Implementation of

Annex 11

PharmaSuite 8.4

How PharmaSuite® is helping regulated companies
to achieve compliance with EudraLex Vol. 4, Annex 11.

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Period of Validity

This document is valid for the release on the cover page – PharmaSuite 8.4.

Color Code

The purpose of this document is to demonstrate the compliance of Rockwell Automation's PharmaSuite solution with Annex 11 as far as technical, functional, and SW development process requirements are affected. As not all requirements can be directly addressed by the computerized system or the supplier thereof, the following distinction has been made and color-coded:

	Directly addressed by RA / PharmaSuite
	Indirectly addressed / supported by RA / PharmaSuite
	Not applicable to RA / PharmaSuite, to be covered by regulated company
	Irrelevant, e.g. explanation only

Wherever useful, a distinction has been made between the basic application ("Product view") and possible customer-specific extensions ("Project view").

Abbreviations

- RA: Rockwell Automation
- QMS: Quality Management System

Language & Spelling

For all quotes of Annex 11 [1], the original wording including typos etc. and the original spelling using “English (UK)” has been kept, whereas for all PharmaSuite-related texts and comments the text has been written using “English (US)”, as Rockwell Automation is headquartered in the U.S. Therefore, as an example, you may find both versions, “computerised” and “computerized” in this document.

Introduction

PharmaSuite

PharmaSuite® is a suite of software applications that is tailored to the needs of the Pharmaceutical and Biotech industry (in general: regulated companies). Special regulations are in place for these industries, and many of them also apply to software that is used during the course of production of a drug product. Therefore, the software has to be developed under consideration of the pertinent regulations and related requirements. In addition, appropriate validation of the deployed software system has to be performed before it can be used in the production environment.

PharmaSuite is developed under consideration of all pertinent regulations that are relevant for its use in the Pharmaceutical and Biotech industry. This is particularly true for the features of the software itself, but also for the process how the software is developed, which is based on a mature Quality Management System. Moreover, PharmaSuite includes extensive technical, functional, and quality documentation. With that, PharmaSuite meets all pre-requisites required for a successful deployment and validation at customer's site.

Annex 11

The Annex 11 (an annex to EudraLex Volume 4) is a rule on Computerised Systems. While the general requirements are clear, there is still some need for clarification of the detailed implementation. Rockwell Automation (RA) is strongly committed to GxP compliance of its products and services by keeping track of any evolving new requirements and interpretations. New insights are fed back to product development in an immediate and continuous manner.

Principle

Paragraph / Sentence	Rockwell Automation Comment
This annex applies to all forms of computerised systems used as part of a GMP regulated activities.	The PharmaSuite application is a computerized system, so Annex 11 is applicable to it in general. However, this does not imply that all aspects of Annex 11 are 1:1 to be transferred to RA as a whole or to the Business Units involved in designing, developing, and testing PharmaSuite, because Annex 11 as a whole is clearly applicable to regulated companies only and should not be transferred 1:1 to software suppliers. As an annex to Volume 4, Annex 11 is limited to "principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use", whereas RA (as software supplier) develops the applications to do so.
A computerised system is a set of software and hardware components which together fulfill certain functionalities.	N/A
The application should be validated;	**Product view**: PharmaSuite is pre-qualified and comes with a set of release documents supporting the regulated company's validation process. **Project view**: The Project team may closely collaborate with the regulated company to achieve successful validation. → See also section **4. Validation**
IT infrastructure should be qualified.	This is generally targeting at the IT infrastructure of the regulated company and does not apply to RA's infrastructure. However, as customers strive to leverage supplier's activities and may want to refer to verification / testing activities being carried out by the supplier, RA is using a qualified infrastructure for its formal testing.
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.	**Product view**: PharmaSuite has been designed, developed, and tested to fulfill these requirements. **Project view**: Project specific configurations and extensions follow proven processes documented in our QMS to fulfill these requirements.

General

1. Risk Management

Paragraph / Sentence	Rockwell Automation Comment
Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. 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.	The regulated company is held accountable for the overall risk management, but RA processes and PharmaSuite support the risk management process.

2. Personnel

Paragraph / Sentence	Rockwell Automation Comment
There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT.	To be addressed by the regulated company, does not apply to RA personnel.
All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.	In general to be addressed by the regulated company, but applies to RA personnel developing PharmaSuite, too. However, required qualification differs from regulated company and is defined per role by RA within the guidelines and procedures as part of the QMS.

3. Suppliers and Service

Sec.	Paragraph / Sentence	Rockwell Automation Comment
3.1	When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party.	To be addressed by NDAs, SLAs, and other contracts between the regulated company and RA.
	IT-departments should be considered analogous.	To be addressed by the regulated company, does not apply to RA.
3.2	The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.	RA supports this requirement by hosting customer / supplier audits upon request.
3.3	Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.	RA supports this requirement by providing extensive release documentation with PharmaSuite. → See also reference document [3], Version-controlled System Documentation
3.4	Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.	To be addressed by the regulated company, does not apply to RA.

Project Phase

4. Validation

Sec.	Paragraph / Sentence	Rockwell Automation Comment
4.1	The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.	In general to be addressed by the regulated company, but RA provides release documentation with PharmaSuite as well as validation documentation in the course of customer projects and allows access to additional documented evidence during audits so that RA's documents and activities can be leveraged. → See also reference document [3], Validation & Qualification
4.2	Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.	In general to be addressed by the regulated company, but RA applies revision management, change control, reviews, and approvals to relevant documents as well. → See also reference document [3], Version-controlled System Documentation
4.3	An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.	To be addressed by the regulated company, does not apply to RA.
	For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.	In case PharmaSuite is rated to be a critical system, this requirement is supported by RA as PharmaSuite comes with a set of up to date Functional Descriptions. In addition, up to date system descriptions (Requirements Specification, Functional Specification, etc.) are available to be reviewed during audits. → See also reference document [3], Version-controlled System Documentation

Sec.	Paragraph / Sentence	Rockwell Automation Comment
4.4	User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.	**Product view**: In general to be addressed by the regulated company, but RA's Functional Descriptions and Requirements Specifications for PharmaSuite can be leveraged to support fulfilling this requirement. **Project view**: Requirements Specifications for project specific extensions are typically included in the project scope. → See also reference document [3], Version-controlled System Documentation
4.5	The regulated user should take all reasonable steps, to ensure …	To be addressed by the regulated company (see below)
	… that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.	PharmaSuite is "developed in accordance with an appropriate" QMS. RA is willing to demonstrate this during an audit.
4.6	For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.	**Product view**: PharmaSuite by itself is a basic product that allows customization. **Project view**: In case PharmaSuite is being customized, RA has all the required processes in place (and defined in its QMS) to fulfill this requirement.
4.7	Evidence of appropriate test methods and test scenarios should be demonstrated.	**Product view**: The test approach is defined in RA's QMS. RA allows access to documented evidence during audits so that RA's documents and activities can be leveraged. **Project view**: The standardized test approach as defined in RA's overall delivery model is included in RA's QMS. This approach may be adjusted and tailored to customer purposes, if needed.
	Particularly, system (process) parameter limits, data limits and error handling should be considered.	The risk-based approach applied by RA is gauging the rigor of testing, including boundary tests etc.

Sec.	Paragraph / Sentence	Rockwell Automation Comment
	Automated testing tools and test environments should have documented assessments for their adequacy.	**Product view**: RA has documented this in an internal guideline: “PS Testing Tools Guideline, Doc No. 104709”. **Project view**: The project delivery organization is currently not running automated testing tools and test environments.
4.8	If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.	**Product view**: In general to be addressed by the regulated company, but RA provides a pre-qualified upgrade mechanism from one release to the next consecutive release. **Project view**: Subject to negotiation in case data transfer is included in a project’s scope.

Operational Phase

5. Data

Paragraph / Sentence	Rockwell Automation Comment
Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.	**Product view**: As far as PharmaSuite is concerned, respective checks have been built in and tested. **Project view**: Should PharmaSuite be used to exchange data with other systems, these aspects are typically included in the project scope.

6. Accuracy Checks

Paragraph / Sentence	Rockwell Automation Comment
For critical data entered manually, there should be an additional check on the accuracy of the data.	As far as PharmaSuite is concerned, respective checks have been built in and tested. However, checks are subject to configuration.
This check may be done …	N/A
… by a second operator or …	This defines a witness role that is supported in PharmaSuite by implementing a double signature where needed.
… by validated electronic means.	Accuracy checks have been specified and tested within PharmaSuite.
The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.	In general to be addressed by the regulated company with respect to the production use cases. **Product view**: RA applies a risk-based approach to appropriately address the criticality of system functionality during testing. Also, different risk levels can be assigned to exceptions during production to support further review processes of recorded data. **Project view**: RA applies a risk-based approach during testing to appropriately address the criticality of any changes, e.g. new or changed functionality, bug fixes, etc., to system functionality.

7. Data Storage

Sec.	Paragraph / Sentence	Rockwell Automation Comment
7.1	Data should be secured by both physical …	Physical protection needs to be implemented by the regulated company.
	… and electronic means against damage.	PharmaSuite supports this aspect by implementing user and user group management with access privileges and authorization checks. However, configuration and administration of users, user groups, and privileges is subject to the regulated company. → See also reference document [3], User Authorization and [3], Access Restrictions
	Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.	This requirement needs to be implemented by the regulated company.
7.2	Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.	Archiving, backup, and disaster recovery are not part of PharmaSuite, but need to be achieved through operational means by the regulated company.

8. Printouts

Sec.	Paragraph / Sentence	Rockwell Automation Comment
8.1	It should be possible to obtain clear printed copies of electronically stored data.	PharmaSuite comes with a number of preconfigured reports that can be extended depending on project scope. → See also reference document [3], Reporting of Electronic Records
8.2	For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.	PharmaSuite comes with a Batch Production Record Report that clearly lists all exceptions (which in turn include all subsequently applied data changes).

9. Audit Trails

Paragraph / Sentence	Rockwell Automation Comment
Consideration should be given, based on a risk assessment, …	This part needs to be covered by the regulated company, although RA may assist upon request.
… to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented.	PharmaSuite's audit trail is in compliance with 21 CFR Part 11 and is configurable (which data to record, if a reason is required etc.). → See also reference document [3], Audit Trail
Audit trails need to be available and convertible to a generally intelligible form …	PharmaSuite comes with a UI for its audit trails. → See also reference document [3], Audit Trail
… and regularly reviewed.	To be addressed by the regulated company, does not apply to RA. However, PharmaSuite comes with a UI allowing review of its audit trails.

10. Change and Configuration Management

Paragraph / Sentence	Rockwell Automation Comment
Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.	In general to be addressed by the regulated company, but RA applies revision management, change control, reviews, and approvals to its code and to relevant documents as well. → See also section **4. Validation**, entry **4.2** and reference document [3], Version-controlled System Documentation

11. Periodic Evaluation

Paragraph / Sentence	Rockwell Automation Comment
Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.	Periodic review and evaluation needs to be achieved by the regulated company.

12. Security

Sec.	Paragraph / Sentence	Rockwell Automation Comment
12.1	Physical and/or …	Physical controls need to be implemented by the regulated company.
	… logical controls should be in place to restrict access to computerised system to authorised persons.	PharmaSuite employs stringent controls to maintain the integrity of user names and passwords. → See also reference document [3], User Authorization
	Suitable methods of preventing unauthorised entry to the system may include the use of …	N/A
	… keys, pass cards, …	Physical controls need to be implemented by the regulated company.
	… personal codes with passwords, biometrics, …	PharmaSuite employs stringent controls to maintain the integrity of user names and passwords. → See also reference document [3], Access Restrictions
	… restricted access to computer equipment and data storage areas.	Physical controls need to be implemented by the regulated company.
12.2	The extent of security controls depends on the criticality of the computerised system.	The criticality of PharmaSuite – and therefore the decision on the extent of controls – needs to be determined by the regulated company. However, PharmaSuite supports different levels of controls (e.g. single or double signature).
12.3	Creation, change, and cancellation of access authorisations should be recorded.	PharmaSuite supports this aspect by implementing audit trail capability for users, user groups, and access privilege management. → See also reference document [3], Access Restrictions
12.4	Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.	Assuming that PharmaSuite is a "management system for data and for documents", this aspect is supported by recording each user login (and login attempt), by providing audit trail capabilities, and by the support of electronic signatures to sign-off for recorded data. → See also section **9. Audit Trails** and reference document [3], Audit Trail, and [3], Access Restrictions

13. Incident Management

Paragraph / Sentence	Rockwell Automation Comment
All incidents, not only system failures and data errors, should be reported and assessed.	Although these aspects needs to be taken care of by the regulated company (especially the reporting of incidents that happen outside the boundaries of computerized systems), PharmaSuite supports assessment of incidents by implementing checks and recording exceptions, and by offering a dashboard client for review by exception. Actually, all product-related incidents are being recorded as an exception and are becoming part of the batch record (and the Batch Production Record Report, the Device History Report or the Workflow Report).
The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.	Root cause analysis needs to be implemented by the regulated company.

14. Electronic Signature

Paragraph / Sentence	Rockwell Automation Comment
Electronic records may be signed electronically. Electronic signatures are expected to: …	PharmaSuite offers an electronic signature implementation that is fully compliant with 21 CFR Part 11. → See also reference document [3]
a. have the same impact as hand-written signatures within the boundaries of the company,	This specific aspect, analogous to 21 CFR Part 11 § 11.100 (c), must be realized by the regulated company.
b. be permanently linked to their respective record,	The PharmaSuite database architecture provides a secure structure to protect the signature/object relationship. PharmaSuite relies on a relational database to store this vital data. PharmaSuite users do not have access to this database, thus making the signature/object history very secure. → See also reference document [3], Signature/Record Linking
c. include the time and date that they were applied.	PharmaSuite offers an electronic signature implementation that is fully compliant with 21 CFR Part 11, including time and date as per § 11.50 (2). → See also reference document [3], Electronic Signature Manifestation

15. Batch Release

Paragraph / Sentence	Rockwell Automation Comment
When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.	PharmaSuite supports this aspect by implementing user and user group management with access privileges and authorization checks. However, configuration and administration of users, user groups, and privileges is subject to the regulated company. → See also section **7.** Data Storage, entry **7.1**, section **12.** Security, entry **12.3**, and reference document **[3]**, User Authorization

16. Business Continuity

Paragraph / Sentence	Rockwell Automation Comment
For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.	Business continuity planning needs to be implemented by the regulated company.

17. Archiving

Paragraph / Sentence	Rockwell Automation Comment
Data may be archived. This data should be checked for accessibility, readability and integrity.	In general, archiving, backup, and disaster recovery are not part of PharmaSuite, but need to be achieved through operational means. However, since release 8.0, PharmaSuite provides mechanisms to export orders and workflows in PDF/A format for archiving.
If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.	Backup and disaster recovery are not part of PharmaSuite, but need to be achieved through operational means.

EMA, Annex 11, and Data Integrity

According to [6], this is the mapping of ALCOA aspects to Annex 11 paragraphs as of August 2016:

		Annex 11
A	Attributable (data can be assigned to the individual performing the task)	[2], [12.4], [15]
L	Legible (data can be read by eye or electronically and retained in a permanent format)	[7.1], [9], [10], [17]
C	Contemporaneous (data is created at the time the activity is performed)	[12.4], [14]
O	Original (data is in the same format as it was initially generated, or as a ‘verified copy’, which retains content and meaning)	[8.2], [9]
A	Accurate (data is true / reflective of the activity or measurement performed)	[Paragraph "Principles"], [5], [6], [10], [11]

References

[1] EudraLex Volume 4 –Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice; European Commission; Annex 11: Computerised Systems; Jun. 2011, http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

[2] 21 CFR Part 11 – Electronic Records; Electronic Signatures; Final Rule; Part II; Department of Health and Human Services, FDA; March 20, 1997, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=11

[3] PharmaSuite 8.4 – Implementation of 21 CFR Part 11, DIR 10003305443/PUB

[4] Rockwell Automation Document Management System (DMS), , basic functionality included in central SAP

[5] PharmaSuite 8.3 – Implementation of Annex 11, DIR 10002925830/PUB

[6] EMA, Questions and answers: Good manufacturing practice; Data integrity (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section16); Question #13

Revision History & Approvals

Revision History

The following table describes the history of this document. The dates of each version are captured in the Document Management System [4].

Version	Author	Description
1.0	Stefan Muench	Initial document creation, based on [5], updated for release 8.4. Minor editorial changes only.

Approvals

Approvals are captured electronically on the organization's Document Management System [4]. The required approvers of this document include the following:

Name	Role
Martin Dittmer	Product Manager
Steffen Landes	Development Manager
Martin Irmisch	Test Manager