Cross-walk between EU Annex 11 and US FDA – 211, 820, 11; other guidelines and regulations

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	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
Principle.					GAMP 5 –Management Appendix M3. Data integrity element: Accurate.
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 Directives 2003/94/EC and 91/412/EEC. PIC/S PI 011-3. ISO 13485 7.5.2. Article 1 draft Annex 2 CFDA GMP.
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. ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Sections 5.40 and 5.41. WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 7.1 (Hardware). ISO 13485 7.5.2; 7.3.6; 7.2; 7.2.1; 7.2.2 Article 10 draft Annex 2 CFDA GMP. GAMP GPG: IT Infrastructure Control and Compliance, 2005. Draft OECD Guidance Document, Sections 1.1 and 1.4. ICH E6 Guideline for GCP (June

[1] O. López, "*A Historical View of 21 CFR Part 211.68*", Journal of GXP Compliance, Vol. 15 No. 2, Spring 2011.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					1996), Section 5.5.3(a) ANMAT (Argentina) 5.21 US FDA General Principles of Software Validation, Section 5.2.6. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.40.
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. Brazilian GMPs Title VII Art 570. Thailandia CSV GMPs. Article 2 draft Annex 2 CFDA GMP.
General.					
1. Risk Management. 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.		211.68(b)[2]	820.30(g)		812.66[3] ICH Q9 Quality Risk Management. ICH Q7 5.40 NIST, Risk Management Guide for Information Technology Systems, Special Publication 800- 30. GHTF, Implementation of risk management principles and activities within a Quality Management

[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.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					System. ISO 14971:2007 , Medical devices -- Application of risk management to medical devices GAMP Forum, Risk Assessment for Use of Automated Systems Supporting Manufacturing Process -- Risk to Record, Pharmaceutical Engineering, Nov/Dec 2002. GAMP/ISPE, Risk Assessment for Use of Automated Systems Supporting Manufacturing Process -- Functional Risk, Pharmaceutical Engineering, May/Jun 2003. EU Annex 20. US FDA Guidance for the Content of Pre Market Submission for Software Contained in Medical Devices, May 2005. Pressman, Roger S., Software Engineering – A Practitioner's Approach, McGraw Hill. GAMP 5 –Management Appendices M3 and M4; Operational Appendices O2, O6, O8, O9. Brazilian GMPs Title VII Art 572. ISO 13485 7.3.6 WHO, Technical Report Series No. 281, 2013. Health Canada API , C.02.05,

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Interpretation #12. Articles 3. 6, 12 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Section 1.2. ANMAT (Argentina) 5.21 US FDA General Principles of Software Validation Section 4.8 PIC/S Guidance PI 011-3, Sections 4.5 and 4.6. Establishing data criticality and inherent integrity risk, MHRA July 2016 (Draft). Sections 5.3 and 5.4, PIC/S PI 041-1 (Draft2). Section 5.0, WHO, Technical Report Series No. 995, 2016.
2. Personnel. 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. (Data integrity element: Attributable)	11-1	Sub Part B	820.20(b)(1) and (2); 820.25	11.10(i) 11.10(j) 11.100(b)	EudraLex, The Rule Governing Medicinal Products in the European Union, Volume 4, EU Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use, Part 1, Chapter 2 – Personnel, February 2014 21 CFR 110(c). 21 CFR 606.160(b)(5)(v). ICH E6 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).

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					21 CFR 58.29 WHO - Technical Report Series, No. 937, 2006. Annex 4, Section 13 GAMP 5 6.2.3.1, 6.2.3.3, 6.2.3.3. 6.2.3.5 and Operational Appendix O12. Brazilian GMPs Title VII Art 571. ISO 13485 5.5; 5.5.1; 5.5.3; 6.2; 6.2.1; 6.2.2 Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi-drugs, October 2010) , Section 6.8. Thailandia CSV GMPs, Clause 510. Health Canada API , C.02.006 Draft OECD Guidance Document, Section 1.3. Brazil API (RDC Resolution #69 Chapter VI Section VI Art. 258)) US FDA Data Integrity (Draft) Guidance III.16 Section 8.0, WHO, Technical Report Series No. 995, 2016.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
3. Suppliers and Service Providers. 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. 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. 3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled. 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. 4.5 The supplier should be assessed appropriately.	11-18	Sub Part B 211.34	820.20(b)(1) and (2), 820.50		EudraLex, The Rules Governing Medicinal Products in the European Union Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Chapter 7: Outsourced Activities, January 2013. 21 CFR 110(c). ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients ICH Q10 Section 2.7 Management of Outsourced Activities and Purchased Materials. ICH E6 Section 5.2.1. WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 6.2. GAMP 5 Section 6.1.4. GAMP 5 –Management Appendices M2 and M6. Brazilian GMPs Title VII Art 589. ISO 13485 5.5; 5.5.1; 5.5.3; 6.2; 6.2.1; 6.2.2' 7.4; 7.4.1. China GMPs, Section 7. Thailandia CSV GMPs, Clause 527. PDA, Technical Report No. 32 Auditing of Supplier Providing Computer Products and Services for Regulated Pharmaceutical

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Operations, PDA Journal of Pharmaceutical Science and Technology, Sep/Oct 2004, Release 2.0, Vol 58 No 5. CEFIC CSV Guide, Section 7.4.6. Article 4 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Sections 1.5 and 1.6. PIC/S Guidance PI 011-3 Sections 5.1, 5.2, 11. Section 20.0, MHRA July 2016 (Draft). Section 10.0, PIC/S PI 041-1 (Draft2). Section 7.0, WHO, Technical Report Series No. 995, 2016.
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	11-2; 11-4; 11-5; 11-7	211.68; 211.100(a), (b).	820.3(z), 803.17 820.40 820.170 820.30(g), 820.70(g) 820.70(i). 820.70(i)	11.10(a); 11.10(k); 11.10(h); 11.300(e)	Article 9 Section 2, Commission Directives 2003/94/EC. ISO 90003:2004, Sections 7.3.2; 7.3.3; 7.3.4; 7.3.5; 7.3.6.2a; 7.3.6.2.b; 7.3.6.2.c; 7.5.1.5; 7.5.1.6; 7.3.6.2d; 7.3.7; 7.5.3.2 ISO-27000, Sections 12.1, 12.2 Medicines and Healthcare products Regulatory Agency (MHRA) (UK). IEEE. PIC/S PI 011-3 Sections 6.3, 7, 9, 10, 13.2, 14.3, 23.8, 23.10

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
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]. 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. 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. 4.7 Evidence of appropriate test methods[5] and test scenarios should be demonstrated. Particularly, system (process)			820.30(c); 820.3(z) and (aa); 820.30(f) and (g) 820.30 820.50		21 CFR 606.160(b)(5)(ii) and 606.100(b)(15). ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Sections 5.41, 12.2. ICH Q9 Quality Risk Management. 11-1 ICH E6 GCP 2.10, 2.11, 5.5.3 (a) and (b), 5.5.4 21 CFR 58.61; 63(a) and (c); 58.81(c) and (d); 58.33 21 CFR 59.190 Blood Establishment Computer System Validation in the User's Facility, April 2013. US FDA General Principles of SoftwareValidation. WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5 GAMP 5 Sections 4.2.1, 4.2.3, 4.2.4, 5.2.3, 5.2.5, 6.1.5, 6.1.6, 6.2.6, 6.2.8,

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

[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.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
parameter limits, data limits and error handling should be considered[6]. Automated testing tools and test environments should have documented assessments for their adequacy. 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[7].					6.2.9, 6.2.10 GAMP 5 Development Appendices: D1 – D7; Management Appendices M1 – M10; Operational Appendix O1 21 CFR 1271.160(d) 21 CFR 803.17; 21 CFR 803.18 EU Annex 15. Brazilian GMPs Title VII Art 573, 574, 575, 576, 578. Brazilian Medical Devices (RDC No 16) Sections 1.2.4, 4.1.8, 4.2.1.1, 5.4.6, 5.5.2 and 5.5.3, 5.6. ISO 13485 2.3; 7.2; 7.2.1; 7.2.2; 7.5.1.2.2; 7.3.6; 6.3; 7.5.2. ISO/TR 14969:2004 7.5.2 ISO 27000 Section 7.1 Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi- drugs, October 2010) , Sections 4, 5 and 9. China GMPs Article 109. Thailandia CSV GMPs, Clauses 511,

[6] This sentence is related with the additional checks covered in Accuracy Checks (11-6).
[7] Annex 11-4.8 is complemented with 11-7.1.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					512, 513, 514, 516. Health Canada API , C.02.05 Interpretation #12; #13; #14; 17. C.02.015 Interpretation #3; #13.5 Articles 5, 7, 8, 9, 11, 13 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Section 1.1 Item 3, Sections 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7. 2.8, 2.9 ANMAT (Argentina) 5.25 US FDA General Principles of Software Validation 4.1, 4.5, 5.1, 5.2, 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6, 23.10 Brazil API (RDC Resolution #69 Chapter VI Section VI) WHO Technical Report 986 Annex 2 (Section 15.9) ITIL Service Design (Section 5.2.8) US FDA Data Integrity (Draft) Guidance III.3 Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.41 and 5.42. Sections 7.0 and 19.0, MHRA July 2016 (Draft). Section 9.0, WHO, Technical Report Series No. 995, 2016.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
Operational Phase.					GAMP 5 –Operational Appendix O12. Draft OECD Guidance, Section 3 Item 85. ANMAT (Argentina) 5.22 and 5.23 Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.44.
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.[8] (Data integrity element: Accurate)	11-6	211.68(b). 211.194(d)	806.1 820.25 820.70(a) 820.180 820.184	11.10(a); 11.10(b); 11.10(e); 11.10(f); 11.10(g); 11.10(h); 11.30.	US FDA 425.400; 803.1; 803.10; 803.14; 806.10; 806.30; 58.15; 58.33; 58.35; 59.190 EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Part I – Basic Requirements for Medicinal Products, Chapter 4 – Documentation. GAMP 5 –Operational Appendix O9. Brazilian GMPs Title VII Art 577. ISO 134854 6.2; 6.2.1; 6.2.2 7.5; 7.5.1; 7.5.1.1; 4.2.4; 7.5.1. Thailandia CSV GMPs, Clause 515. Draft OECD Guidance, Section 3.1. ICH E6 Section 2.10. ICH Q7 Section 5.45.

[8] Annex 11-5 is fundamental in erecs integrity and it is related with Annex 11-4.7.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					ITIL, Service Design (Chapter 5.2.10) Section 9.2.1 (Data transfer between systems) and 9.5, PIC/S PI 041-1 (Draft2).
6. Accuracy Checks. For critical data[9] 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.[10] (Data integrity element: Accurate)	11-9	211.68(c).	820.25 820.70	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. Brazilian GMPs Title VII Art 577, 580. ISO 13485 6.2; 6.2.1; 6.2.2; 7.5. Thailandia CSV GMPs, Clause 518. Health Canada API , C.02.015 Interpretation #18.

[9] The term "critical data" in this context is interpreted as meaning data with high risk to product quality or patient safety. ISPE GAMP COP Annex 11 – Interpretation, July/August 2011.
[10] Annex 11-6 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Article 15 draft Annex 2 CFDA GMP. Draft OECD Guidance, Section 3.2. ANMAT (Argentina) 5.26 and 5.30 Brazil API (RDC Resolution #69 Chapter VI Section VI **Article** 265**)** ITIL, Service Design (Chapter 5.2.10) Part II - Basic Requirements for Active Substances used as Starting Materials, Sections 5.45 and 5.49.
7. Data Storage. 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. (Data integrity element: Legible) 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.[11]	11-13 11-14	211.68(b).	803.1 820.20 820.40 820.180 806.1	11.10(c) 11.10(d) 11.10(e) 11.10(g) 11.10(h) 11.30.	812.38. Chapter II 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 E6 GCP 5.5.3(d) and (f). ICH Q7 5.48. 21 CFR 58.33; .190(d); .35; .195 Specific records retention

[11] Annex 11-7 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					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, Sections 5 and 7.2.2. 21 CFR 123.9(f) GAMP Appendix O9 and O11. Brazilian GMPs Title VII Art 585. ISO 13485 6.2; 6.2.1; 6.2.2; 7.5 Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi-drugs, October 2010) , Section 6.3. Japan's Pharmaceutical and Food Safety Bureau "Using electromagnetic records and electronic signatures for application for approval or licensing of drugs", Section 3, April 2005. Thailandia CSV GMPs, Clause 517, 522, 523. Health Canada API , C.02.05, Interpretation #16. Article 19 draft Annex 2 CFDA GMP.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Draft OECD Guidance, Section 3.3. GAMP 5, Section 4.3.6.1. ISO 27000, Section 10.5 Brazil API (RDC Resolution #69 Chapter VI Section VI Article 269) WHO Technical Report 986 Annex 2 (Section 15.9) ITIL, Service Design (Chapter 5.2.11) US FDA Data Integrity (Draft) Guidance III.1.e 211.68(b); 211.188; 211.194. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.48. Section 17.2, MHRA July 2016 (Draft). Section 9.7, PIC/S PI 041-1 (Draft2).

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
8. Printouts. 8.1 It should be possible to obtain clear printed copies of electronically stored e-records. 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.[12] (Data integrity element: Original)	11-12	211.180(c)	43 FR 31508, July 21, 1978 803.1 803.10 803.14 806.30 820.40 820.180 806.1	11.10(b)	812.150, 58.15 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, Electronic Records; Electronic Signatures — Scope and Application, August 2003. The APV Guideline, "Computerized Systems" based on Annex 11 of the EU-GMP Guideline. US FDA CPG Sec. 130.400 Use of Microfiche and/or Microfilm for Method of Records Retention. Brazilian GMPs Title VII Art 583. ISO 13485 4.2.3; 4.2.4. Thailandia CSV GMPs, Clause 521. Draft OECD Guidance Document, Section 3.4.

[12] Annex 11-8 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
9. Audit Trails 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.[13] (Data integrity elements: Legible and Original) 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 computer system generated audit trail.	11-10		803.18 820.40	11.10(e); 11.10(k)(2); 11.50 (a)(2)	1978 US CGMP rev. Comment paragraph 186. FDA, Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application, August 2003. The APV Guideline "Computerized Systems" based on Annex 11 of the EU-GMP Guideline. PIC/S PI 011-3. ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. ICH E6 GCP 4.9.3; 5.5.3(c); 5.5.4 21 CFR 58.130(d); 211.160(a); 211.194; 212.110(b) Glossary of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Brazilian GMPs Title VII Art 581. ISO 13485 4.2.3 Thailandia CSV GMPs, Clause 519. Health Canada API , C.02.05, Interpretation #15. Draft OECD Guidance Document,

[13] Annex 11-9 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Section 3.5. WHO Technical Report 986 Annex 2 (Section 15.9) US FDA Data Integrity (Draft) Guidance III.1.c; 7 & 8. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.43. Sections 8.0 and 13, MHRA July 2016 (Draft). Section 9.4, PIC/S PI 041-1 (Draft2).
10. Change and Configuration Management Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure. (Data integrity elements: Legible and Accurate)	11-11	211.68.	820.30(i). 820.70(i). 820.40.	11.10(d); 11.10(e)	SO 90003, 2004, Sections 7.3.7 and 7.5.3.2 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., *Software Engineering – A Practitioner's Approach*, McGraw Hill. GAMP 5 –Management Appendix M3; GAMP 5 –Operational Appendices O6 and O7. GAMP 5 Section 4.3.4.1. Brazilian GMPs Title VII Art 582. ISO 13485 7.3.7; 7.5.2; 4.2.3

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi-drugs, October 2010) , Section 6.6. China GMP, Articles 240 - 246. Thailandia CSV GMPs, Clause 520. Health Canada API , C.02.015 Interpretation #20. Article 17 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Sections 1.7 and 3.6. ANMAT (Argentina) 5.28. ICH E6 Section 5.5.4. ICH Q7 Section 5.47. General Principles of Software Validation Sections 4.7 and 5.2.7. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.47.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
11. Periodic evaluation 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). (Data integrity element: Accurate)		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, 12.60 WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5, Section 1.5 GAMP 5 Section 4.3.5. GAMP 5 –Management Appendix M3; GAMP 5 –Operational Appendices O3 and O8 58.35; 58.190; 58.195. Annex 15 clauses 23 and 45. ISO 13485 5.6; 5.6.1; 5.6.2; 5.6.3; 8.2.2; 8.5; 8.5.1. China GMPs Section 8. Draft OECD Guidance Document, Section 3.7. ITIL, Service Design (Chapter 5.2.13)
12. Security 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. 12.2 The extent of security controls depends on the criticality of	11-8	211.68(b)		11.10(b); 11.10(c); 11.10(d); 11.10(g); 11.300.	PIC/S PI 011-3, Sections 19.2; 19.3. ICH E6 GCP 4.1.5; 5.5.3(c), (d) and (e) ICH Q7 Section 5.43. 21 CFR Part 58.51; 58.190(d); 211.68(b) WHO - Technical Report Series, No. 937, 2006. Annex 4. Appendix 5 Section 4

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
the computerised system. 12.3 Creation, change, and cancellation of access authorisations should be recorded. 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.[14] (Data integrity elements: Attributable and Contemporareous)					GAMP 5, Section 4.3.7.1 GAMP 5 –Management Appendix M9; GAMP 5 –Operational Appendix O11. Brazilian GMPs Title VII Art 579. Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi-drugs, October 2010) , Section 6.4. Thailandia CSV GMPs, Clause 517. Health Canada API , C.02.05, Interpretation #15. Articles 14, 16 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Section 3.8. ANMAT (Argentina) 5.24. ISO-27000, Sections 12.1 and 11.2. Brazil API (RDC Resolution #69 Chapter VI Art. 106 Paragraph 2) WHO Technical Report 986 Annex 2 (Section 15.9) ITIL, Service Design (Chapter 5.2.13)

[14] Annex 11-12 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					US FDA Data Integrity (Draft) Guidance III.4 & .5. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.43. Section 16.0, MHRA July 2016 (Draft). Section 9.3, PIC/S PI 041-1 (Draft2).
13. Incident Management. 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.	11-17	211.100(b)	820.100		ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 5.46. ICH E6, Section 5.1.3. GAMP 5 - Operational Appendices O4. O5,and O7. Brazilian GMPs Title VII Art 588. ISO 13485 8.5; 8.5.1; 8.5.2; 8.5.3 Japan CSV Guideline (Guideline on Management of Computerized Systems for Marketing Authorization Holder and Manufacturing of Drugs and Quasi-drugs, October 2010) , Sections 6.7 and 7.2. China GMPs, Sections 5 and 6. Thailandia CSV GMPs, Clause 526. Health Canada API , C.02.015 Interpretation #19. Articles 20 and 21 draft Annex 2 CFDA GMP.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Draft OECD Guidance Document, Section 3.9. ANMAT (Argentina) 5.27. US FDA General Principles of Software Validation, Section 5.2.7. Part II - Basic Requirements for Active Substances used as Starting Materials, Section 5.46.
14. Electronic Signature. Electronic records may be signed electronically. Electronic signatures are expected to: • have the same impact as hand-written signatures within • the boundaries of the company[15], • be permanently linked to their respective record, • include the time and date that they were applied. (Data integrity element: Contemporaneous)				11.3(b)(7); 11.10(e); 11.50; .70, .100, .200, .300	EU GMP Chapter 4 Principle Annex 11-8.1, 9, 12.4, 17 ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 5.43. 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 Japan's Pharmaceutical and Food Safety Bureau "Using electromagnetic records and electronic signatures for application for approval or licensing of drugs",

[15] The phase "within the boundaries of the company" clarifies that such signatures applied to records maintained by the regulated company are not subject to Directive 1999/93/EC on a Company framework for esigs, nor the 2000/31/EC Directive on electronic commerce, nor any associated national regulations of EU member states on such topics.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					Section 4, April 2005. Article 22 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Section 3.10. ICH E6 Sections 2.8, 2.10, 2.11, 4.9.1, 4.9.7, 5.5.1, 5.5.3 (a)-(g), 5.5.4, 5.5.5, 5.5.6, 5.23.4. US FDA Data Integrity (Draft) Guidance III.11 Section 14.0, MHRA July 2016 (Draft). Section 9.3 (Item #3), PIC/S PI 041-1 (Draft2).
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. (Data integrity element: Attributable)	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. Brazilian GMPs Title VII Art 590. Thailandia CSV GMPs, Clause 528. Article 21 draft Annex 2 CFDA GMP. Draft OECD Guidance Document, Section 3.11.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
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.[16]	11-15 11-16				PIC/S PI 011-3. GAMP 5, Sections 4.3.6.2 and 4.3.6.3. GAMP 5 –Operational Appendix O10. Brazilian GMPs Title VII Art 586, 587. Thailandia CSV GMPs, Clause 524, 525. Draft OECD Guidance Document, Section 3.13. ANMAT (Argentina) 5.29. ICH Q7, Section 5.48. Brazil API (RDC Resolution #69 Chapter VI Section VI Articles 271 and 272)
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.[17] (Data integrity element: Legible)		211.68(b)		11.10(c)	Scientific Archivists Group, A Guide to Archiving of Electronic Records, 2014 www.sagroup.org.uk/images/documents/AGuidetoArchivingElectronicRecordsv1.pdf DOD 5015.2-STD, Design Criteria Standard for E-records Management Software Applications. GAMP 5 –Operational Appendix

[16] Annex 11-16 is another fundamental section related with erecs integrity.
[17] Annex 11-17 is another fundamental section related with erecs integrity.

	References				
	Old Annex 11	**211**	**820**	**11**	**Others/Guidelines**
					O13. GAMP GPG: Electronic Data Archiving, 2007. Brazilian GMPs Title VII Art 584. Draft OECD Guidance Document, Section 3.12. Scientific Archivists Group, "A Guide to Archiving of Electronic Records" ITIL, Service Design (Chapter 5.2.13) Sections 7.0 and 17.1, MHRA July 2016 (Draft). Section 9.7, PIC/S PI 041-1 (Draft2).

Cross-walk between EU Annex 11 and US FDA – 211, 820, 11; other guidelines and regulations

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Revision History

02-FEB-2011	Creation of the Annex 11 matrix.
21-FEB-2011	Updated 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 E6 GCP, 21 CFR 58, and 21 CFR 312.
09-APR-2011	Added ISO 14971 as a 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), "*Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials*."; 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.
24-OCT-11	Added Tissues Reg 21 CFR 1271.160(d); Food 21 CFR 123.9(f)
17-MAR-2012	Updated based on NEMA Presentation. "Part 11 Recommenations for Changes", June 2004.
21-OCT-12	Updated based on presentation FDA Public Meeting June 2004 (R. Eaton and R. Nabar)
15-NOV-2012	Updated various references based ICH Q10, ISPE GAMP COP Annex 11 – Interpretation, July/August 2011.
2-DEC-12	Updated based on Brazilian GMPs, Title VII Resolution of the Executive Board No. 17, Computerized Information Systems. This can be found on page 109 de 148,

	http://www.in.gov.br/imprensa/visualiza/index.jsp?jornal=1&pagina=94&data=19/04/2010
07-APR-13	Updated guideline Blood Establishment Computer System Validation in the User's Facility, from October 2007 (Draft Guidance) to April 2013 (Final Guidance).
24-AUG-13	Updated with ISO 134854.
24-Oct-13	Added Japanese CSV Guidelnes (Guidelines on Management of Computerized Systems for Marketing Auhtorization Holders and Manufacturers of Drugs and Quasi-drugs, October 2010) and Japan's Pharmaceutical and Food Safety Bureau "Using electromagnetic records and electronic signatures for application for approval or licensing of drugs", April 2005.
31-Oct-13	Added State Food and Drug Administration, P.R. China, March 2011 and Thailand CSV GMPs contained in the Prescription of Details regarding and Procedures of Manufacture pof Modern Medicinal Products in compliance with Drug Lawa B.E.2554.
08-Feb-14	Added 91/412/EEC; WHO, Technical Report Series No. 981 PDA, Technical Report No. 32; CEFIC CSV Guide Rev 2, December 2002. Health Canada GMP Guidelines for API (GUI-0104) Dec 2013.
08-Feb-14b	Corrected copy. Added couple of sections left out from the Health Canada GMP Guidelines for API.
26-Mar-14	Updated application sections based on ICH E6 GCP.
09-Jul-14	Incorrect references in 21 CFR Part 58, Security. China Food & Drug Administration (CFDA) draft of GMP Annex 2 Computerized Systems.
12-Sep-14	Added reference GAMP GPG: Electronic Data Archiving, 2007 to Archiving; Added reference GAMP GPG: IT Infrastructure Control and Compliance, 2005 to Principle b. Added reference ISO/TR 14969:2004 Medical devices -- Quality management systems -- Guidance on the application of ISO 13485. Added EudraLex, The Rules Governing Medicinal Products in the European Union Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Chapter 7: Outsourced Activities, January 2013 to Suppliers and Service Providers.
23-Sep-14	Added Draft OECD Guidance Document – The Application of GLP Principles to Computerised Systems, September 2014.
10-Oct-14	Based on the definition by the NIST (SP 800-33), highlighted the data integrity related items on Annex 11.
19-Dec-14	Added ISO 90003:2014 applicable sections related with Configuration Management and applicable development phase activities.
05-Mar-15	Added ICH E6, Guideline for GCP (Jun 1996). Added Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medicas (ANMAT) (Argentina's Ministerio de Salud Presidencia de la Nacion). Added ISO/IEC 27000 Information Security Management Systems. Added US FDA General Principles of Software Validation. Fixed minor errors.
01-Aug-15	In 11-17 added Scientific Archivists Group, "A Guide to Archiving of Electronic Records", as a reference. Added Brazil API Regulations (RDC Resolution #69)

14-Nov-15	Added WHO Guide regarding the Principles of GMP Technical Report 986, Annex 2 WHO good manufacturing practices for pharmaceuticalproducts: main principles. Added ITIL Service Design, Chapter 5.2 – Management of data and information, 2011 Edition
22-Apr-16	Added US FDA Guidance for Industry: Data Integrity and Compliance with CGMP (Draft)
11-Aug-16	Added Part II - Basic Requirements for Active Substances used as Starting Materials Added EMA Q&A: GMP Data Integrity, August 2016. Added MHRA GxP Data Integrity Definitions and Guidance for Industry, July 2016 (Draft) Added PIC/S, Good Practices for Data Management and Integrity in Regulated GMP/GCP Environments," PI 041-1 (Draft2), August 2016. Added WHO Guidance on Good Data and Record Management Practices, Technical Report 966, Annex 5 WHO Expert Committee on Specifications for Pharmaceutical Preparations..