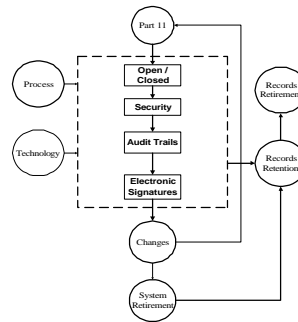


21 CFR 11 as CSV Model

by

Orlando Lopez



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- ❶ Objectives.
- ❷ Introduction.
- ❸ Regulatory requirements.
- ❹ The Model.
- ❺ Examples.
- ❻ Conclusion.
- ❼ Q&A.

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Objectives

- To proposed a new CSV Model.
- To explain how this new CSV model is applicable to all computer systems.
- To make evident the relevance of Part 11 as the new CSV model.

Introduction

Ground rules...

- **CSV Elements**

- **Type of project ==> SDLC Methodology ==> QA Activities (CSV Methodology)**
- **SDLC Methodology ==> Not constant: Type of software.**
- **Key practices ==> Changing according to the maturity of the practice and technology.**
- **CSV Methodology ==> Not constant: Type of software**
- **User's requirements ==> Not constant: Type of system**
- **Regulatory requirements ==> constant!**

The model is driven by the regulatory requirements.

Introduction -- Key practices situation

- **CSV based on key practices.**
 - **Need to be monitored and evaluated periodically.**
 - **Not all key practices are implemented at the same time.**
 - **Contrasting key practices.**

Introduction -- Part 11 situation

- **Mechanism to submit signed information in electronic format.**
- **Provides the explicit and current regulatory trends.**
- **Contingent to the availability of applications supporting pharmaceutical implementations.**
- **CSV regulatory requirements.**

Regulatory Requirements

Regulatory requirements

- **21 CFR 211.2(b) -- 1963**
 - **backups**
 - **documentation**
 - ✓ **master formulas**
 - ✓ **specifications**
 - ✓ **test records**
 - ✓ **master production and control records**
 - ✓ **batch production records**
 - ✓ **calculations**

Regulatory requirements

- **21 CFR 211.68 -- 1976**
 - **maintenance of computer systems**
 - **control of changes**
 - **I/Os checks => validation**
 - **data accuracy and security**
 - **e-records shall be controlled**
 - ✓ **backups**
 - ✓ **security**
 - ✓ **retention**

Validation

- Establishing a development methodology that best suits the nature of the system under development.
- Selection of hardware based on capacity and functionality.
- Identification and consideration of the operational limits to establish production procedures.
- Identification of operational functions associated with the users, process, regulatory, company standards, and safety requirements.
- Identification and testing of "worst case" production conditions.
- Reproducibility of the testing results based on statistics.
- Documentation of the validation process.
- Availability of written procedures to maintain the validation state of the computer system.

Validation

- **SDLC model defines the activities and order of activities applicable to CSV.**
 - Waterfall
 - Incremental
 - Spiral
 - Component assembly (Object Oriented)
 - Many more...

Regulatory requirements

- **CPG 7132a.07 -- 1982**
 - **I/O Checking**
 - ✓ data accuracy
 - during validation
 - after validation (on-going program)
 - ✓ frequency, level and extent of verification
 - based on complexity and criticality
 - written in a procedure

Regulatory requirements

- **CPG 7132a.08 -- 1982**
 - **Identification of 'Persons' on Batch Production and Control Records**
 - ✓ replacement of certain functions performed by operators with computer systems
 - applicable 211.101(d)
 - e.g., labels verification

Regulatory requirements

- **Guide to Inspection of Computerized Systems in Drug Processing ('83) and CPG 7132a.11 ('84)**
 - **CGMP Applicability to Hardware and Software**
 - ✓ confirms the applicability of the CGMP regulations to computer hardware and software
 - ✓ in the absent of explicit regulations addressing computer systems, the CGMP regulations provide the implicit guidelines to comply with the FDA
 - ✓ **Note:** explicit CSV regulation contained in proposed CGMP regulations, 21 CFR 211.220(a)

Implications of CPG 7132a.11 and Inspection guideline

- Hardware classified as equipment
 - ✓ 21 CFR 211.22 responsibilities of QC unit
 - ✓ 21 CFR 211.25 qualification of personnel
 - ✓ 21 CFR 211.63 (suitable) location of equipment
 - ✓ 21 CFR 211.67 cleaning and maintenance
 - ✓ 21 CFR 211.100 written procedures and deviations
 - ✓ 21 CFR 211.105(b) identification
 - ✓ 21 CFR 211.180 records
 - ✓ 21 CFR 211.182 cleaning and use log.

Implications of CPG 7132a.11 and Inspection guideline

- Software regarded as records
 - ✓ 21 CFR 211.101(d) verification of records
 - ✓ 21 CFR 211.180(a) record retention
 - ✓ 21 CFR 211.180(c) record access
 - ✓ 21 CFR 211.180(d) record media
 - ✓ 21 CFR 211.180(e) record review
 - ✓ 21 CFR 211.188(a) reproduction accuracy
 - ✓ 21 CFR 211.188(b) (11) documentation
 - ✓ 21 CFR 211.192 QC record review

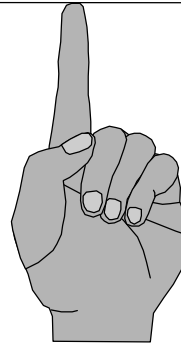
Other Key Regulations / Guidelines

- **EU GMP, Annex 11 -- Computerized Systems.**
- **EU E-Commerce Legislation and Regulations**
www.bmck.com/ecommerce/eu.htm
- **GAMP (Rev 3)**
- **Pharmaceutical Inspection Convention, Best Practices for Computerized Systems in Regulated 'GxP' Environments, Draft Version 3.01, Jan 2000.**
- **EC Directive 1999/93/EC, A Community Framework for Electronic Signature, published on the Official Journal of the European Communities, 19.1.2000.**

The Model

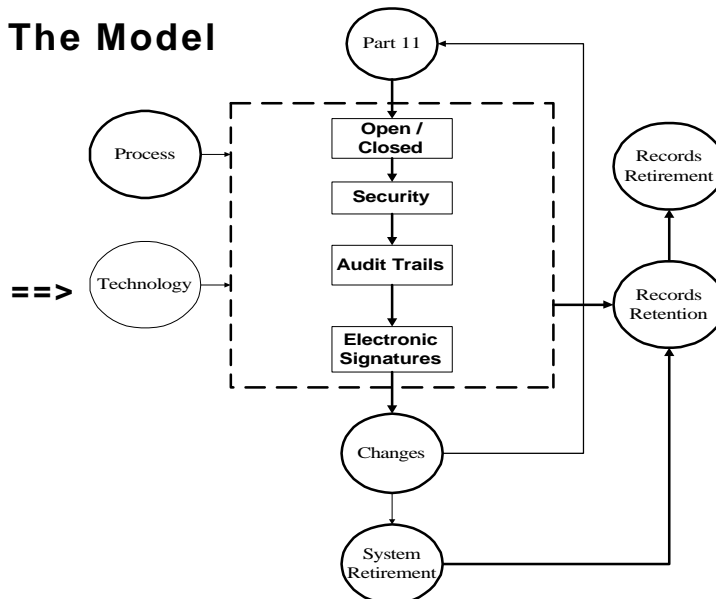
Reminder.....

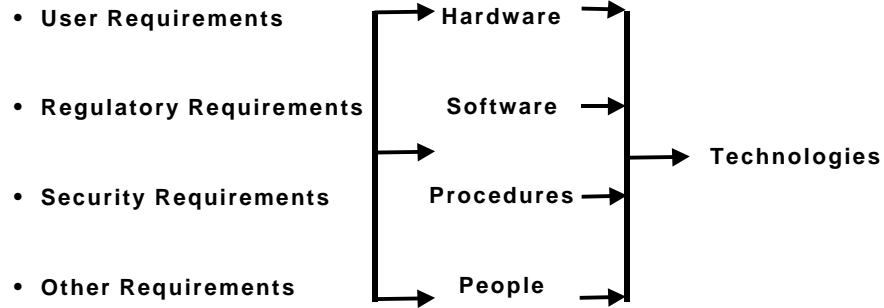
**The model is driven by
the regulatory
requirements.**



**Which requirements need to be
validated?**

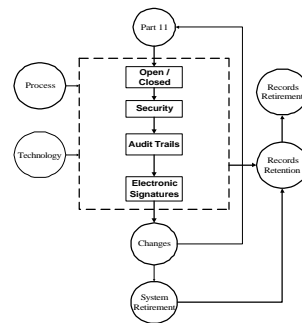
The Model





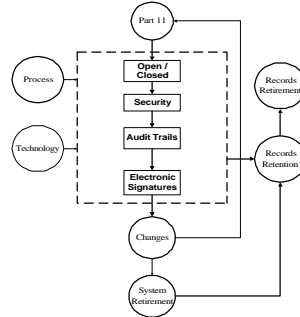
Standard Elements

- **Open/Closed Systems**
- **Security**
 - **System security**
 - **E-sig security**
 - **Code and password maintenance**
 - ✓ Code and password security
 - ✓ Password assignment
 - **Document controls**
 - **Authority, operational, and location checks**
 - **Records protection**



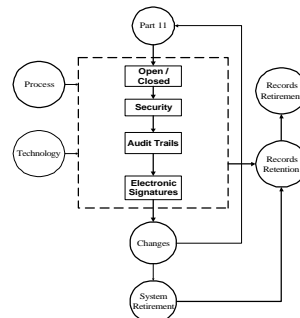
Standard Elements

- **Audit Trails**
 - Audit mechanism
 - Metadata
 - Display and reporting
- **Electronic Signatures**
 - E-sign without biometric/behavioral
 - E-sign with biometric/behavioral
 - E-sign manifestation
 - E-sign purpose
 - E-sign bidding



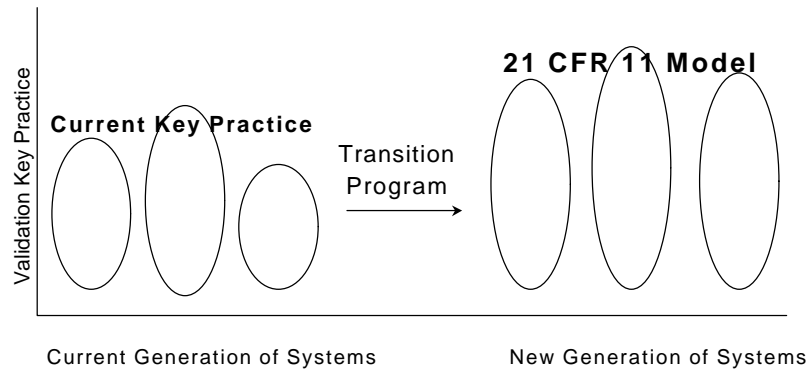
Non-Standard Elements

- **Process controlled by the computer system.**
- **Technologies.**
- **Records retention.**



Progression

Current key practices to Part 11 model



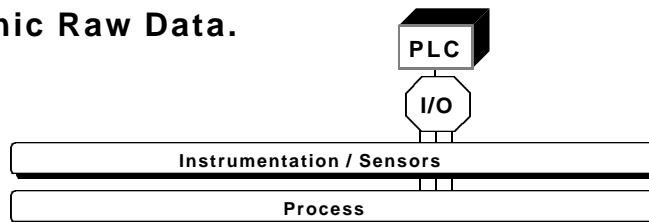
Examples

**Manufacturing equipment controlled
/ monitored by programmable logic
controllers**

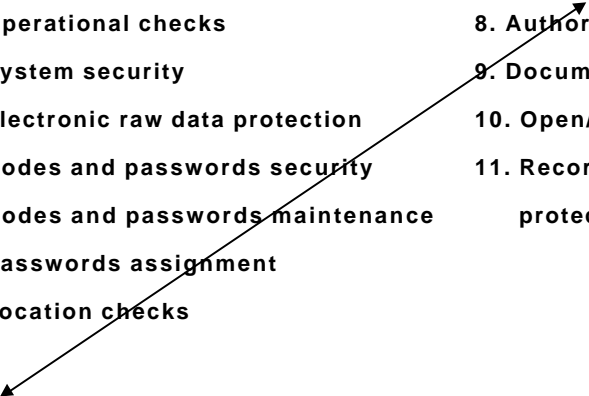
Stand Alone Systems

First example -- manufacturing equipment with a stand-alone PLC.

- i.e., V-shell blender.
- GAMP type software 2 -- Microcontrollers.
- Electronic Raw Data.



Summary of Part 11 Requirements Applicable PLC Systems (optional)

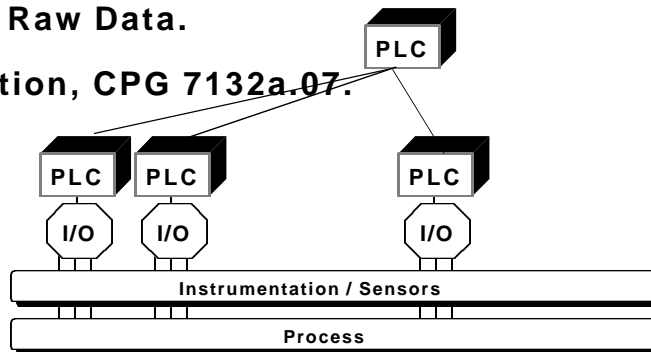
- | | |
|------------------------------------|---------------------------------------|
| 1. Operational checks | 8. Authority checks |
| 2. System security | 9. Document controls |
| 3. Electronic raw data protection | 10. Open/closed systems |
| 4. Codes and passwords security | 11. Records retention / protection |
| 5. Codes and passwords maintenance | |
| 6. Passwords assignment | |
| 7. Location checks | |
- 

Note: Part 11 is applicable to electronic records and the computer system associated with the e-records.

Computer Systems connected to other computer systems / machines

Second example -- manufacturing equipment controlled / monitored by a central controller.

- i.e., packaging lines.
- GAMP type software 5 -- Custom Built.
- Electronic Raw Data.
- Full validation, CPG 7132a.07.



Summary of Part 11 Requirements Applicable PLC Systems (optional)

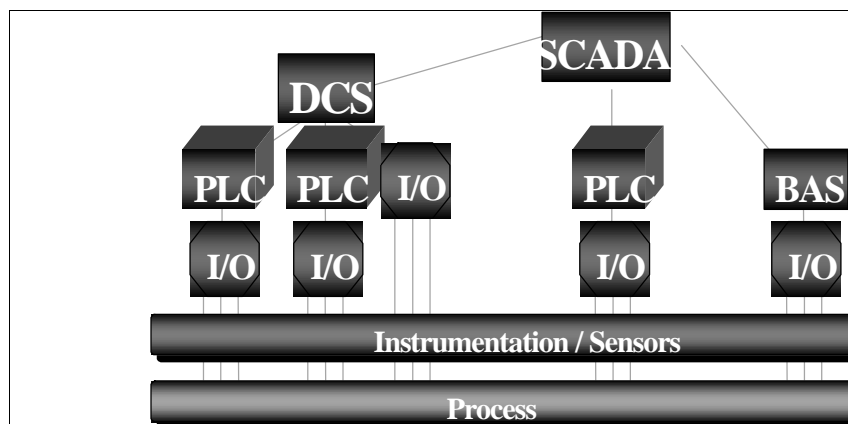
1. Operational checks
2. System security
3. Electronic raw data protection
4. Codes and passwords security
5. Codes and passwords maintenance
6. Passwords assignment
7. Location checks
8. Authority checks
9. Document controls
10. Open/closed systems
11. Records retention / protection

Note: Part 11 is applicable to electronic records and the computer system associated with the e-records.

Hybrid Systems

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Third example -- PLC connected to a SCADA system.



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Third example -- PLC connected to a SCADA system.

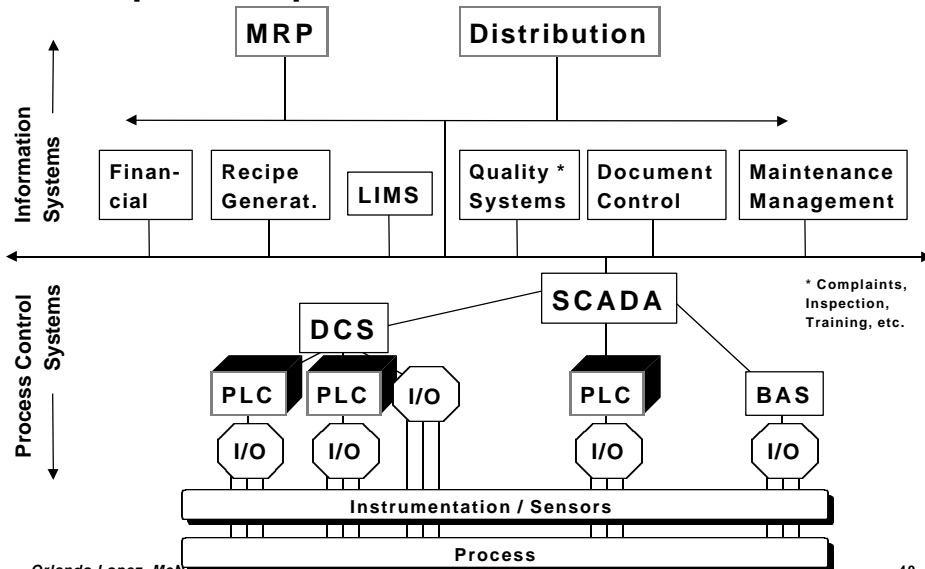
- **ie., batch records without electronic signature.**
- **GAMP types of software 4 and 5 -- Configurable and Custom Built.**
- **Electronic records.**
- **Full validation, CPG 7132a.07.**

Summary of Part 11 Requirements Applicable PLC / SCADA Systems

- 1. Audit trails and metadata**
- 2. Operational checks**
- 3. System security**
- 4. Codes and passwords security**
- 5. Codes and passwords maintenance**
- 6. Passwords assignment**
- 7. Location checks**
- 8. Authority checks**
- 9. Document controls**
- 10. Open/closed systems**
- 11. Records retention / protection**

Complete implementation of e-signature

Complete Implementation



Fourth example -- e-manufacturing.

- **i.e., batch records with electronic signature.**
- **Issue -- records and signatures compatibility between systems.**
- **All GAMP types of software.**
- **Full validation, CPG 7132a.07.**

Summary of Part 11 Requirements Comprehensive Implementation

- | | |
|--|--------------------------------|
| 1. Audit trails and metadata | 10. Operational Checks |
| 2. Records Retention/Protection | 11. Authority Checks |
| 3. System security | 12. Location Checks |
| 4. Electronic signatures security | 13. Document Controls |
| 5. Codes and passwords security | 14. Open/Closed Systems |
| 6. Codes and Passwords maintenance | 15. Signature manifestation |
| 7. Electronic Passwords assignment | 16. Signatures Purpose |
| 8. E-Sig <u>without</u> Biometric/Behavioral | 17. Signatures Binding |
| 9. E-Sig <u>with</u> Biometric/Behavioral | 18. Certification to FDA |

Conclusion

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Conclusions

- **Part 11 provides the regulatory requirements applicable to computer systems performing GxP functions.**
- **The Part 11 CSV model obsoletes the “key practices” model.**
- **The developer can concentrate additional time to specify user requirements and the to search of technologies supporting the implementation.**

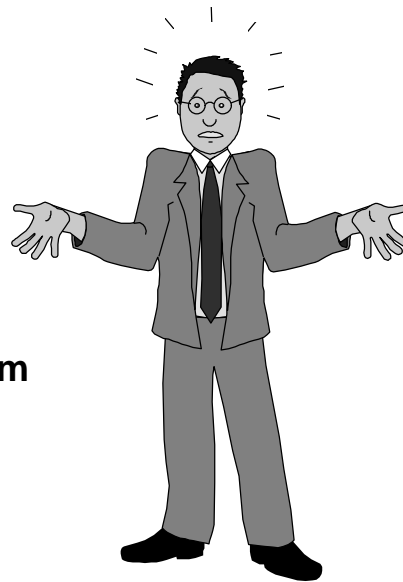
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Thank you for your attention!

Orlando Lopez, McNeil Consumer Healthcare

Questions?

**Orlando López
(215) 273-7903
olopez@mccus.jnj.com**



Orlando Lopez, McNeil Consumer Healthcare