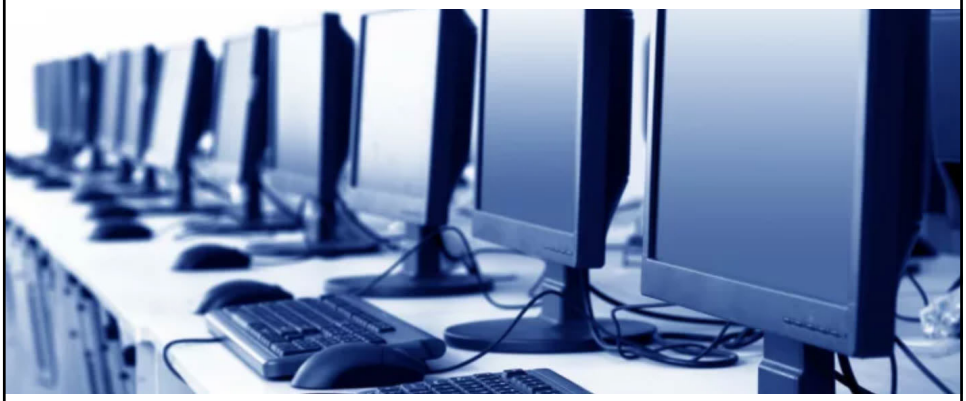
propharma

VALIDATION CENTER



Computer System Validation Basics

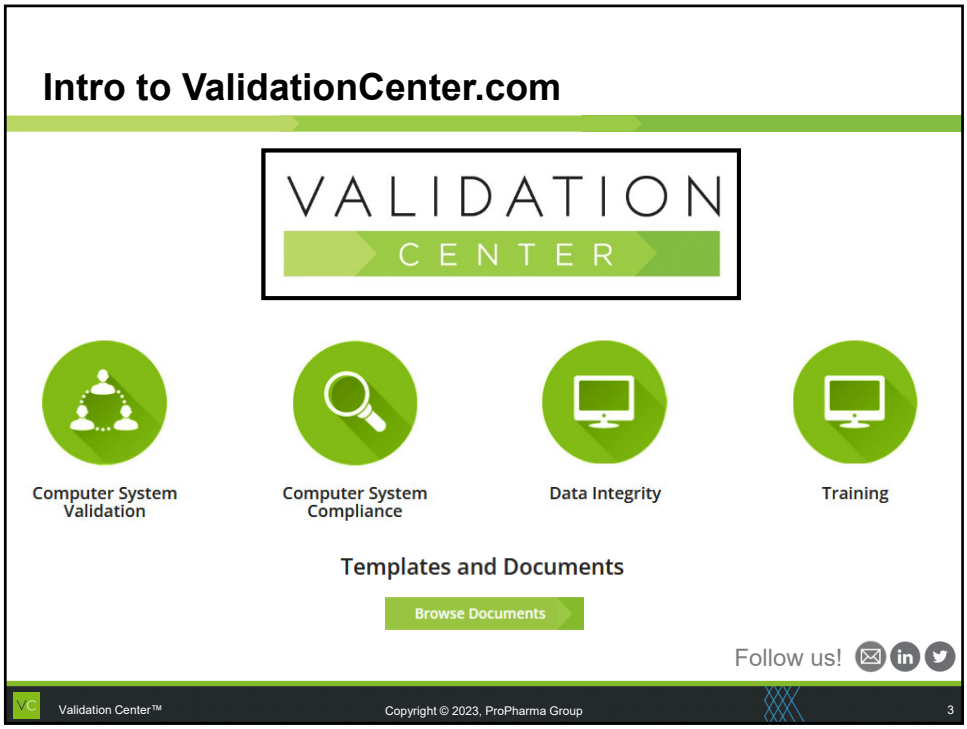
v.23.05

1

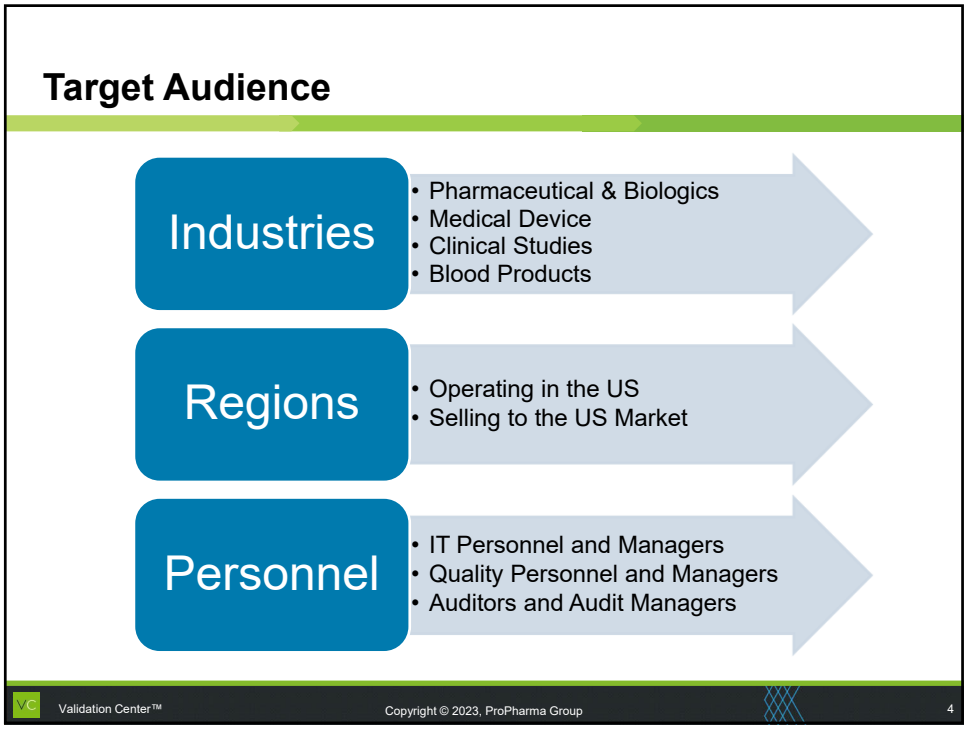
Your Facilitator

- Debra Bartel, MBA, CQA, PMP
- VP, Life Sciences QA
- 30 years' experience specializing in software quality assurance, validation and regulatory compliance, Information Systems project management, and process design.
- Previously held management positions in the pharmaceutical industry in both Quality Assurance and Information Systems organizations
- Active member of American Society for Quality (ASQ), Northeastern Illinois Section, Software Division

2



3



4

Webinar Outline

1. CSV Regulatory Requirements
2. CSV Purpose & Benefits
3. CSV Methodology
4. CSV Scope
5. CSV Failure Consequences
6. CSV Program Implementation

Validation Center™ Copyright © 2023, ProPharma Group 5

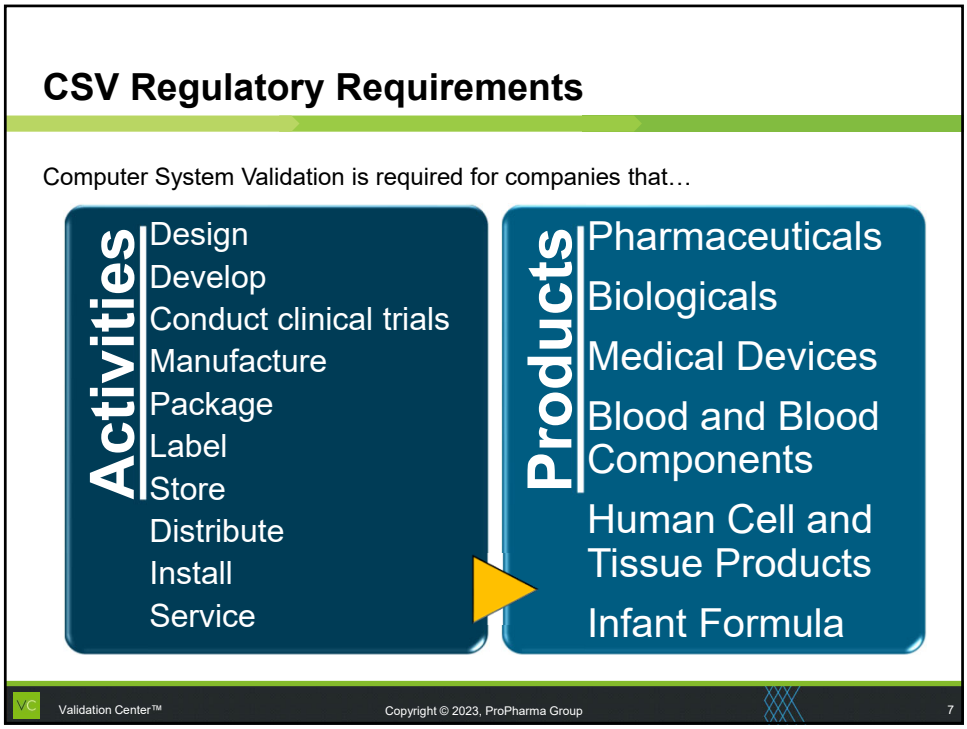
5

CSV Regulatory Requirements

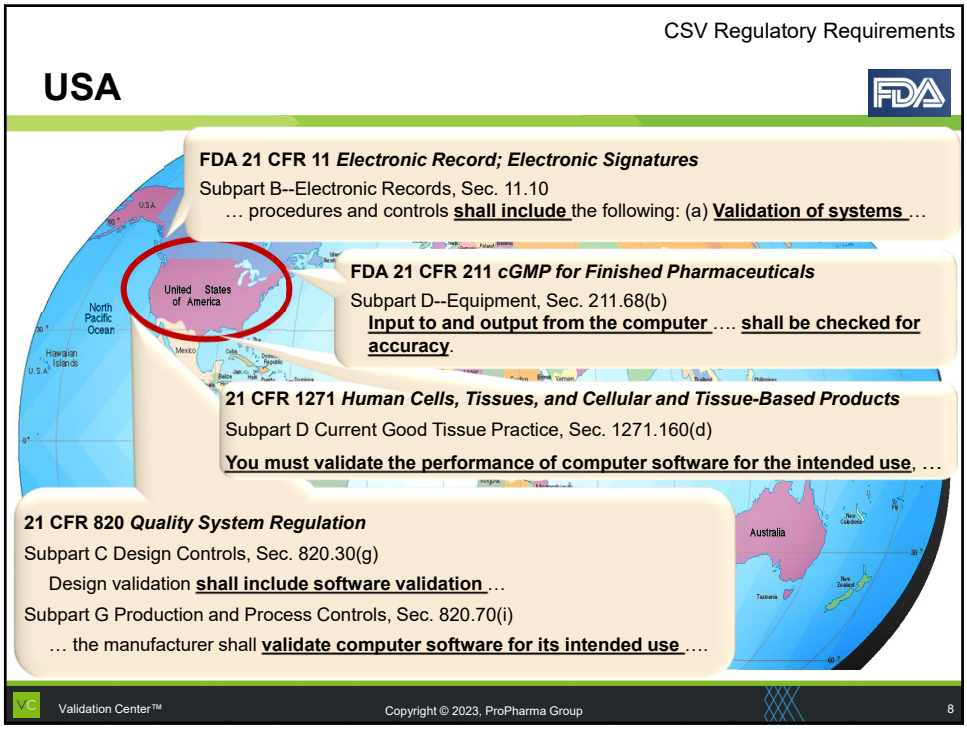
Part 1

Validation Center™ Copyright © 2023, ProPharma Group 6

6



7



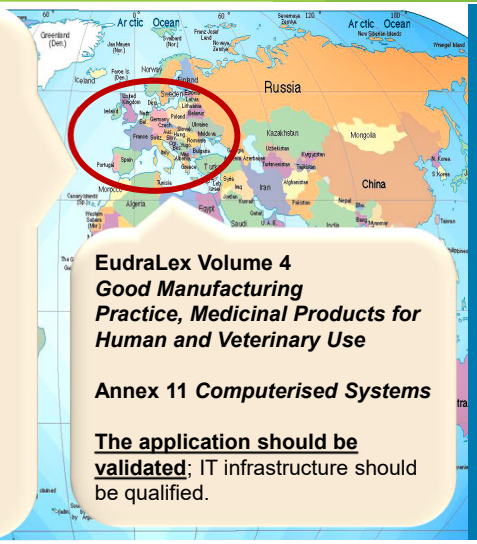
8

European Union

EC COUNCIL DIRECTIVE 93/42/EEC

***ANNEX I* ESSENTIAL REQUIREMENTS**

12.1a For devices which incorporate software or which are medical software in themselves, **the software must be validated** according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.



EudraLex Volume 4 ***Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use***

Annex 11 *Computerised Systems*

The application should be validated; IT infrastructure should be qualified.

- Austria
- Belgium
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Latvia
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden

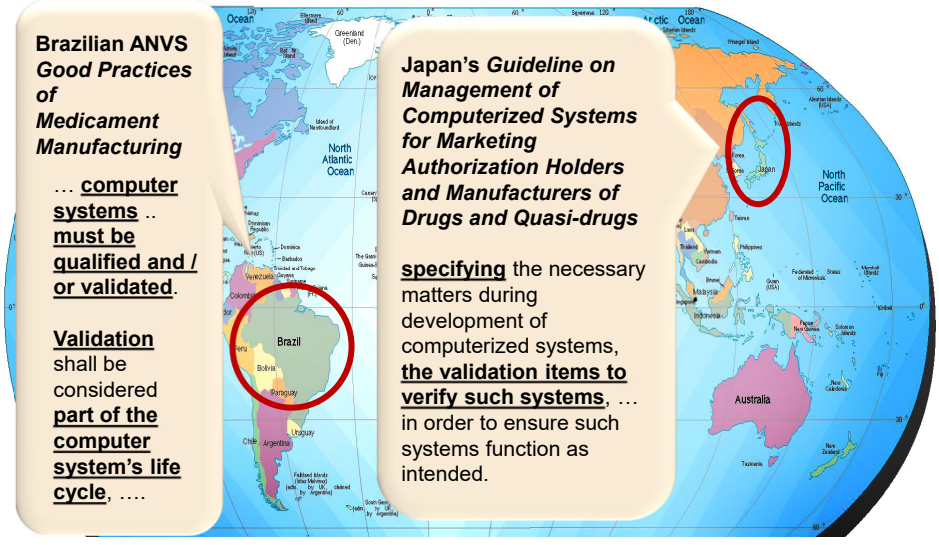
9

Brazil, Japan…

Brazilian ANVS ***Good Practices of Medicament Manufacturing***

… **computer systems** .. **must be qualified and / or validated**.

Validation shall be considered **part of the computer system's life cycle**, ….

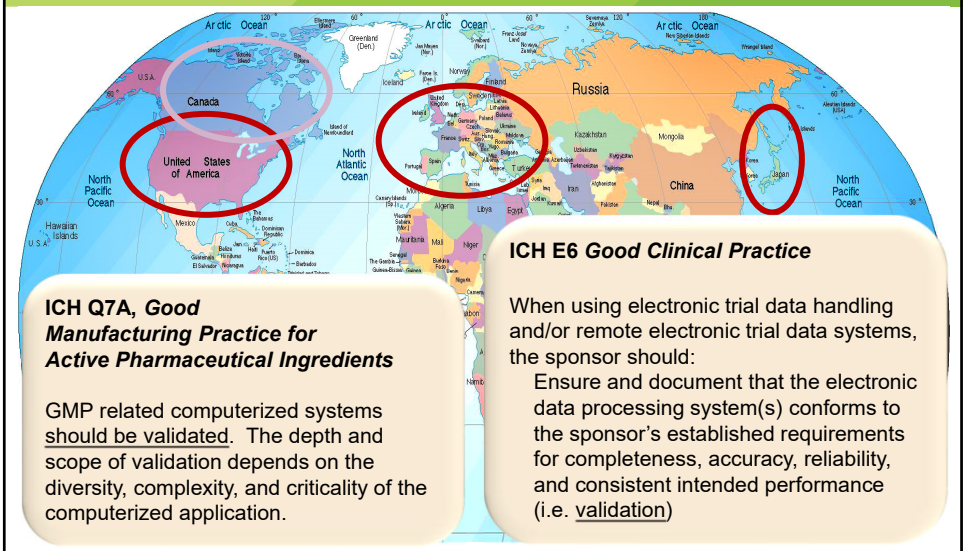


Japan's *Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs*

specifying the necessary matters during development of computerized systems, **the validation items to verify such systems**, … in order to ensure such systems function as intended.

10

ICH



ICH Q7A, *Good Manufacturing Practice for Active Pharmaceutical Ingredients*

GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

ICH E6 *Good Clinical Practice*

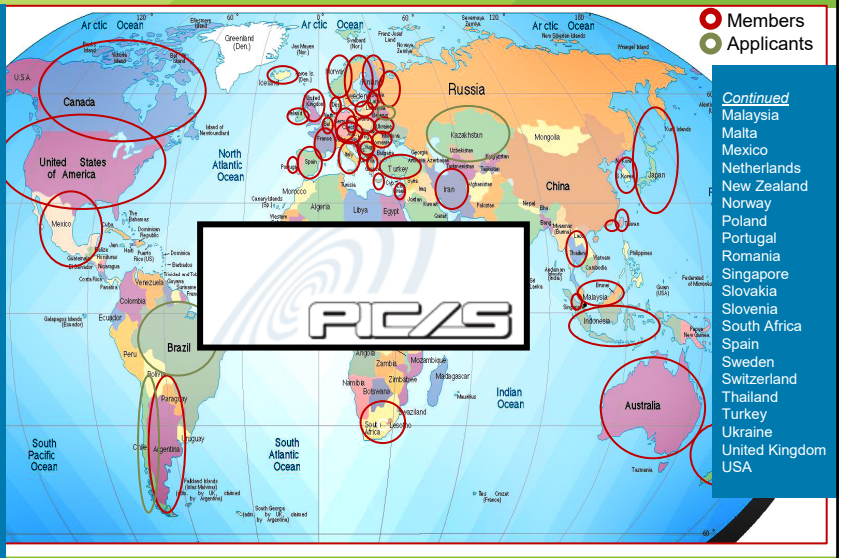
When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation)

11

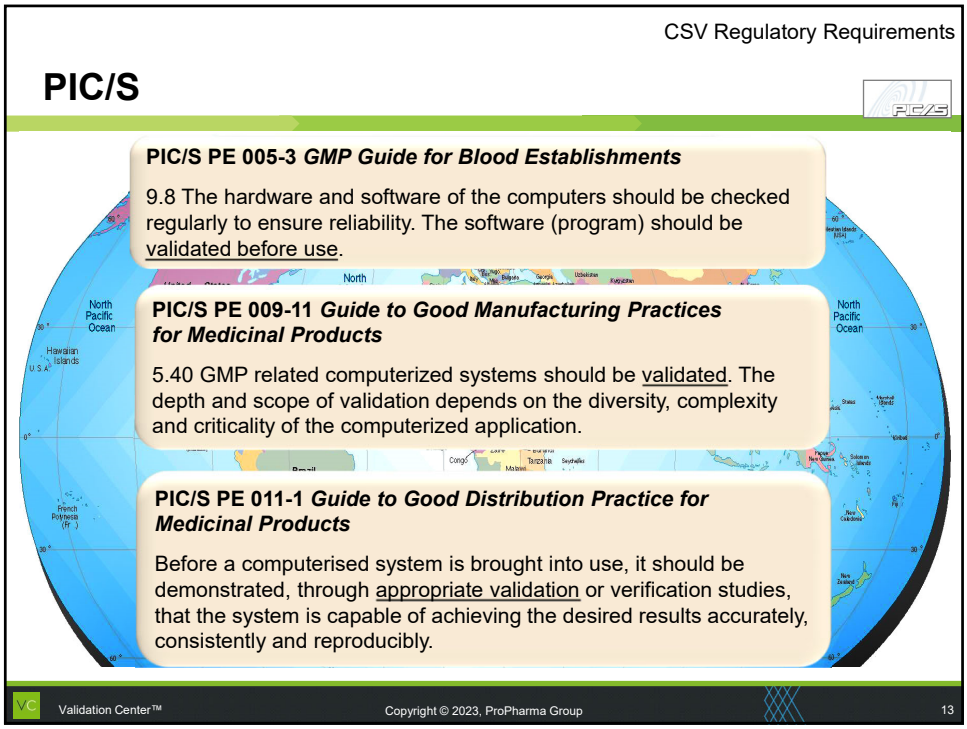
PIC/S

Argentina
Australia
Austria
Belgium
Canada
Chinese Taipei
Croatia
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hong Kong
Hungary
Iceland
Indonesia
Iran
Ireland
Israel
Italy
Japan
Korea
Latvia
Liechtenstein
Lithuania

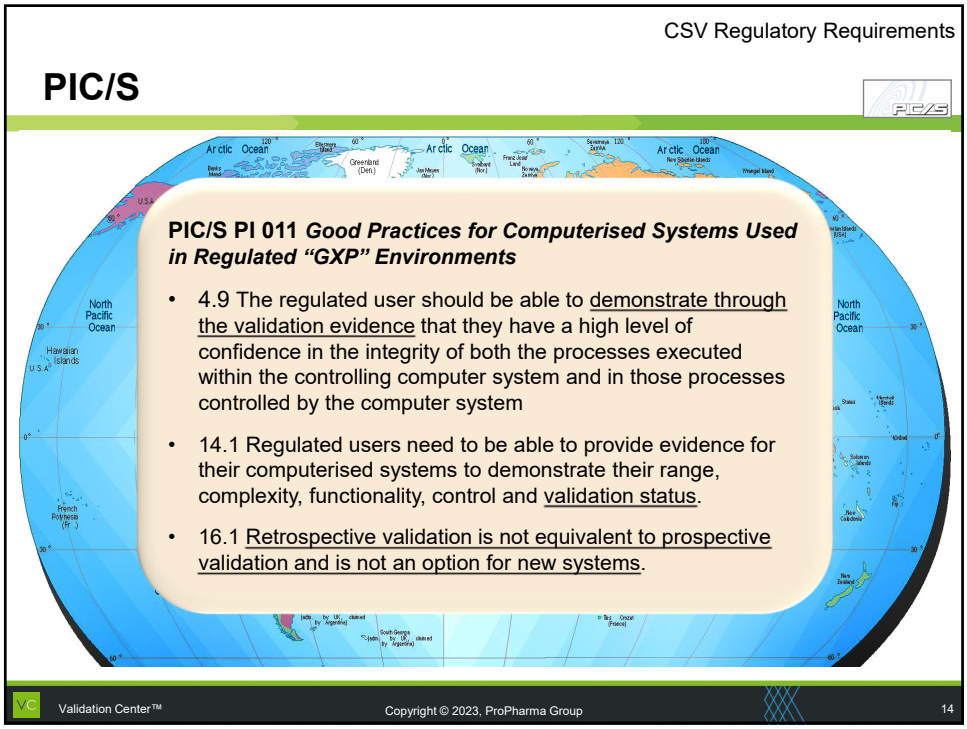


Continued
Malaysia
Malta
Mexico
Netherlands
New Zealand
Norway
Poland
Portugal
Romania
Singapore
Slovakia
Slovenia
South Africa
Spain
Sweden
Switzerland
Thailand
Turkey
Ukraine
United Kingdom
USA

12



13



14

WHO

WHO *Specifications for Pharmaceutical Preparations*

6.3 Critical computerized systems should be validated before use.

WHO *Good Manufacturing Practices for Pharmaceutical Products: Main Principles*

4.11 Particular attention should be paid to the validation of analytical test methods, automated systems and cleaning procedures.

15

CSV Purpose and Benefits

Part 2

16

CSV Purpose and Benefits

Effectiveness

Safety

Integrity

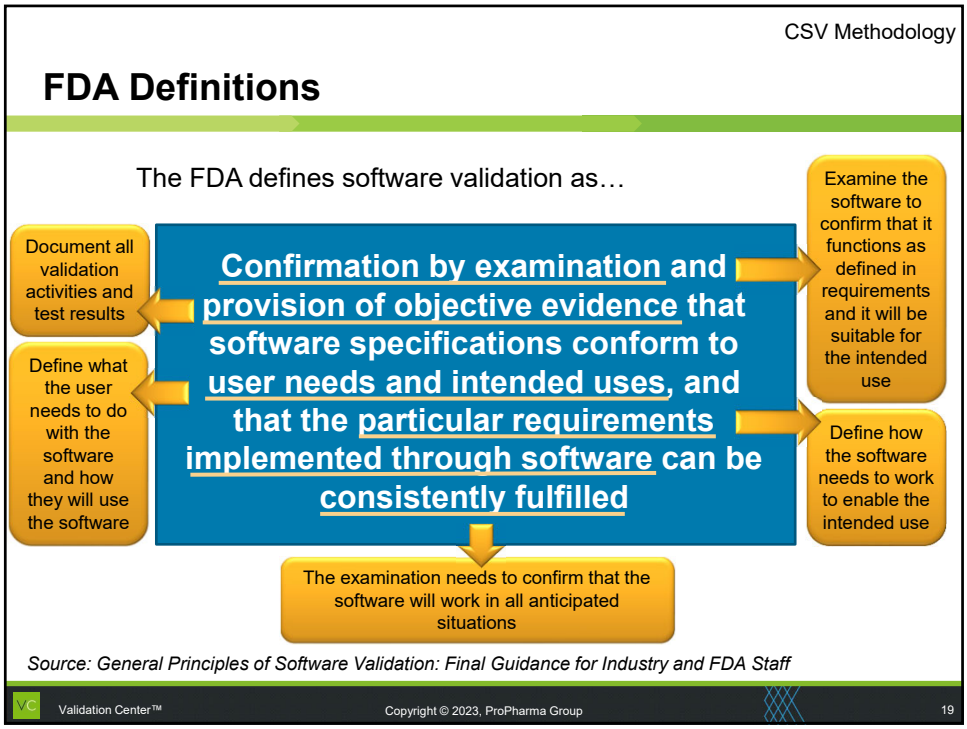
Accuracy

17

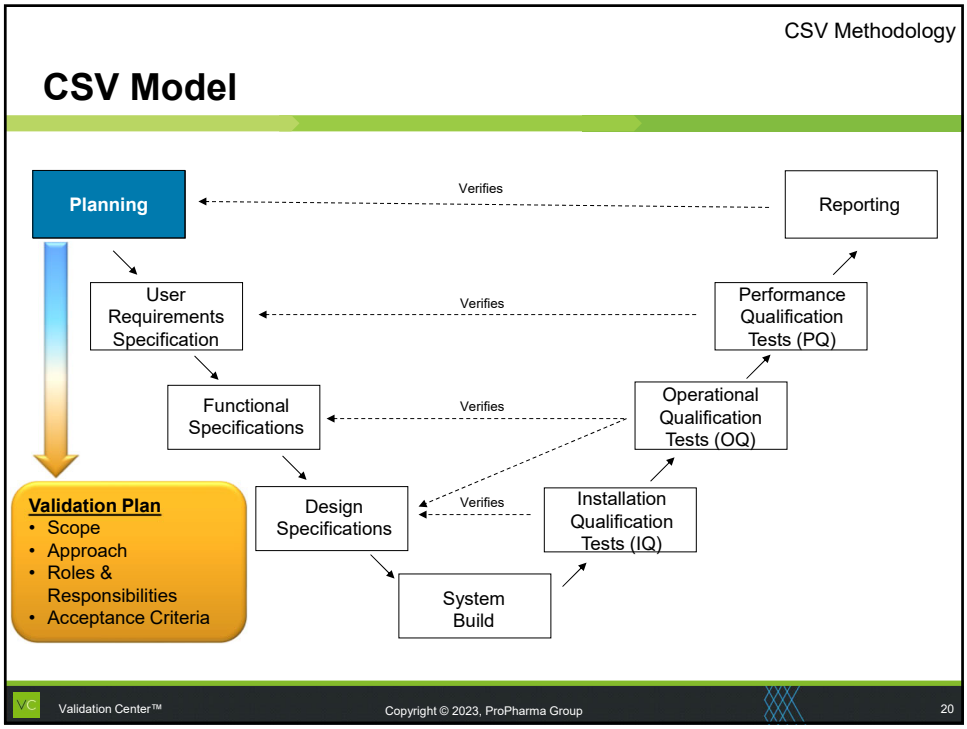
CSV Methodology

Part 3

18

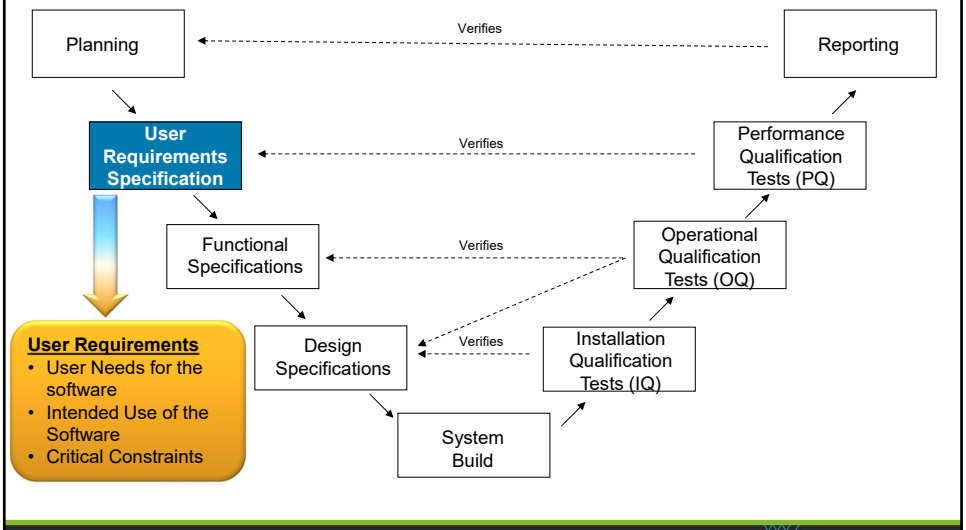


19



20

CSV Model



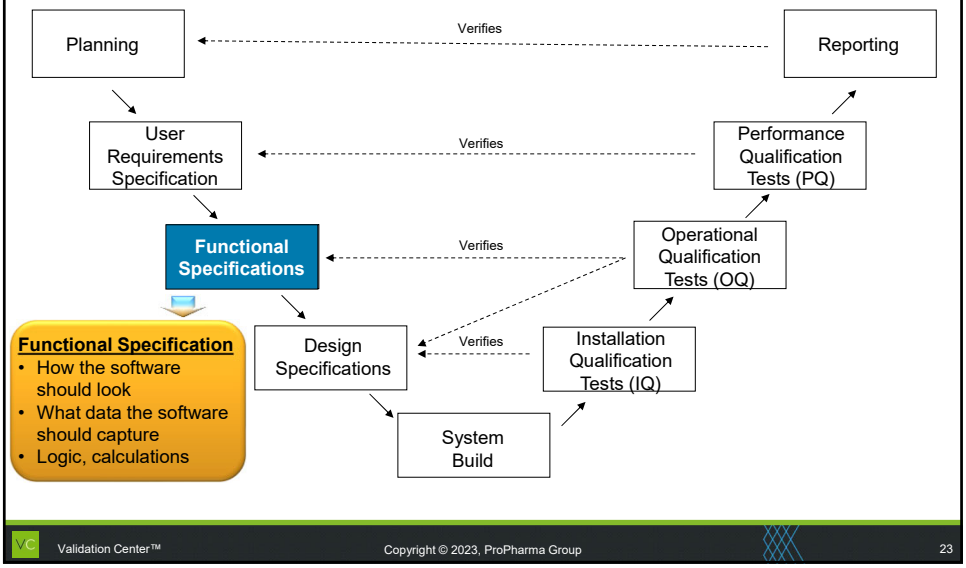
21

User Requirement, examples

1.0 The system shall provide the capability for managing the training requirements for each job	**2.0** The system shall provide the capability for managing the training for each employee	**3.0** The system shall track completion of employee training
14.0 The system shall restrict user access to authorized personnel	**15.0** The system shall require User IDs to be unique	**16.0** The system shall require passwords that cannot be easily guessed
25.0. The system shall provide reports of employee training status	**26.0.** The system shall provide reports of training charges by department	**32.** The system shall provide an audit trail that complies with 21 CFR Part 11

22

CSV Model



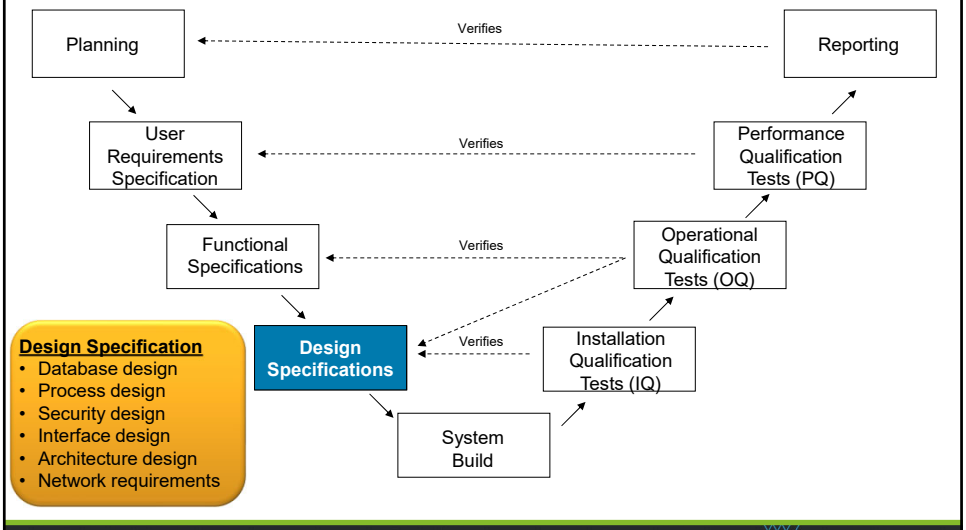
23

Functional Requirements, example

User Requirement 2.0	Functional Requirements
The system shall provide the capability for managing the training for each employee	2.1 The system shall require that each employee is assigned to a 2.1.1 Job ID 2.1.2 Department.
	2.2 For each employee, the system shall require entry of 2.2.1 the employee's e-mail address 2.2.2 the supervisor's e-mail address.
	2.3 The system shall send an email notification to employees assigned to a Job ID for any new of revised training courses assigned to the Job ID.
	2.4 The system shall send assigned trainees an email training notification reminder every day until training is complete.
	2.5 For overdue training, the system shall send the assigned trainee's supervisor an email training notification reminder every day until training is complete.

24

CSV Model



25

Design Element, examples

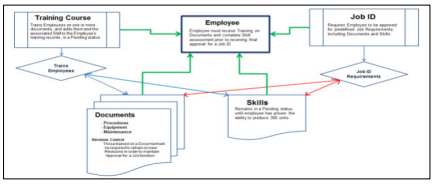
Hardware

Application Server Requirements	Component Specification
Processor	Intel Xeon E5506 Nehalem-EP 2.13 GHz 4 x 256 KB L2 Cache 4 MB L3 Cache LGA 1366 80W 64-bit
Memory	8 GB (30 GB Available)
HDD Configuration	300.0 GB 10K RAID 5
Operating System	Windows Server 2012

Configuration

Access Configuration • M: Add, Change, Inactivate • V: View only • X: No Access	Job Data	Doc. Data	Course Data	Audit Trails
System Admin	M	M	M	V
Training Manager	M	M	M	V
Training Personnel	M	M	M	V
Laboratory Supervisor	V	V	V	X
Laboratory Personnel	X	V	X	X

Database Structure



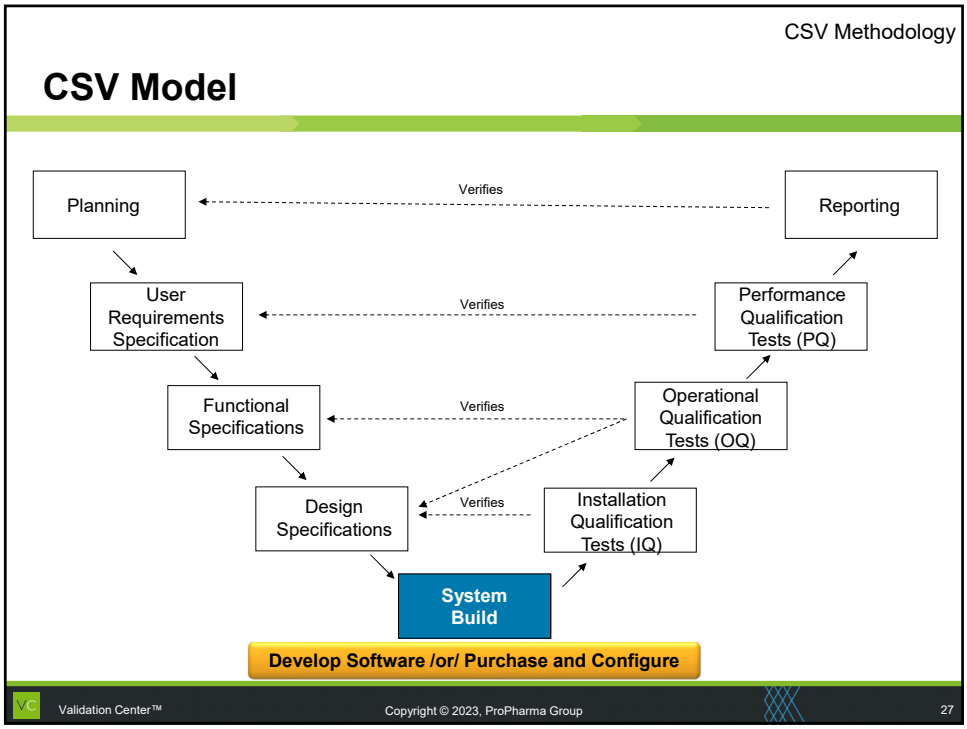
Customization

Technology: Develop CLASS/SAP interface in JAVA v7.1 and AIP AT.

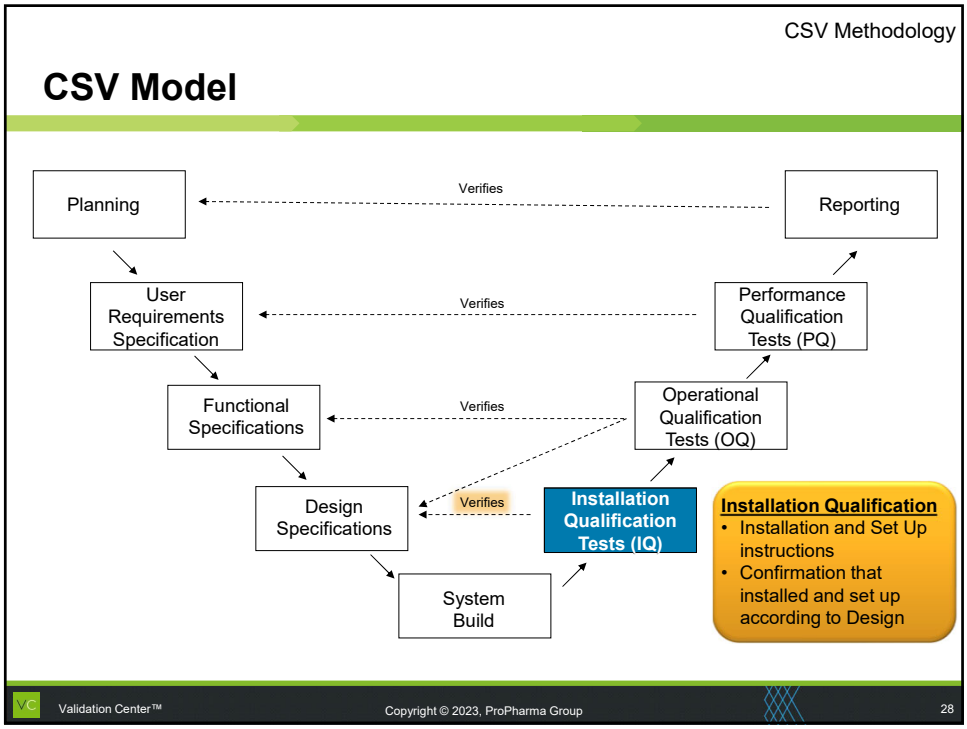
Data Mapping	CLASS Field	AIP AT Field	Transformation
Course Identifier	Course ID	Expense Reference 1	None
Training Date	Course Date	Expense Date	None
Department Identifier	Employee Department	Expense Department	AIP AT: look-up GL-Dept value associated with xxxx in D-XREF-GL Table
Cost	Course Cost	Expense	None

Failure Notifications must be sent in the following situations:
- Interface job fails to complete within 15 minutes
- No value found in table D-XREF-GL

26



27



28

IQ, examples

Hardware

Step	Element	Specification	Actual	Pass/Fail	Verified By
1	Processor	Intel Xeon E5506 Nehalem-EP 2.13 GHz 4 x 256 KB L2 Cache 4 MB L3 Cache LGA 1366 80W 64-bit			
2	Memory	8 GB (30 GB Available)			
3	HDD Configuration	300.0 GB 10K RAID 5			
4	Operating System	Windows Server 2012			

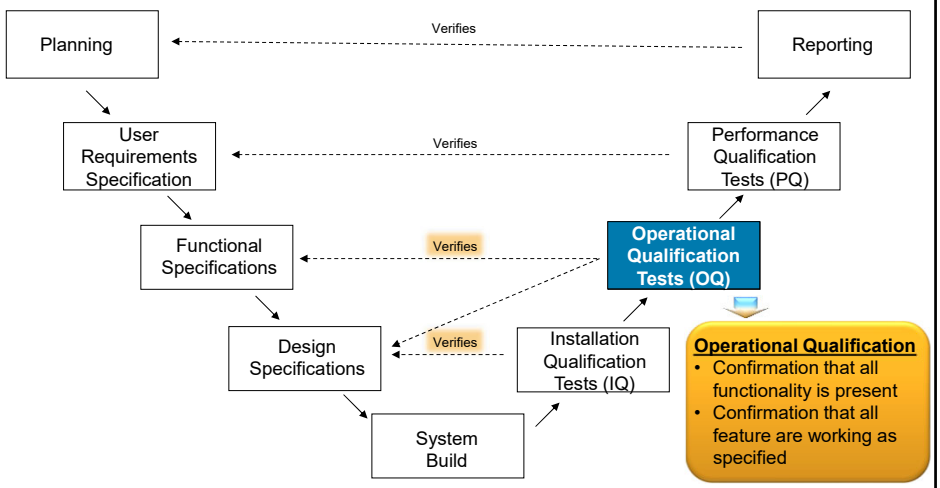
Customization

Section 1.0 Installation of CLASS/SAP Interface version 1

Step	Action	Expected Result	Actual Result	Pass/ Fail	Executor Initial/Date
1.1	Move object "CL-SP-098-VS" to folder D:/Interface/Prod/Program	Object "CL-SP-098-VS" exists in folder D:/Interface/Prod/Program			
1.2	Set permission for object "CL-SP-098-VS" to Security Level ADMIN-ONLY	Permission for object "CL-SP-098-VS" is Security Level ADMIN-ONLY			
1.3	Move the following files to folder D:/Interface/Prod/Data • D-XREF-098 • MSG-098-V1	The following files are in folder D:/Interface/Prod/Data • D-XREF-098 • MSG-098-V1			

29

CSV Model



30

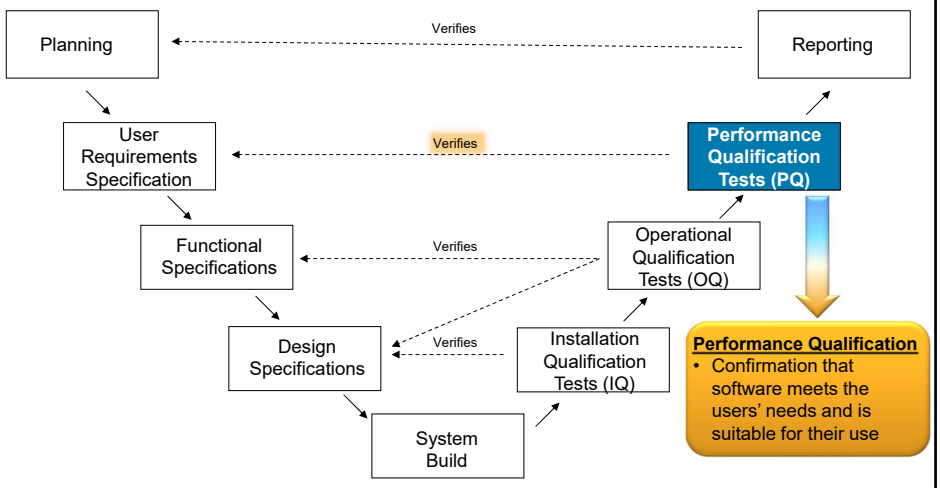
OQ, example

Data Setup		
Step	**Description/Action**	**Verifier Initial/Date**
1.	Employees 3010, 3011, and 3012 are assigned to complete training on Document QLY-003	
2.	Employee 2010 is the supervisor for Employees 3010, 3011, and 3012	
3.	Employee 3012 has completed training on Document QLY-003 Employees 3010 and 3011 have not completed training on Document QLY-003	
End of Data Setup		

Test Case 3					
Step	**Description/Action**	**Expected Result**	**Actual Result**	**Pass/ Fail**	**Tester Initial/Date**
3.3	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 3010. - Capture Screen Shot of the Overdue Training email	An Overdue Training email notification for Document QLY-003 was received.			
3.4	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 2010. - Capture Screen Shot of the Overdue Training email	An Overdue Training email notification for Document QLY-003 was received for employee 3010			
3.5	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 3012…	No Overdue Training email notification for Document QLY-003 was received…			

31

CSV Model



32

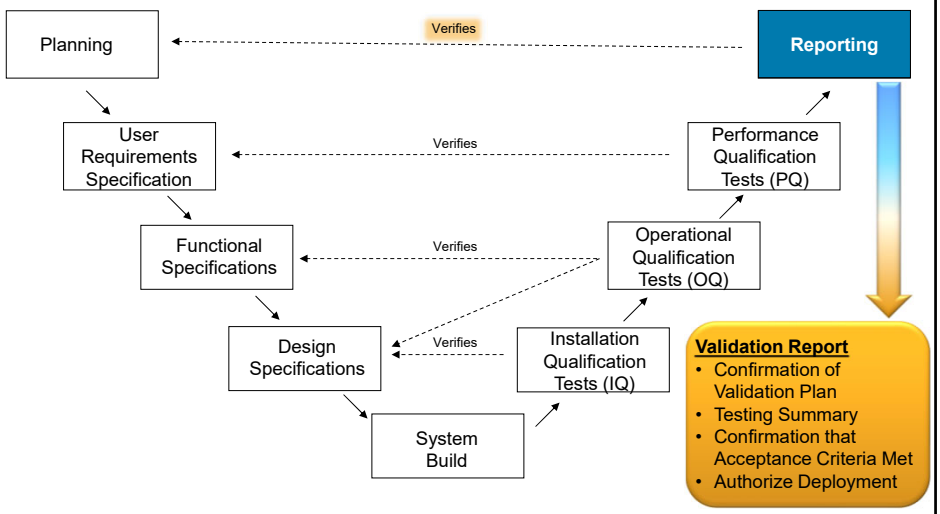
PQ, example

Data Setup		
Step	**Description/Action**	**Verifier Initial/Date**
1.	Employees 3010, 3011, and 3012 are assigned to complete training on Document QLY-003	
2.	Employee 2010 is the supervisor for Employees 3010, 3011, and 3012	
3.	Employee 3012 has completed training on Document QLY-003 Employees 3010 and 3011 have not completed training on Document QLY-003	
End of Data Setup		

Test Case 3					
Step	**Description/Action**	**Expected Result**	**Actual Result**	**Pass/ Fail**	**Tester Initial/Date**
3.3	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 3010. - Capture Screen Shot of the Overdue Training email	An Overdue Training email notification for Document QLY-003 was received.			
3.4	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 2010. - Capture Screen Shot of the Overdue Training email	An Overdue Training email notification for Document QLY-003 was received for employee 3010			
3.5	On the day after the Training Due Date recorded in step 1.9, launch email application for Employee 3012…	No Overdue Training email notification for Document QLY-003 was received…			

33

CSV Model



34

Terminology

VALIDATION

Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

VERIFICATION
…consistency, completeness, and correctness of the software and its supporting documentation, ….

- URS Approval
- FS Approval
- Design Review
- Code Walkthrough
- Unit Testing
- Trace Matrix
- Validation Report
- Performance Qualification
- Operational Qualification
- Installation Qualification
- SOP Review
- Training Review

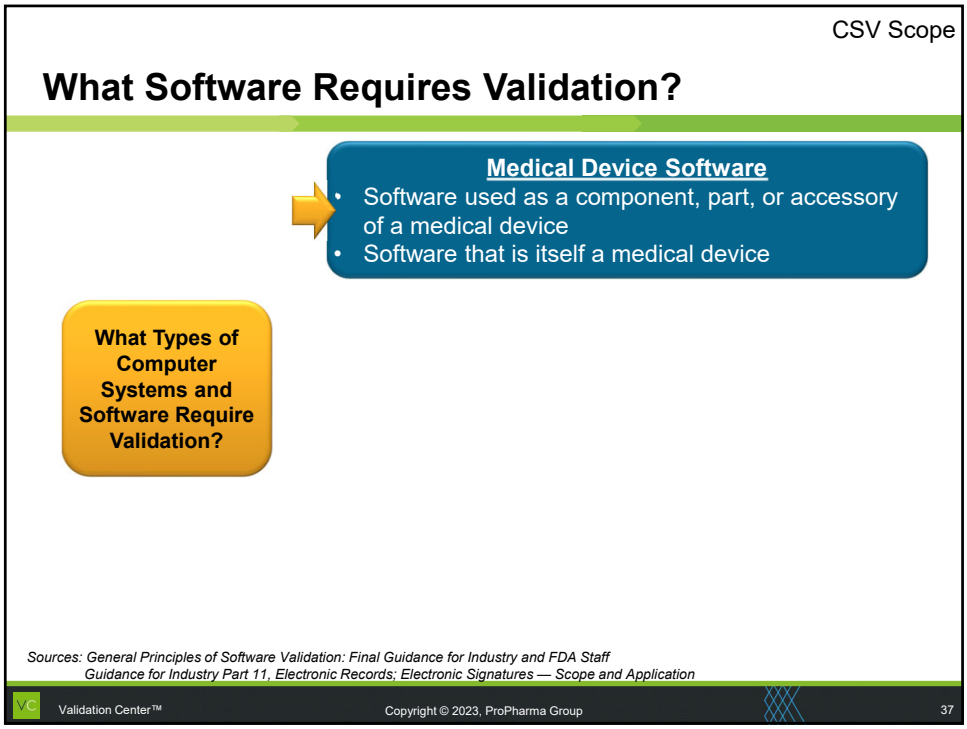
QUALIFICATION
Formal testing to demonstrate that the software meets its specified requirements.

35

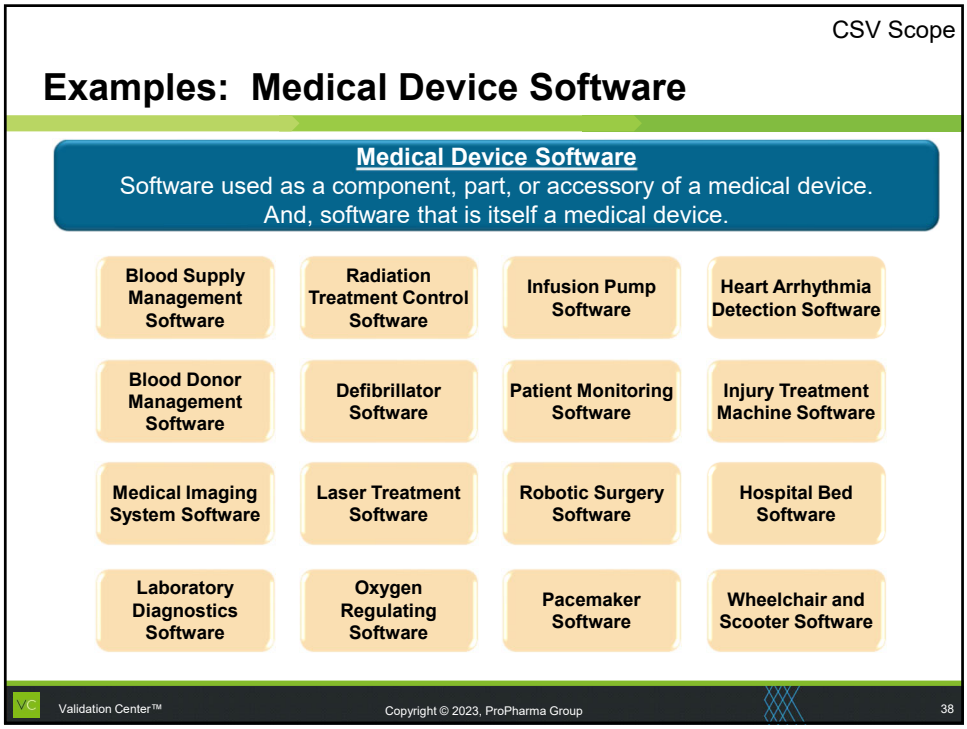
CSV Scope

Part 4

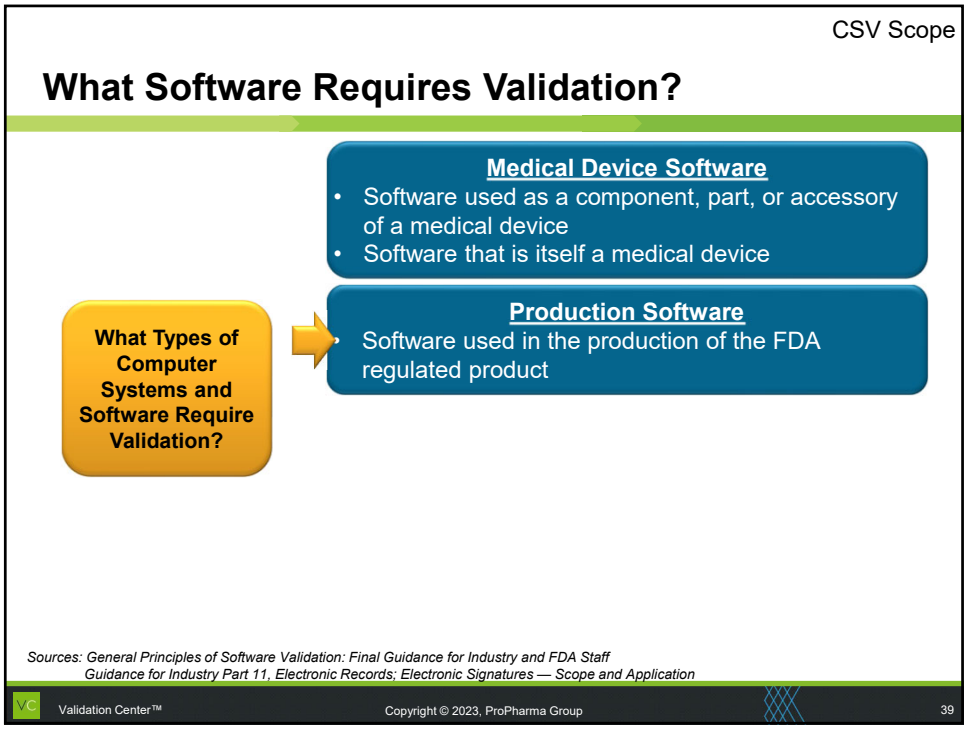
36



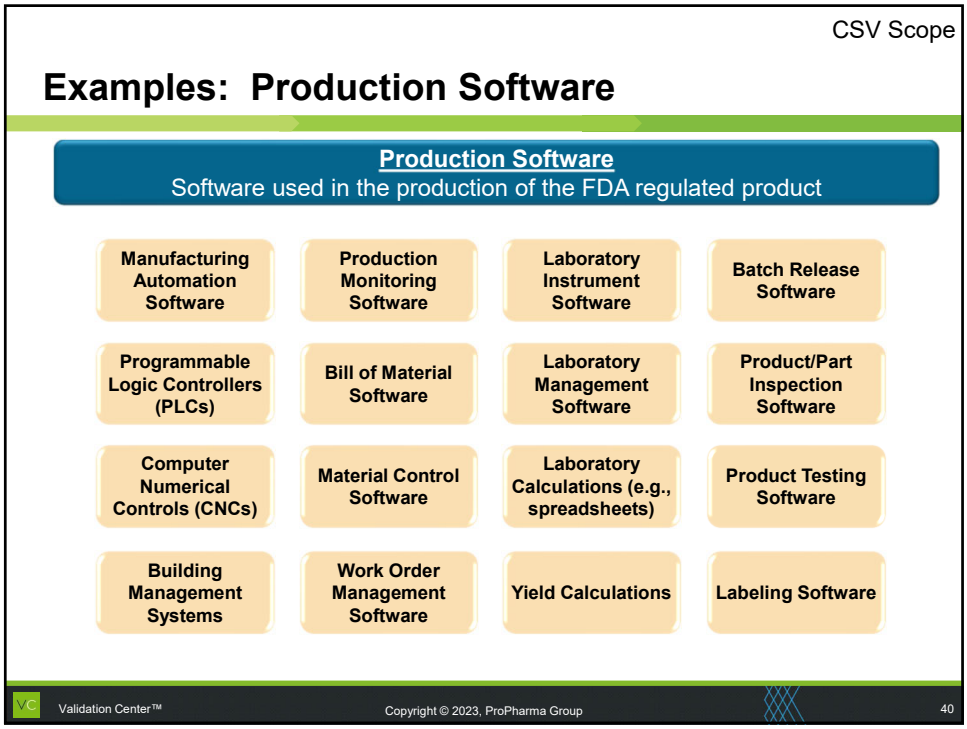
37



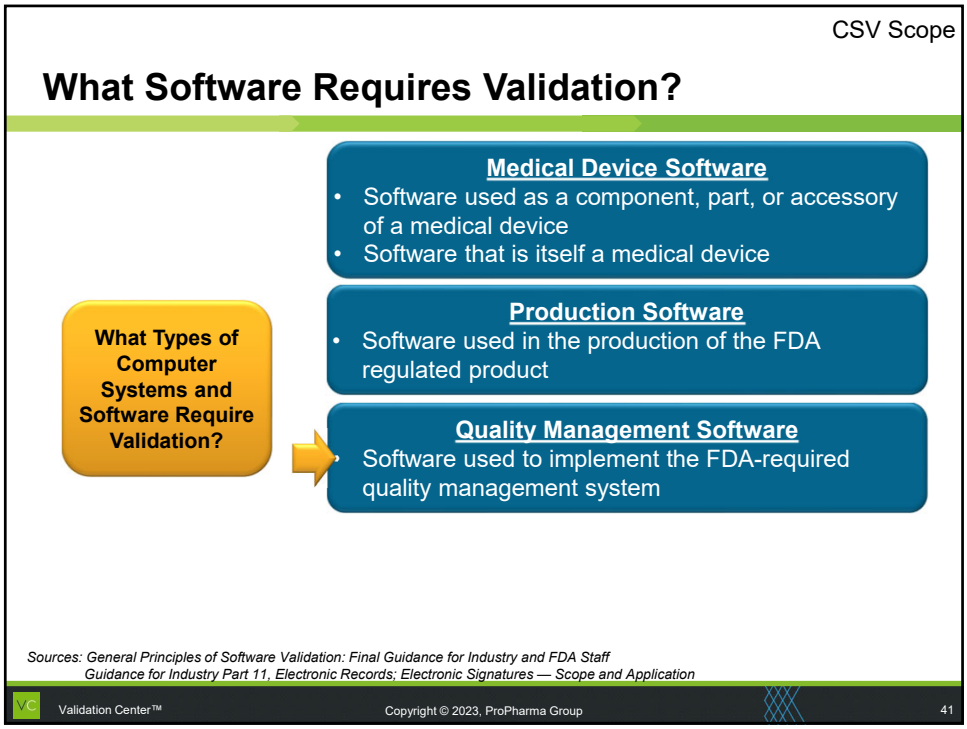
38



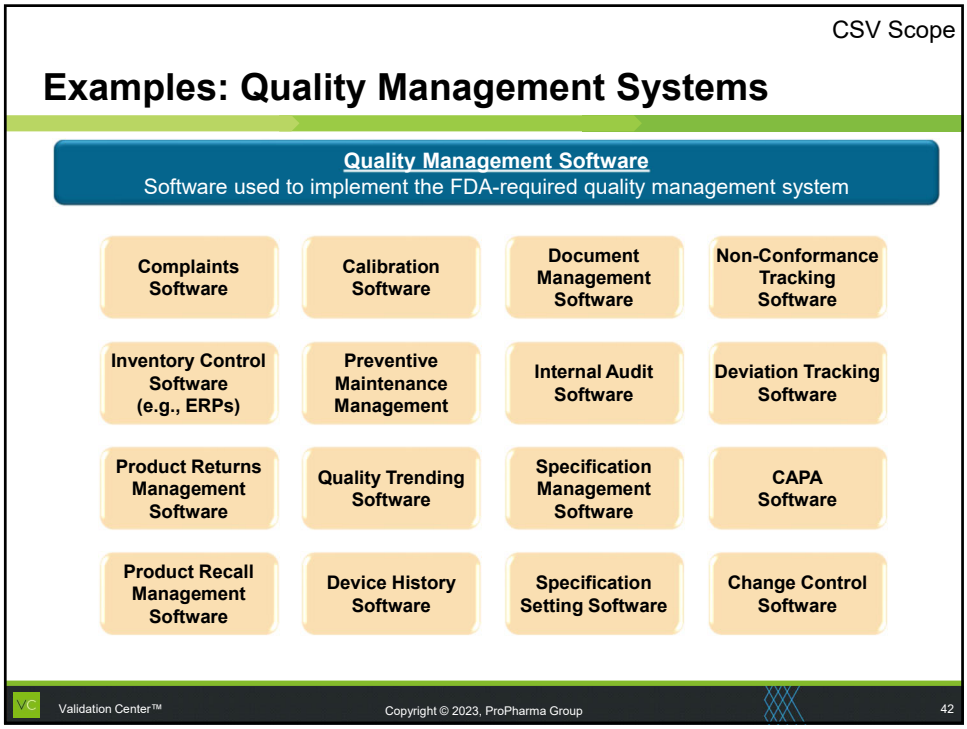
39



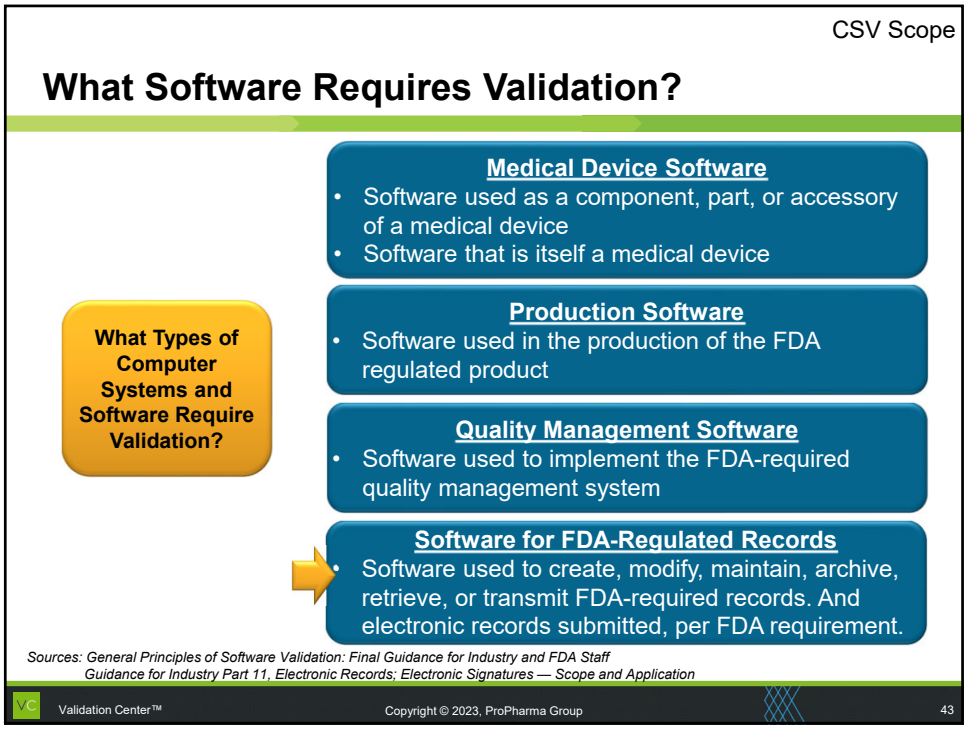
40



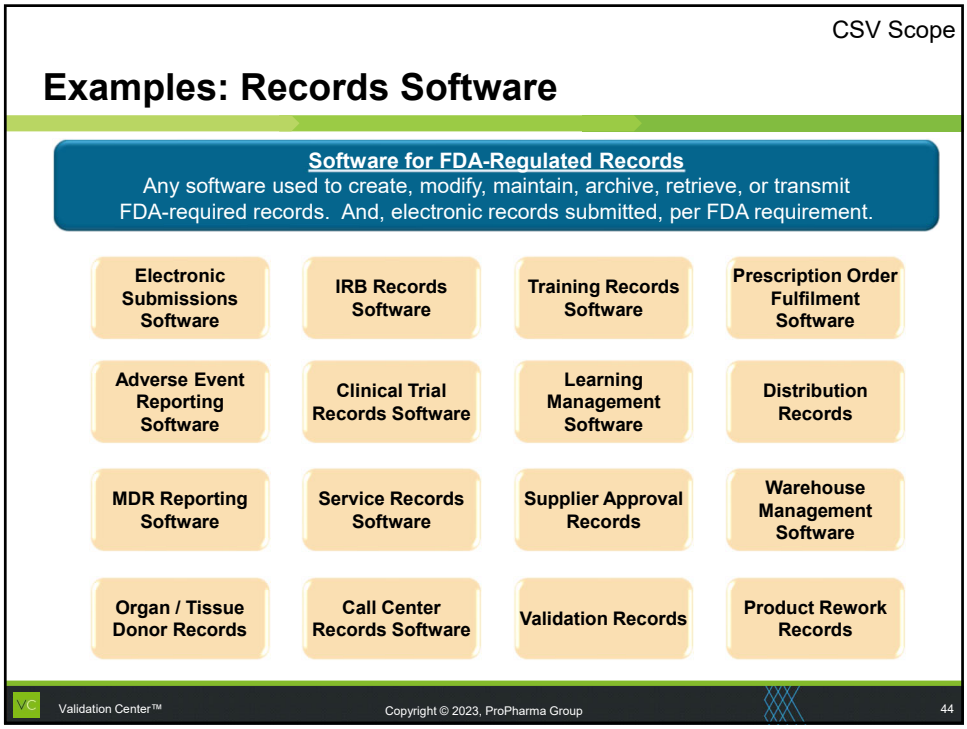
41



42



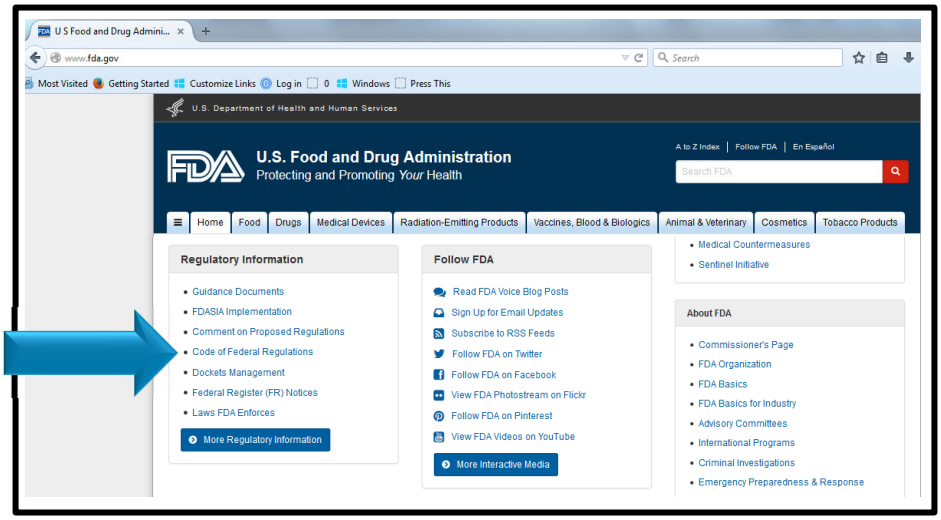
43



44

CSV Scope

FDA Regulations



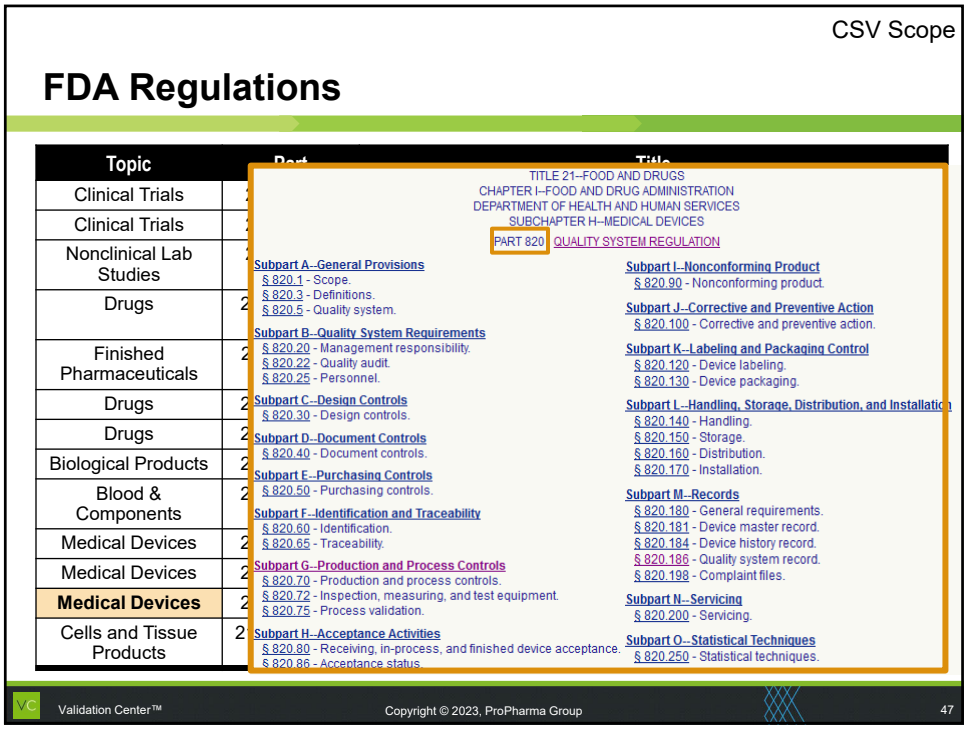
45

CSV Scope

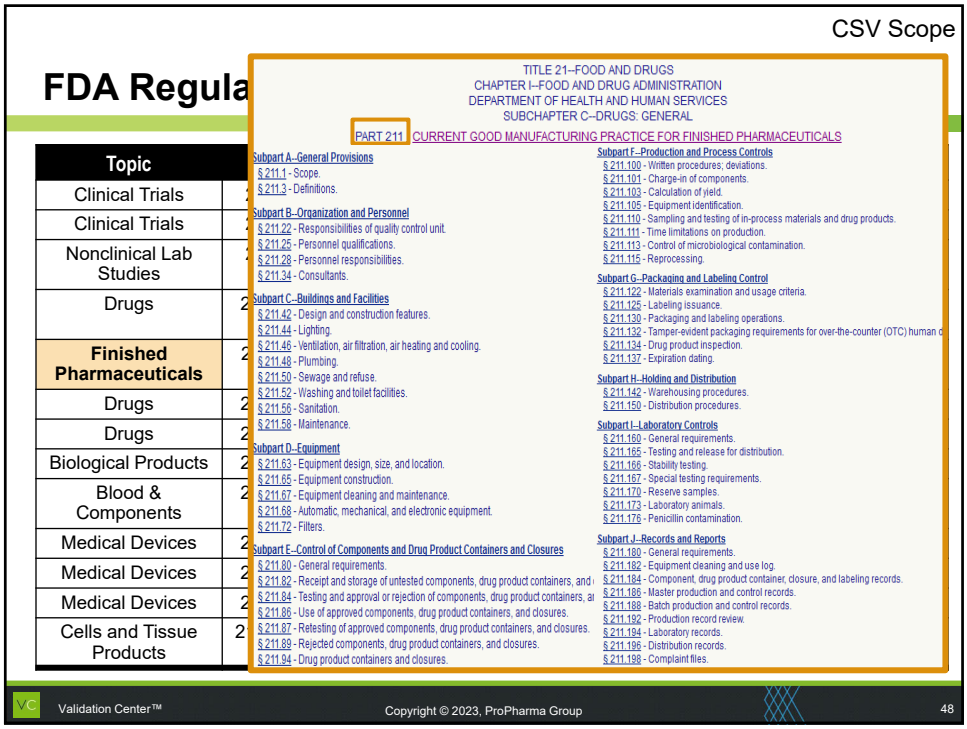
FDA Regulations

Topic	Part	Title
Clinical Trials	21 CFR 50	Protection of Human Subjects
Clinical Trials	21 CFR 56	Institutional Review Boards
Nonclinical Lab Studies	21 CFR 58	Good Laboratory Practice for Nonclinical Laboratory Studies
Drugs	21 CFR 210	Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
Finished Pharmaceuticals	21 CFR 211	Current Good Manufacturing Practice for Finished Pharmaceuticals
Drugs	21 CFR 312	Investigational New Drug Application
Drugs	21 CFR 314	Application for FDA Approval to Market a New Drug
Biological Products	21 CFR 600	Biological Products: General
Blood & Components	21 CFR 606	Current Good Manufacturing Practice for Blood and Blood Components
Medical Devices	21 CFR 803	Medical Device Reporting
Medical Devices	21 CFR 806	Medical Devices: Reports of Corrections and Removals
Medical Devices	21 CFR 820	Quality System Regulation
Cells and Tissue Products	21 CFR 1271	Human Cells, Tissues, and Cellular and Tissue-Based Products

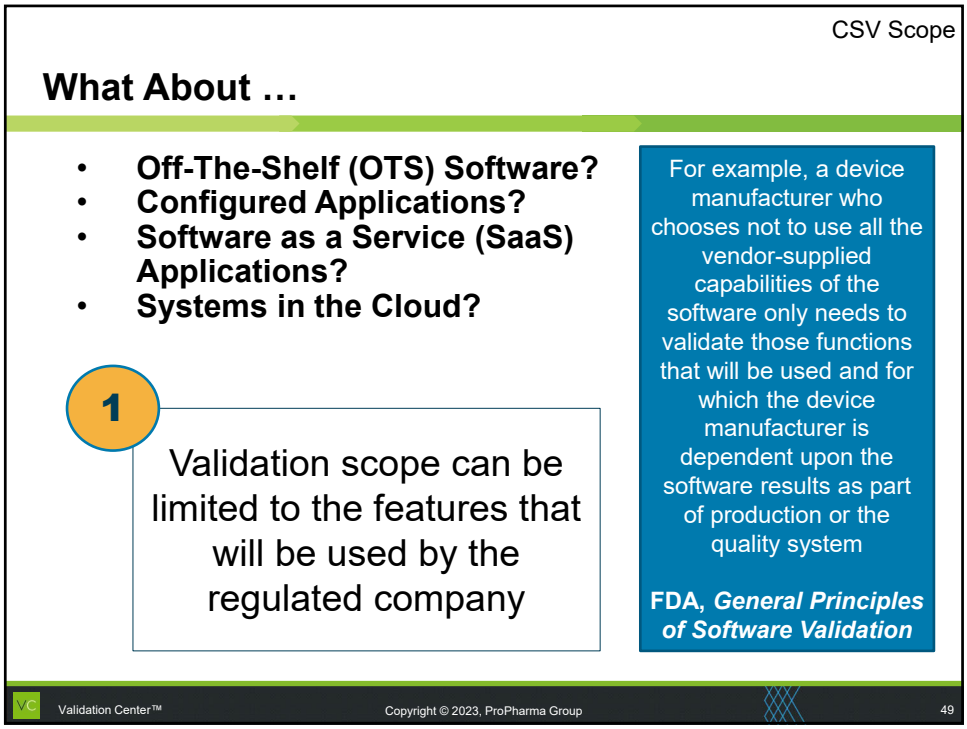
46



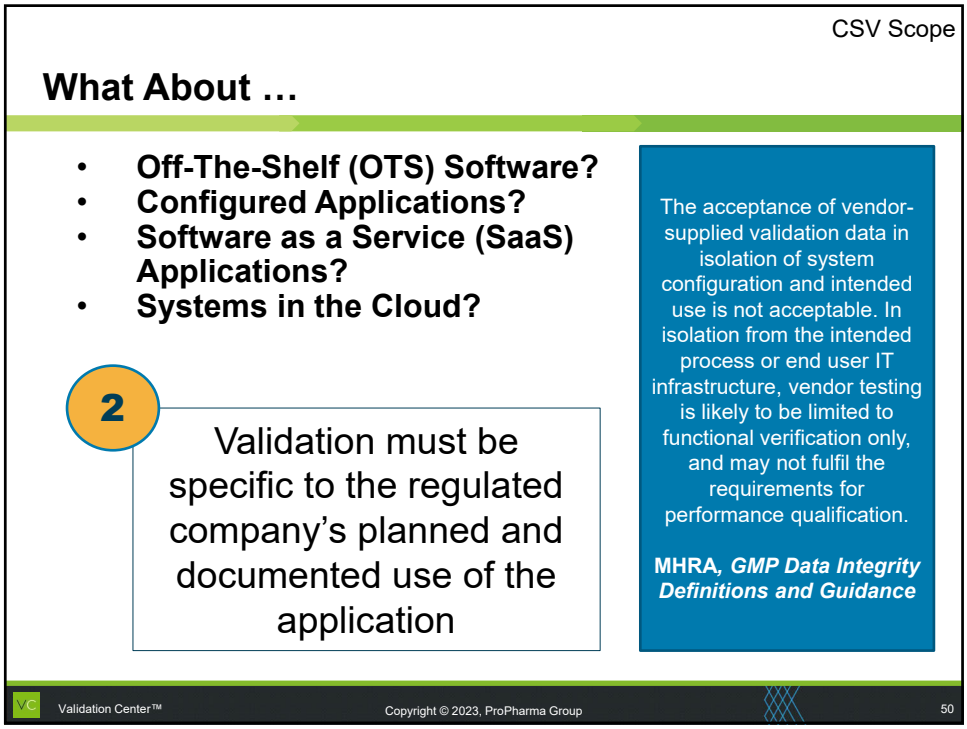
47



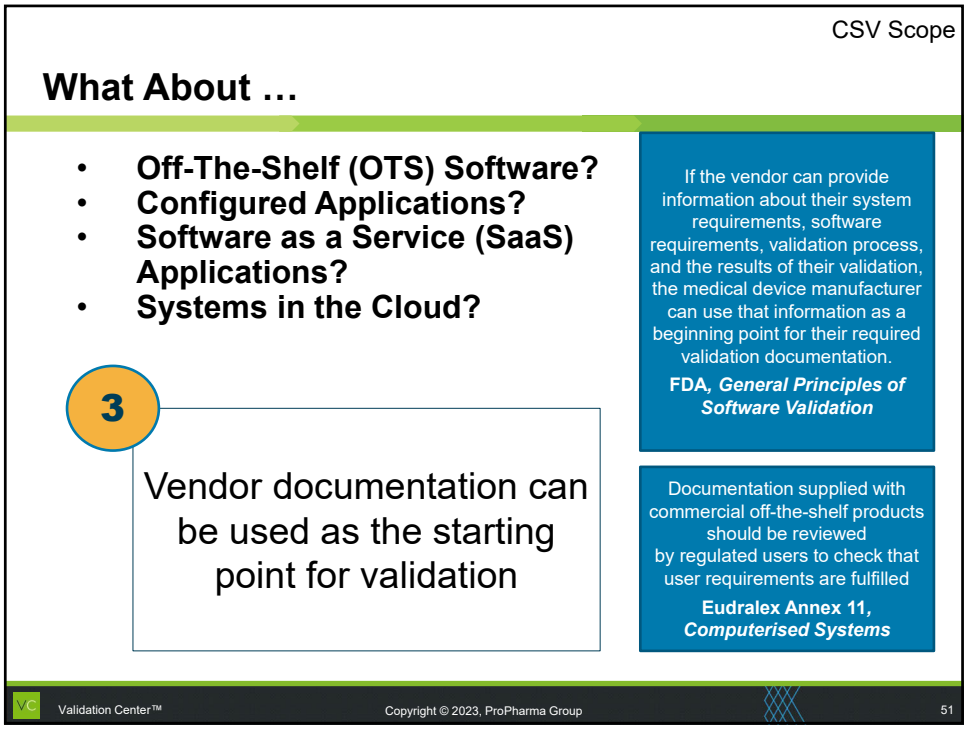
48



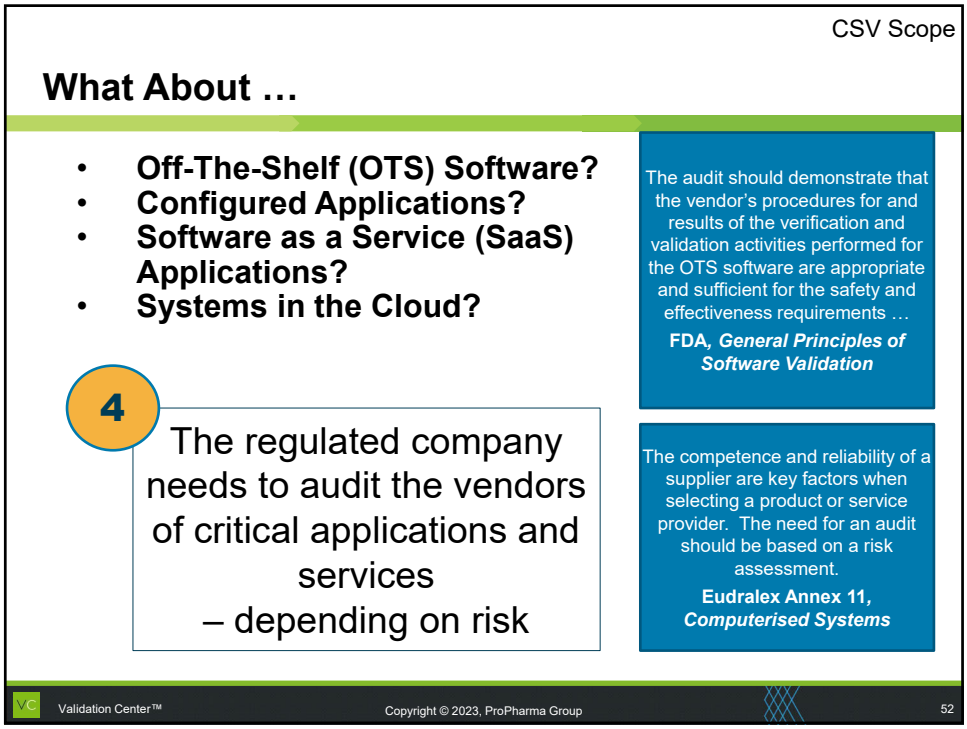
49



50



51



52

What About …

- **Off-The-Shelf (OTS) Software?**
- **Configured Applications?**
- **Software as a Service (SaaS) Applications?**
- **Systems in the Cloud?**

5

Formal agreements are required to document responsibilities

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.

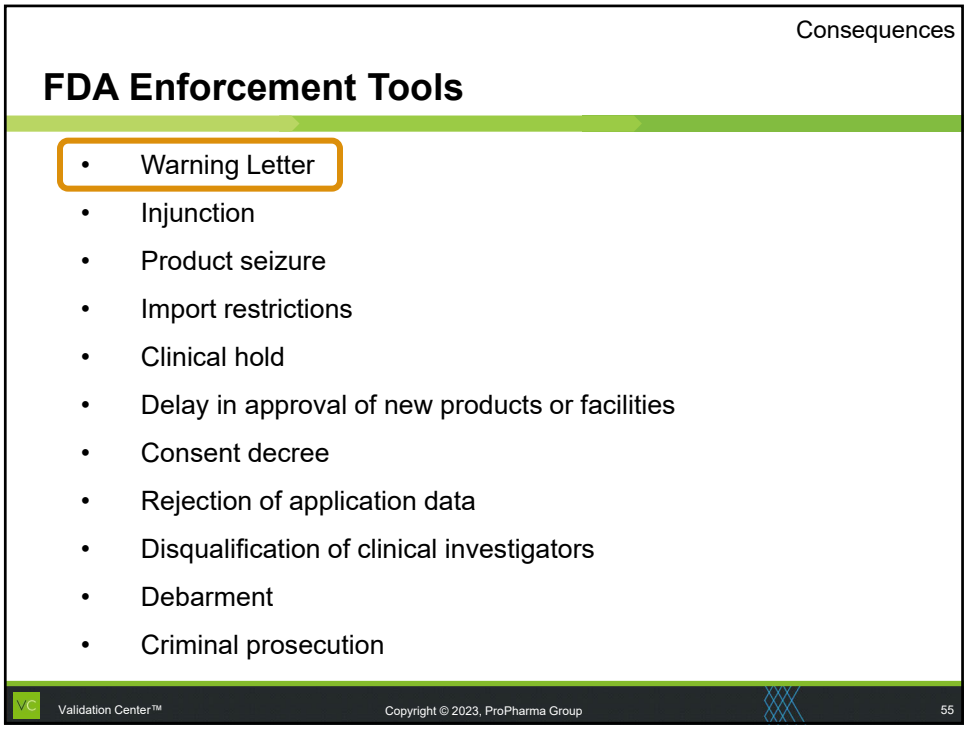
Eudralex Annex 11, *Computerised Systems*

53

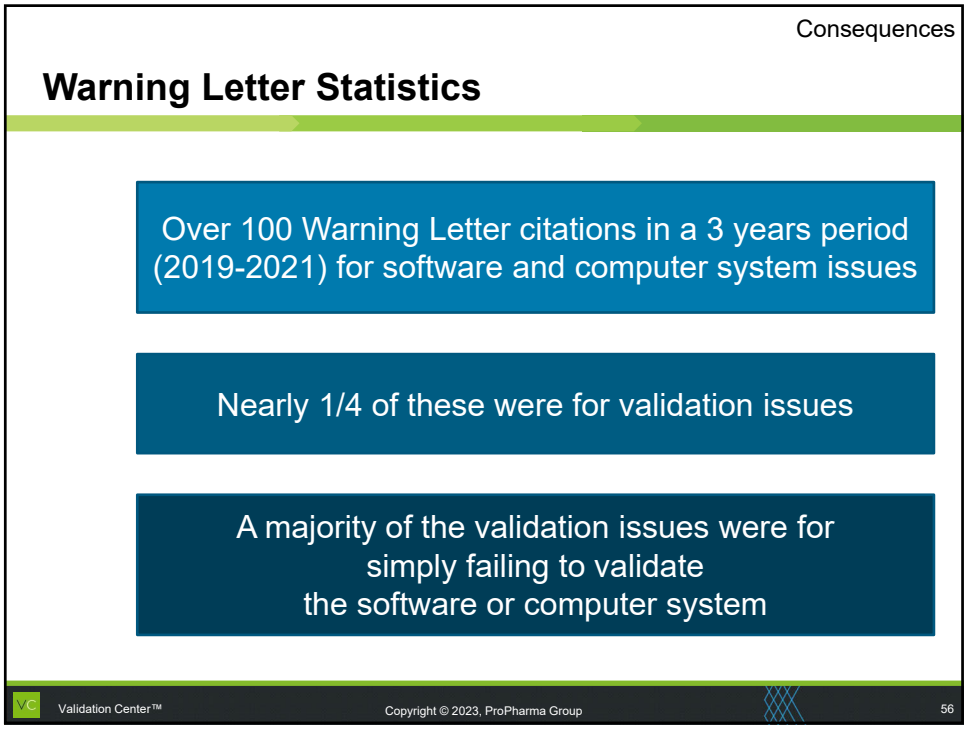
CSV Failure Consequences

Part 5

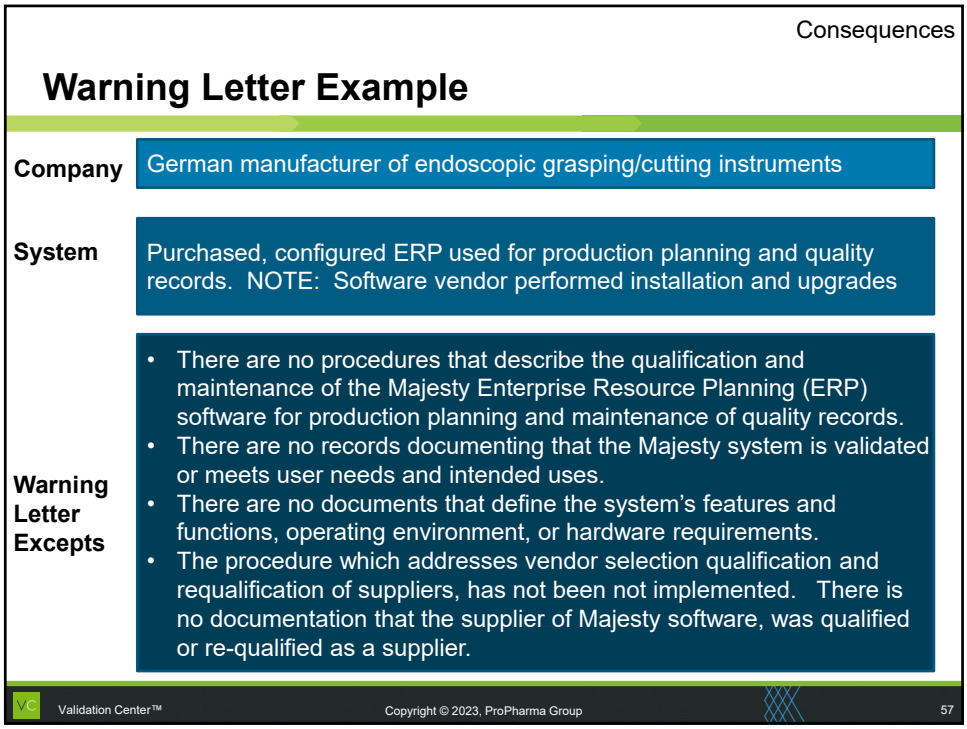
54



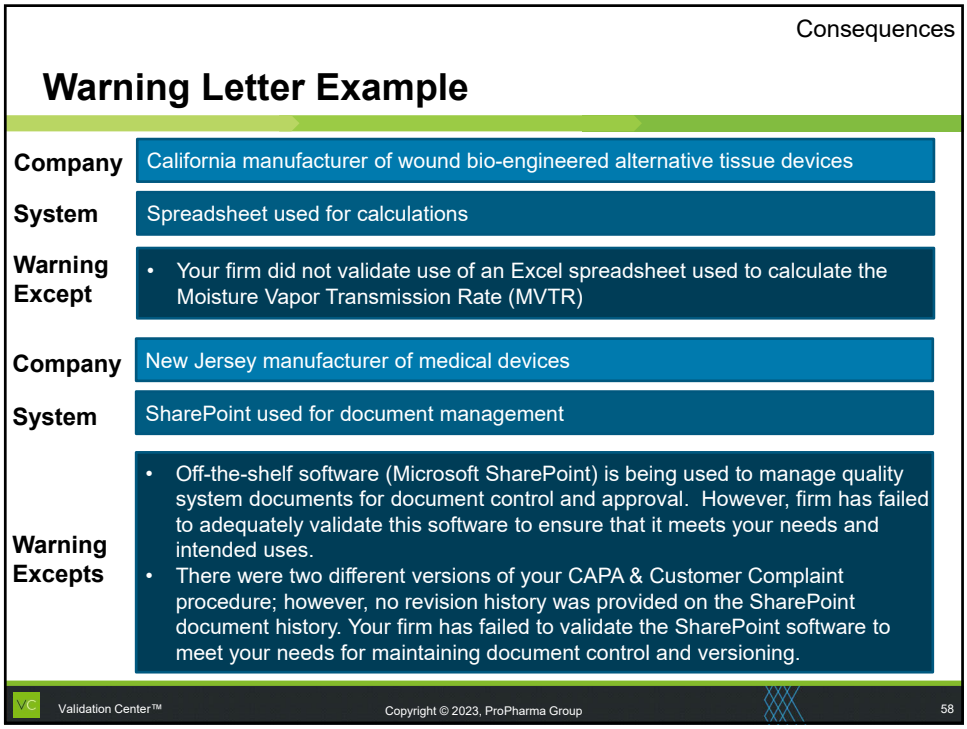
55



56



57



58

Warning Letter Example

Company	Idaho manufacturer of radiopharmaceuticals
System	Custom developed system for batch records, calculations, and label generation
Warning Letter Excepts	• Firm's custom software for Master Batch Production record has not been validated. This software is responsible for generating the batch production record, performing calculations to produce varying concentrations of drug product, and generating label information for customer vials and lead pigs.
Company	Italian manufacturer of laser devices
System	Custom developed system for tech calls, complaints, and service records
Warning Letter Excepts	• The software developed by your firm to record, evaluate, investigate, correct and repair incoming technical assistance calls, complaints, and service records was implemented and has not been validated. • No validation documentation was available for an established protocol, any testing data, or a finished report for the validation of this system.

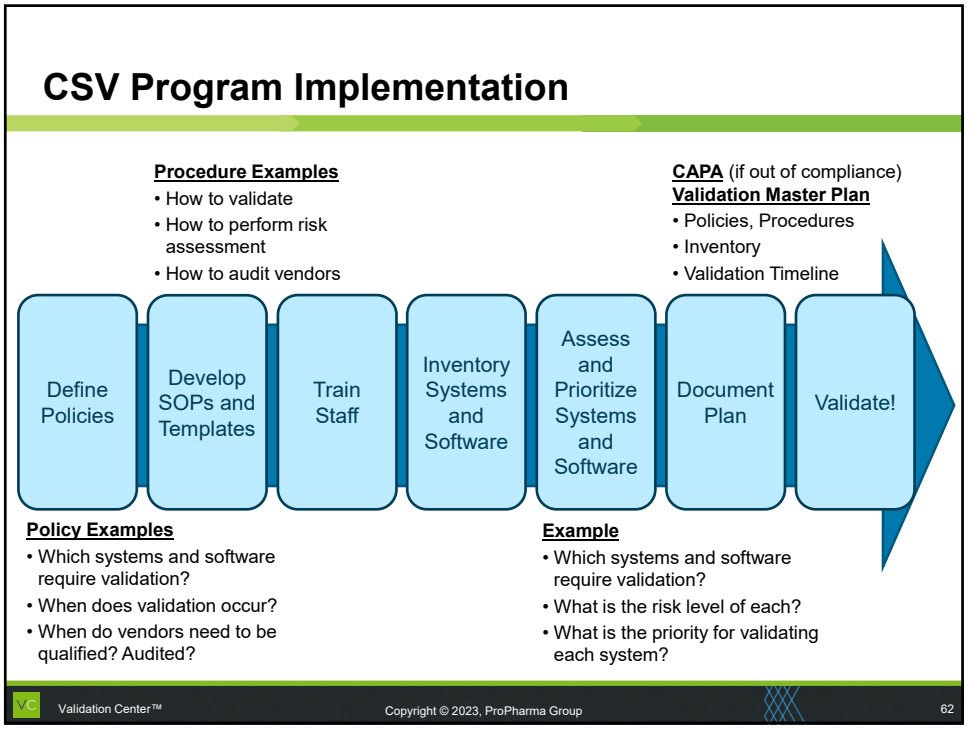
59

Warning Letter Example

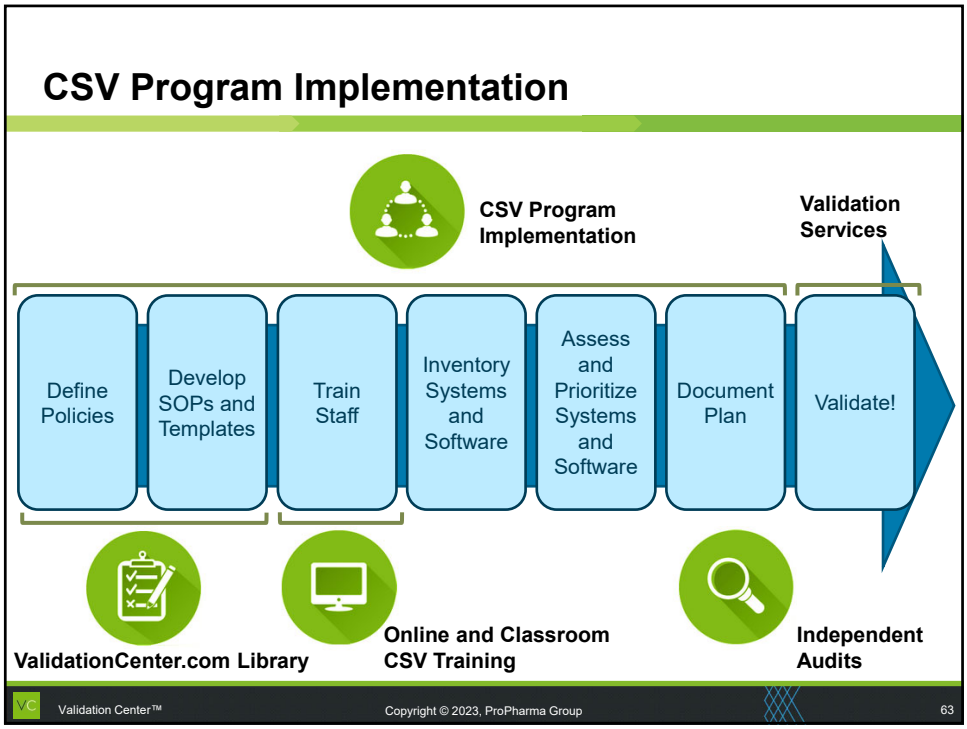
Company	German manufacturer of sterile and non-sterile needles and sutures
System	Software controlling the machinery making needles
Warning Letter Except	• Your firm uses custom automatic machines in the needle production process. Your firm stated that it performed software validation for the automatic machines and that the software protocol was tested, but these validation activities were not documented.
Company	Kentucky medical center
System	Blood management
Warning Letter Except	• Your firm went live with version 2.0.0 of the Hemocare Lifeline (HCLL) Donor Module; however, the validation of Module 15, Product Labeling, was incomplete in that it was not reviewed, accepted, or signed off by a responsible individual.

60

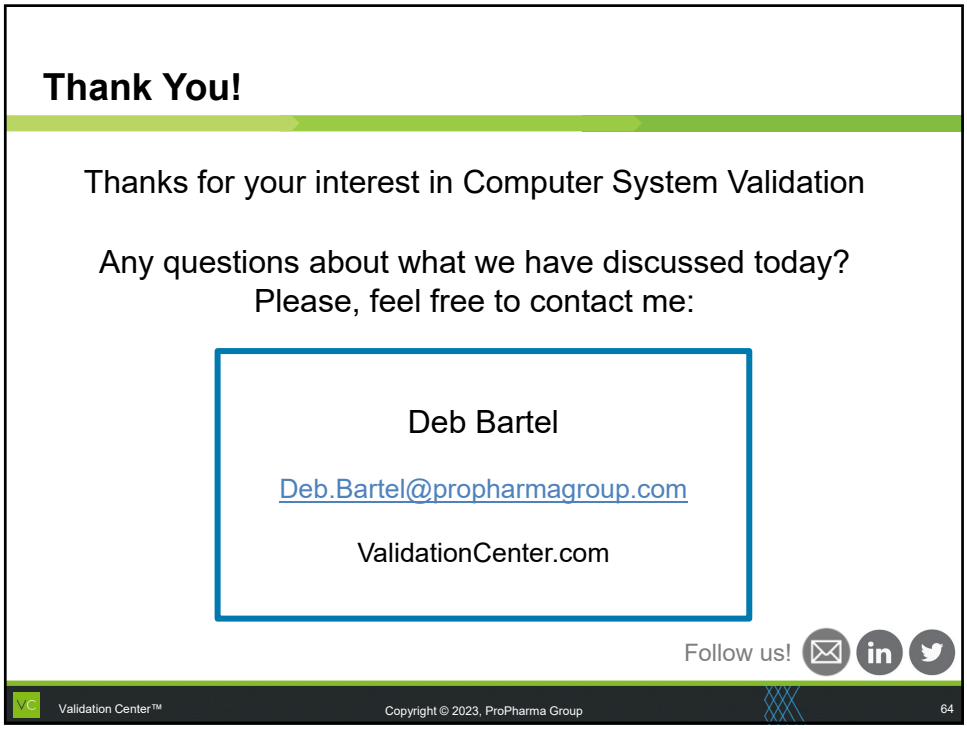
61



62



63



64