and change control of critical documents will be automated, making it easy to track updates and changes in documents. MasterControl provides a time-stamped audit trail that captures any changes, documents the reasons for the changes, as well as the user’s identity. Revision control will be automatic, so obsolete versions of a document will not resurface and be used inadvertently.

**Compliant Electronic Signatures:** MasterControl provides electronic signatures that include the time and date they were applied as recommended by Annex 11. The system can automatically append a signature manifestation (name, date, time, and meaning of e-signature) to every document approved.

**Increased Security:** MasterControl’s security features comply with Annex 11 recommendations. The system features dual passwords for document approval; password expiration, encryption, and certification; account lockout to stop unauthorised users.
**Connected Processes:** Compliance requires close coordination of different departments within a company, such as regulatory affairs, quality, and manufacturing, as well as nonclinical and clinical teams in pharmaceutical companies, or R&D and engineering departments in medical device companies. Many companies also work closely with outside parties (CROs, consultants, suppliers) that need to participate in different compliance processes. By using MasterControl as a platform, all of these processes and stakeholders can come together. While there are many software that specialize in specific processes (Laboratory Information Management System, Quality Management System, etc.), they do not necessarily provide the connectivity that MasterControl offers. Using a single platform for all compliance processes gives users more mileage out of an electronic system.

**Validation Solutions and Services:** MasterControl provides an array of validation solutions and services based on industry best practices. MasterControl experts can provide thorough assistance, from validation training for staff to protocol development and all the way to IQ, OQ, and PQ execution. For companies that prefer to conduct their own validation, MasterControl’s Validation Toolkit provides procedural templates, validation test protocols, and forms and scripts designed to help speed up the validation process. MasterControl’s Transfer Operational Qualification (TOQ) was designed for companies looking to reduce the pain and cost of validation by “transferring” OQ documentation as part of the overall validation effort.

**Inspection Readiness:** With MasterControl, users will always be ready for inspections because the system streamlines all processes, improves coordination and collaboration among different departments, and provides inspectors with transparency and access to critical information. For example, in a hybrid or manual process, changes in batch records for a manufacturing process may be highlighted on paper, but not explained. During inspection, those changes may have to be accounted for and users will have to scramble to find the appropriate paperwork. With MasterControl, document and revision control is automated, making all changes (and corresponding information related to the changes) transparent to the inspector.

**Conclusion**

The revised Annex 11 may not have the teeth of a regulation, but it is a good barometer of how life science companies will be evaluated and the level of standards they will be held accountable for. Annex 11 shares a similar goal—ensuring electronic record integrity in order to ensure product safety—with the U.S. FDA’s 21 CFR Part 11, so it should be familiar territory for companies already complying with Part 11.

If your company uses a paper-based or hybrid system, this is the best time to upgrade to a fully automated system. You can use Annex 11 to guide you in looking for an electronic system to support your GMP activities. An end-to-end solution like MasterControl provides a robust platform that can connect all critical
processes and bring your entire organization together for a holistic approach to compliance. It will help increase efficiency, improve coordination and collaboration among various teams, and get your product to market sooner.

About MasterControl
MasterControl Inc. creates software solutions that enable life science and other regulated companies to deliver life-improving products to more people sooner. MasterControl’s integrated solutions accelerate ROI and increase efficiencies by automating and securely managing critical business processes throughout the entire product lifecycle. More than 1,000 companies worldwide, ranging in size from five employees to tens of thousands, rely on MasterControl cloud solutions to automate processes for new product development, clinical, regulatory, quality management, supplier management, manufacturing and postmarket surveillance. MasterControl solutions are well-known for being scalable, easy to implement, easy to validate and easy to use. For more information, visit www.mastercontrol.com.

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