

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
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Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
Principle.					GAMP 5 –Management Appendix M3
a. This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfill certain functionalities.		211.68 ¹	820.70(i).	11.2(b).	EU Directive 2003/94/EC.
b. The application should be validated; IT infrastructure should be qualified.	11-3	211.68	820.70(i). 820.30(g) 820.170	11.10(a).	Eudralex Volume IV, Glossary PIC/S PI 011-3. Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 7.1 (Hardware)
c. 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.	Principle				PIC/S PI 011-3. US FDA CPG 7348.810 - Sponsors, CROs, and Monitors
General.					
1. Risk Management. Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data		211.68(b) ²	820.30(g)		812.66 ³ ICH Harmonized Tripartite Guideline, Quality Risk Management, Q9.

¹ O. López, “A Historical View of 21 CFR Part 211.68”, Journal of GXP Compliance, Vol. 15 No. 2, Spring 2011.

² Federal Register, Vol 60 No. 13, 4087-4091, January 20, 1995.

³ All 21 CFR Part 812 regulations apply equally to both paper records and electronic records. The use of computer systems in clinical investigations does not exempt IDEs from any Part 812 regulatory requirement

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
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.					<p>NIST, Risk Management Guide for Information Technology Systems, Special Publication 800- 30.</p> <p>GHTF, Implementation of risk management principles and activities within a Quality Management System.</p> <p>ISO 14971:2007 , Medical devices -- Application of risk management to medical devices</p> <p>GAMP Forum, Risk Assessment for Use of Automated Systems Supporting Manufacturing Process -- Risk to Record, Pharmaceutical Engineering, Nov/Dec 2002.</p> <p>GAMP/ISPE, Risk Assessment for Use of Automated Systems Supporting Manufacturing Process -- Functional Risk, Pharmaceutical Engineering, May/Jun 2003.</p> <p>EU Annex 20.</p> <p>US FDA Guidance for the Content of Pre Market Submission for Software Contained in Medical Devices, May 2005.</p> <p>Pressman, Roger S., Software Engineering – A Practitioner’s Approach, McGraw Hill.</p> <p>GAMP 5 –Management Appendices M3 and M4; Operational Appendices O2, O6, O8, O9</p>

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
<p>2. Personnel.</p> <p>There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.</p>	11-1	Sub Part B	820.20(b)(1) and (2)	11.10(i)	21 CFR 110(c). 21 CFR 606.160(b)(5)(v). ICH GCP 4.1; 4.2.3, 4.2.4; 5.4.1; 5.5.1; 5.6.1 21 CFR Part 312.53(a) and .53(d). 21 CFR 58.29. WHO - Technical Report Series, No. 937, 2006. Annex 4, Section 13 GAMP 5 – Operational Appendix O12
<p>3. Suppliers and Service Providers.</p> <p>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. IT-departments should be considered analogous.</p> <p>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.</p> <p>3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.</p>	11-18	Sub Part B 211.34	820.20(b)(1) and (2), 820.50		21 CFR 110(c). ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 6.2. GAMP 5 –Management Appendices M2 and M6

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
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.					
Project Phase.					
4. Validation. 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. 4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process. 4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available. 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. 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 ⁴ .	11-2; 11-4; 11-5; 11-7; 11-9	211.68; 211.100(a), (b).	820.3(z), 820.170 820.30(g), 820.70(g) 820.70(i).	11.10(a); 11.10(k); 11.10(h).	Article 9 Section 2, Commission Directives 2003/94/EC. Medicines and Healthcare products Regulatory Agency (MHRA) (UK). IEEE. PIC/S PI 011-3. 21 CFR 606.160(b)(5)(ii) and 606.100(b)(15). ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. 11-1 ICH GCP 5.5.3 (a) and (b). 21 CFR 58.61; 63(a) and (c); 58.81(c) and (d). Blood Establishment Computer System Validation in the User's Facility, October 2007. (Draft Guidance). US FDA General Principles of SoftwareValidation.

⁴ O. López, "Requirements Management", Journal of Validation Technology, Vol. 17 No. 2., Spring 2011.

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
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<p>4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.</p> <p>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 formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.</p> <p>4.7 Evidence of appropriate test methods⁵ and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.</p> <p>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.</p>			<p>820.30</p> <p>820.50</p>		<p>WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5</p> <p>GAMP 5 Development Appendices: D1 – D7; Management Appendices M1 – M10; Operational Appendix O1</p>

⁵ Test methods -- With the **Black-Box Test**, the test cases are derived solely from the description of the test object, the inner structure of the object is thus not considered when creating the test plan; With the **White-Box Test** the test cases are derived solely from the structure of the test object; With the **Source-Code Review** the source code is checked against the documentation describing the system by one or several professionals. The APV Guideline ÓComputerized SystemsÓ based on Annex 11 of the EU-GMP Guideline, April 1996.

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
Operational Phase.					GAMP 5 –Operational Appendix O12
5. Data. 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.	11-6	211.68(b). 211.194(d)	820.184 820.180 820.70(a)	11.10(a); 11.10(b); 11.10(e); 11.10(f); 11.10(g); 11.10(h); 11.30.	US FDA 425.400. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Part I – Basic Requirements for Medicinal Products, Chapter 4 – Documentation. GAMP 5 –Operational Appendix O9
6. Accuracy Checks. For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.	11-6	211.68(c).	820.25	11.10(f)	The APV Guideline “Computerized Systems” based on Annex 11 of the EU-GMP Guideline. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Part I - Basic Requirements for Medicinal Products, Chapter 4 – Documentation. PIC/S PI 011-3. EU Annex 11-1. WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 4.5

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
<p>7. Data Storage.</p> <p>7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.</p> <p>7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of back-up data and the ability to restore the data should be checked during validation and monitored periodically.</p>	11-13 11-14	211.68(b).	820.180	11.10(c); 11.10(d); 11.10(e); 11.10(g); 11.10(h); 11.30.	812.38. Article 9 Section 2, Commission Directives 2003/94/EC. PIC/S PI 011-3. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Part I - Basic Requirements for Medicinal Products, Chapter 4 – Documentation. ICH GCP 5.5.3(d). 21 CFR 58.33 and .190(d). Specific records retention requirements are found in applicable predicate rule. For example 21 CFR 211.180(c), (d), 108.25(g), and 108.35(h), and 58.195. 812.140(a) and (b). WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 7.2.2.
<p>8. Printouts.</p> <p>8.1 It should be possible to obtain clear printed copies of electronically stored e-records.</p> <p>8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the e-record has been changed since the original entry.</p>	11-12	211.180(c)	43 FR 31508, July 21, 1978 820.180	11.10(b)	812.150. Directive 1999/93/EC of the European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures. PIC/S PI 011-3. FDA, Guidance for Industry Part 11,

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
					<p>Electronic Records; Electronic Signatures — Scope and Application, August 2003.</p> <p>The APV Guideline, “Computerized Systems” based on Annex 11 of the EU-GMP Guideline.</p> <p>US FDA CPG Sec. 130.400 Use of Microfiche and/or Microfilm for Method of Records Retention</p>
<p>9. Audit Trails</p> <p>Consideration should be given, based on a risk assessment, 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. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.</p> <p>Note: In addition to the system generated audit trail, some implementation included the documentation that allows reconstruction of the course of events. Implicitly this approach does not required a system generated audit trail.</p>	11-10			11.10(e); 11.10(k)(2)	<p>1978 US CGMP rev. Comment paragraph 186.</p> <p>The APV Guideline</p> <p>“Computerized Systems” based on Annex 11 of the EU-GMP Guideline.</p> <p>PIC/S PI 011-3.</p> <p>ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.</p> <p>ICH GCP 4.9.3; 5.5.3(c); 5.5.4</p> <p>21 CFR 58.130(d).</p> <p>Glossary of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)</p>

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
<p>10. Change and Configuration Management</p> <p>Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.</p>	11-11	211.68.	820.30(i). 820.70(i). 820.40	11.10(d); 11.10(e)	PIC/S PI 011-3. The APV Guideline “Computerized Systems” based on Annex 11 of the EU-GMP Guideline. WHO - Technical Report Series, No. 937, 2006. Annex 4. Section 12 Pressman, Roger S., <i>Software Engineering – A Practitioner’s Approach</i> , McGraw Hill. GAMP 5 –Management Appendix M3; GAMP 5 –Operational Appendices O6 and O7
<p>11. Periodic evaluation</p> <p>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 report(s).</p>		211.68; 211.180(e).	820.20(c).	11.10(k); 11.300(b) and (e).	US FDA CPG 7132a.07, Computerized Drug Processing; Input/Output Checking. ICH Q7, 12.6 WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 1.5 GAMP 5 –Management Appendix M3; GAMP 5 –Operational Appendices O3 and O8

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
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<p>12. Security</p> <p>12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.</p> <p>12.2 The extent of security controls depends on the criticality of the computerised system.</p> <p>12.3 Creation, change, and cancellation of access authorisations should be recorded.</p> <p>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.</p>	11-8	211.68(b)		11.10(c); 11.10(d); 11.10(e); 11.10(g), 11.300.	PIC/S PI 011-3. ICH GCP 4.1.5; 5.5.3(d) and (e) 58.190 WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5 Section 4 GAMP 5 –Management Appendix M9; GAMP 5 –Operational Appendix O11
<p>13. Incident Management.</p> <p>All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.</p>	11-17	211.100(b)	820.100		Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. GAMP 5 –Operational Appendices O4, O5, and O7
<p>14. Electronic Signature.</p> <p>Electronic records may be signed electronically. Electronic signatures are expected to:</p> <ul style="list-style-type: none"> • have the same impact as hand-written signatures within • the boundaries of the company, 				11.3(b)(7); 11.10(e); 11.50; .70, .100, .200, .300	Directive 1999/93/EC of the European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures. Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Concept	References				
	Old Annex 11	211	820	11	Others/Guidelines
<ul style="list-style-type: none"> • be permanently linked to their respective record, • include the time and date that they were applied. 					Ingredients. Electronic Signatures in Global and National Commerce (E-Sign), a US federal law. (available at: http://thomas.loc.gov/cgi-bin/query/z?c106:S.761:) 21 CFR 58.33; .81; .35; .120; .185
15. Batch release. When a computerized 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.	11-19	211.68 211.186 211.192 211.188(b) (11) 211.188(a)		11.70; Sub Part C	21 CFR 211.68 The APV Guideline “Computerized Systems” based on Annex 11 of the EU-GMP Guideline. 11-9; 11-14 EC Directive 2001/83
16. Business Continuity. 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.	11-15 11-16				PIC/S PI 011-3. GAMP 5 –Operational Appendix O10

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

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17. Archiving. Data may be archived. This data should be checked for accessibility, readability and integrity. 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.		211.68(b)		11.10(c)	DOD 5015.2-STD, Design Criteria Standard for E-records Management Software Applications. GAMP 5 –Operational Appendix O13

EU Annex 11
 US FDA – 211, 820, 11; other guidelines
 Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Raw data and “similar” terms.	References				
	Old Annex 11	211	820	11	Others
<p><i>Definition.</i></p> <p><i>Raw data</i> is all data on which quality decisions are based should be defined as raw data. It includes data which is used to generate other records.</p> <p>For electronic records regulated users should define which data are to be used as raw data.</p> <p><i>Source.</i></p> <p>Volume 4, EU Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Chapter 4: Documentation</p>	N/A			11.3(6) + Part 11, Electronic Records; Electronic Signatures — Scope and Application (III.B.2)	<p>Clinical Trails - <i>Source Data</i>: original data, those values that represent the first recording of clinical trial data elements.</p> <p>Laboratory – <i>Raw data</i>: Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments. Source: 58.3(k)</p>

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

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					<p>Clinical Trails - <i>Source Data</i>: 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).</p> <p><i>Source</i>: EMA/INS/GCP/454280/2010 GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials.</p>

EU Annex 11
US FDA – 211, 820, 11; other guidelines
Orlando López – Rev 25-SEP-2011
www.computer-systems-validation.com

Revision History

02-FEB-2011	Creation of the Annex 11 matrix.
21-FEB-2011	Update format of matrix and updated based on various references.
08-MAR-2011	Updated various 21 CFR 820 references based on the US FDA General Principles of Software Validation, January 2002, CDRH and CBER.
13-MAR-2011	Updated various 21 CFR 211 references based on the US FDA Guide to Inspection of Computerized Systems in Drug Processing, February 1983.
22-MAR-2011	Updated various 21 CFR 11 references based on regulation. Add raw data references. Updated periodic review based on comments by Jeffrey Torres.
31-MAR-2011	Updated “Principle” reference based on US FDA CPG 7348.810 - Sponsors, CROs, and Monitors. Updated various 21 CFR 820 references based on another matrix correlating various regulatory requirements. Updated various references based on ICH GCP, 21 CFR 58, and 21 CFR 312.
09-APR-2011	Added ISO 14971 as reference. Updated 11-7 based on 21 CFR 820.
23-APR-2011	Updated various references based on various CFRs.
11-MAY-2011	Updated based on regulations for Computerized Systems Used in Medical Device Clinical Investigations, 21 CFR 812.
12-JUN-2011	Added 211.194(d) in Data Section; Added reference on my recent article on Requirements Management, published by IVT; Section 4, added the Blood Establishment Computer System Validation in the User's Facility, October 2007 (Draft Guidance); added as a reference EMA/INS/GCP/454280/2010 GCP Inspectors Working Group (GCP IWG), “ <i>Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials.</i> ”; Updated various references based on 21 CFR 58.
03-AUG-2011	Added regulatory requirements about 820 based on the US FDA Medical Devices QS Manual: A small entity compliance guide, Chapter 7; added in periodic review reference of ICH Q7, 12.6; Modifications to Old-New Annex 11 mappings.
23-AUG-2011	Added WHO Technical Report Series, No. 937, 2006. Annex 4. Appendix 5. 2006
26-AUG-2011	Added Electronic Signatures in Global and National Commerce (E-Sign), a US federal law
25-SEP-2011	Added GAMP 5 Cross references (Yve Samson); Added definition of Test Methods based APV guideline.