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Overview on
"Computer System

Computerized system validation

The purpose of the validation process is to provide a high degree of assurance that a specific process will consistently produce a product which meets predetermined specification and quality attributes.

1. It is a process of achieving and maintaining compliance with applicable GxP regulations and fitness for intended use of computerized system.
2. Computerized system validation is the process of testing/validating/qualifying a regulated (E.g., FDA 21CFR11) computerized system to ensure that it does exactly what it is designed to do in a consistent and reproducible manner that is as safe, secure, reliable and traceable
3. The process used to ensure and document that a computer based system will operate according to predefined requirements.
4. Systems meet the business needs of their users.

Difference between Computer System & Computerized System

Computer System

- A computer is a device that accepts information in the form of digitalized data and manipulates it for some result based on a program or sequence of instructions on how the data is to be processed. A system including input of data, electronic processing and output of information to be used either for reporting or automatic control.

Computerized System

- A computerized system consists of hardware, software and network components which together fulfill certain functionalities. It can also be defined as a logical entity partially or entirely controlled by computers but may also include some equipment, utilities, sensors & actuators along with the governing procedures.
- For example Building Management System; Automated manufacturing / Laboratory System; Document Management System; etc.

Computerized system validation

Why needed in pharma industries?

- CSV in pharma helps prove that the company's computerized systems are abiding by the given regulations. It's the responsibility of the CSV specialist to understand each applicable regulation for computerized system compliance.
- CSV is the FDA's response to an increasingly growing demand from pharmaceutical industries to use **paperless systems** and to prevent falsification and misinterpretation while ensuring security, authenticity, integrity, and confidentiality
- Computer system validation is a documented process that is required by regulatory agencies around the world to verify that a computerized system does exactly what it is designed to do in a consistent and reproducible manner.
- To comply with the FDA regulations.
- To avoid failing an FDA audit which can result in FDA inspection observation ("**483s**") and warning letters.

Types of validation

- **Prospective validation** – the validation of a new system as it is developed.
- **Retrospective validation** – the validation of an existing system.
- **Concurrent Validation. -** The validation is based on data collected during actual performance of a process already in place.
- **Revalidation (Periodic and After Change) -** The implementation of a program of repeat validations based on time or due to changes in the operating environment.

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Benefits of CSV Conducting

- Cost of compliance is low comparing with the cost of non-compliance.
- Provide documentation required by FDA, other regulatory agencies.
- Maximizes the value of the computer system and the employees that use it.
- Reduces labour costs by increasing employee's efficiency and effectiveness.
- Saves money by discovering defects early.
- Reduces risk.
- Promotes continual process improvement.

Computerized system validation

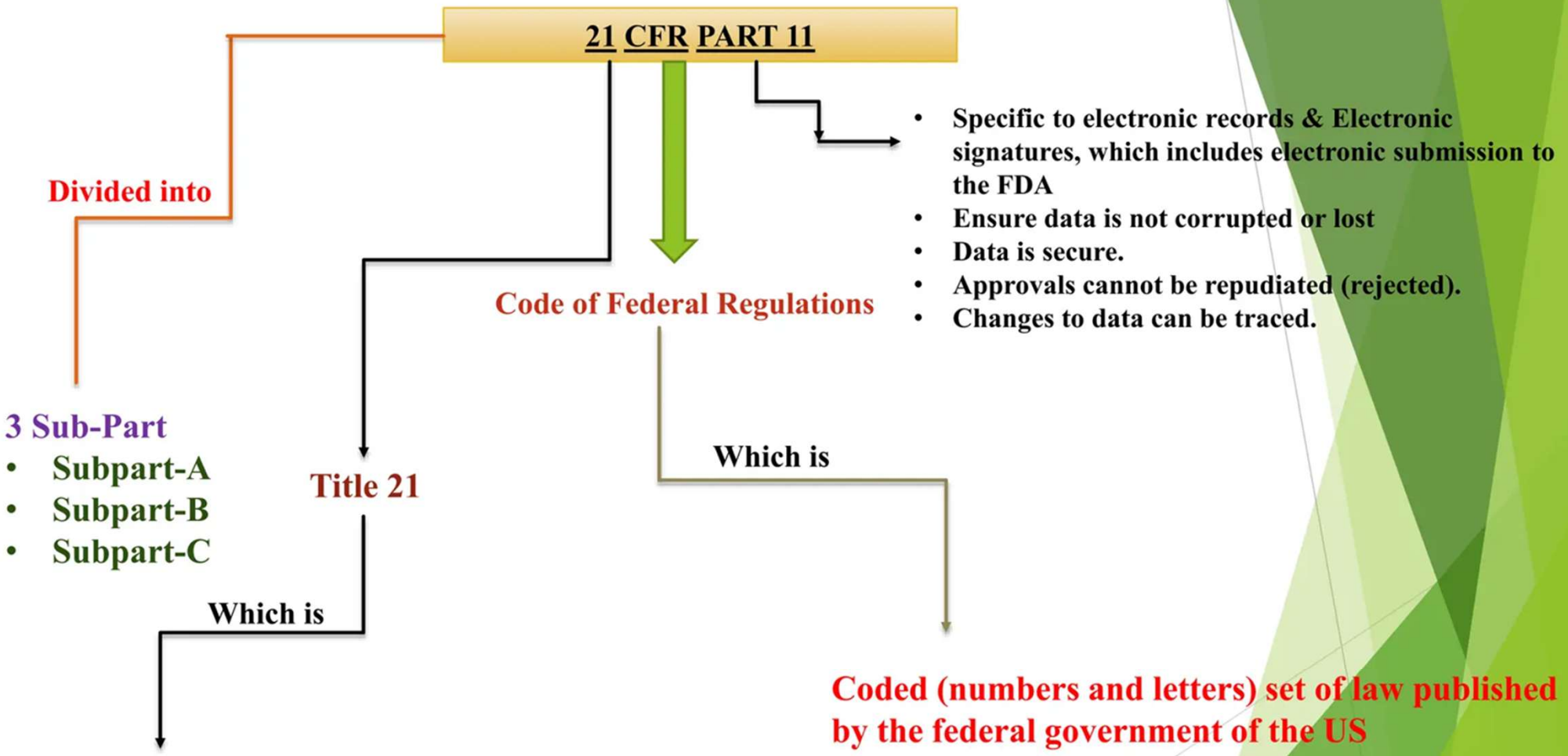
Key Objectives of CSV

Regulatory requirements

- FDA published a guide to the inspection of computerized systems in pharmaceutical processing, also known as the 'bluebook' (FDA 1983).
- Part 11 applies to electronic records and electronics signatures that persons create, modify, maintain, archive, retrieve, or transmit under any records or signature requirement set forth in the federal, drug, and Cosmetic Act, the public health service Act (PHS Act), or any FDA regulation.
- FDA introduced 21 CFR Part 11 for rules on the use of electronic records and electronic signatures (FDA 1997).

CFR (Code of Federal Regulations)

- The **Code of Federal regulations** (CFR) is the codification of the general and permanent rules and regulation published in the federal register by the executive departments and agencies of the federal government of the united states
- The Code of Federal Regulations (CFR) annual edition is the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government. It is divided into **50 titles** that represent broad areas subject to Federal regulation. Each title is divided into **chapters**, which usually bear the name of the issuing agency. Each chapter is further subdivided into **parts** that cover specific regulatory areas. Large parts may be subdivided into **subparts**.


21 CFR PART 11
Divided into
3 Sub-Part
• Subpart-A
• Subpart-B
• Subpart-C
Title 21
Which is
Section of the CFR that applies to food and drugs
Code of Federal Regulations
Which is
Coded (numbers and letters) set of law published by the federal government of the US
• Specific to electronic records & Electronic signatures, which includes electronic submission to the FDA
• Ensure data is not corrupted or lost
• Data is secure.
• Approvals cannot be repudiated (rejected).
• Changes to data can be traced.

21 CFR PART 11

21 CFR Part 11: allow the industry to use electronic records and signature alternatively to paper records and hand written signature.

21 CFR Part 11 applies:

- **To all FDA regulated environments** – when using computers in the creation, modification, archiving, retrieval or transmission of the data or records.
- To records required by predicate rules – GLP, GMP, GxP, that impact patient safety.
- The Following are the sections in which the 21 CFR Part 11 is broadly divided into

SUBPART A **General provisions**	• **Part 11.1 – Scope** • **Part 11.2 – Implementation** • **Part 11.3 – Definitions**
SUBPART B **Electronic records**	• **Part 11.10 – Controls for closed systems** • **Part 11.30 – Controls for open systems** • **Part 11.50 – signature manifestations** • **Part 11.70 – Signature / Record Linking**
SUBPART C **Electronic signature**	• **Part 11.100 – General requirements** • **Part 11.200 - Electronic signature components and controls.** • **Part 11.300 – Controls for identification codes / passwords**

SUBPART – B (**Electronic records**)

- Part 11 defines an electronic record as : any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained by a computer system.
- System generating electronic records shall be adequately validated.
- Any electronic records that require signature must include signer name, time stamp and meaning of signature.
- Organizations using electronic records must establish and documented procedures and controls that ensure the following in their electronic records:

a) **Authenticity**

b) **Integrity**

c) **Confidentiality (when appropriate)**

d) **Irrefutability (i.e. no way to deny that a record is genuine)**

SUBPART – C (**Electronic signature**)

- Part 11 defines an electronic signature as : a computer data compilation of any symbol or series executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.
- The organization seeking to implement electronic signature shall inform FDA prior to implement the E-sign in place to hand written signature.
- There are specific requirement for electronic signatures that are biometric (e.g. fingerprint scan/ face recognition/ retina scan) and those that are not (e.g. user ID and password).
- Each person using an electronic signature must:

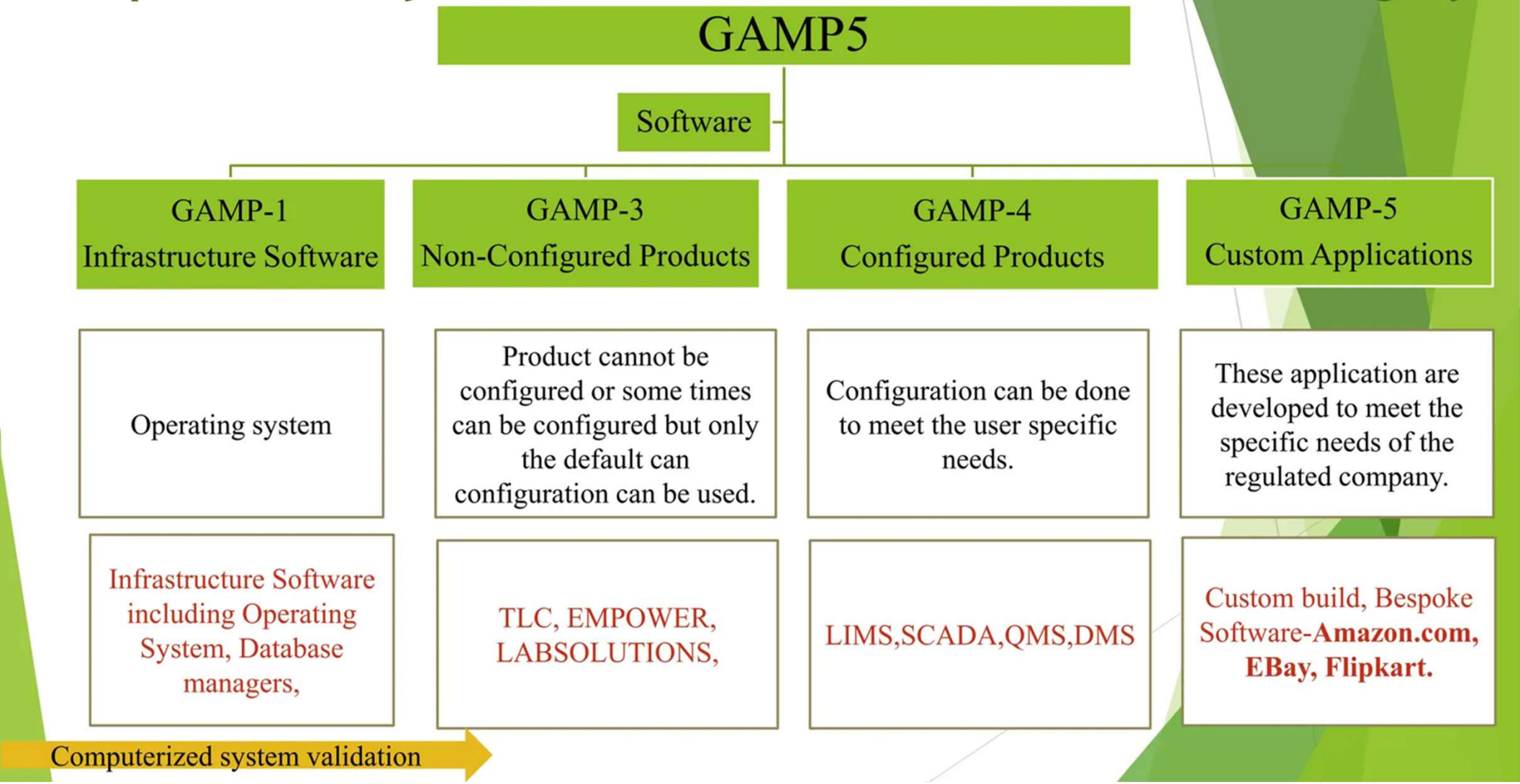
a) **Have their identity confirmed.**

b) **Use a unique signature that has never been and will never be used by another individual.**

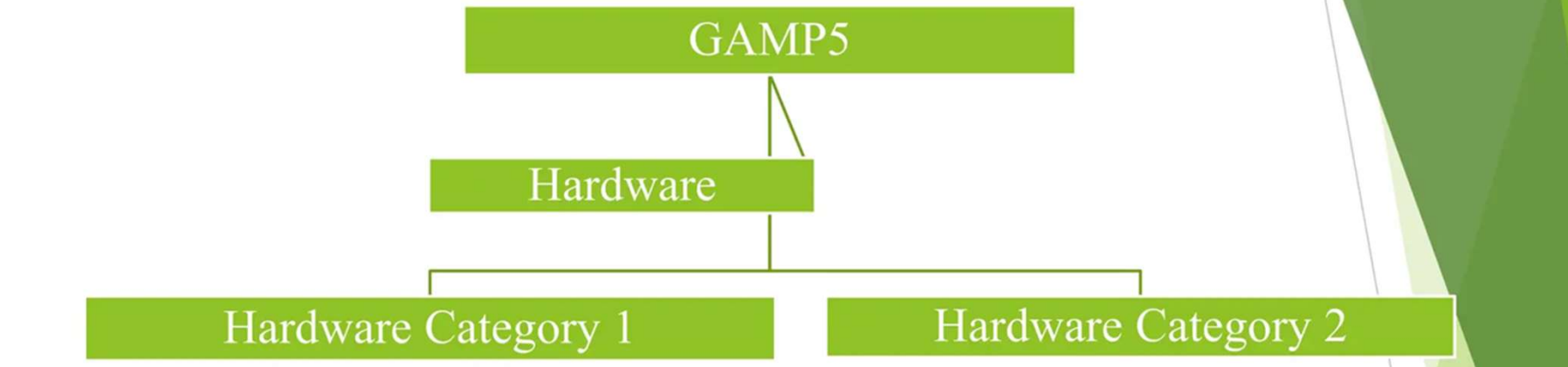
What is GAMP5

- Good Automated manufacturing practice (GAMP) is both a technical subcommittee of the international Society for pharmaceutical engineering (ISPE) and a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry.
- Good Automated manufacturing practice (GAMP) guidance aims to achieve validated and compliant automated systems meeting all current healthcare regulatory expectations, by building upon existing industry good practice in an efficient and effective manner.
- The most well-known guideline is the Good Automated manufacturing practice (GAMP) guide for validation of automated systems in pharmaceutical manufacture. The last major revision (GAMP5) is being released in February 2008.
- The purpose of GAMP 5 is to achieve compliant computerized systems that are fit for intended use in an efficient and effective manner to meet current regulatory requirements.
- The following GAMP 5 software and hardware categories are used to establish the validation approach and determine the deliverables:

Computerized System Classification based on GAMP Category



Computerized System Classification based on GAMP Category



Standard Hardware Components	Custom Built Hardware Components
• Record model, version, serial number, verify correct installation/ connection, apply change control • Hard drives, Monitors, CPU, scanners, Printers	• As for standard components but also require a design specification and acceptance test, Supplier may be audited. • PCB, finger print machine.

Key points of Computerized system validation

GAMP5

- Category 1 – Infrastructure Software
- Category 3 – Non-Configured Products
- Category 4 – Configured Products
- Category 5 – Custom Applications
- Hardware Category 1 – Standard Hardware Components
- Hardware Category 2-- Custom built hardware component

21 CFR Part 11

1. Electronic records
2. Electronic signature
3. Audit trail.

GDP

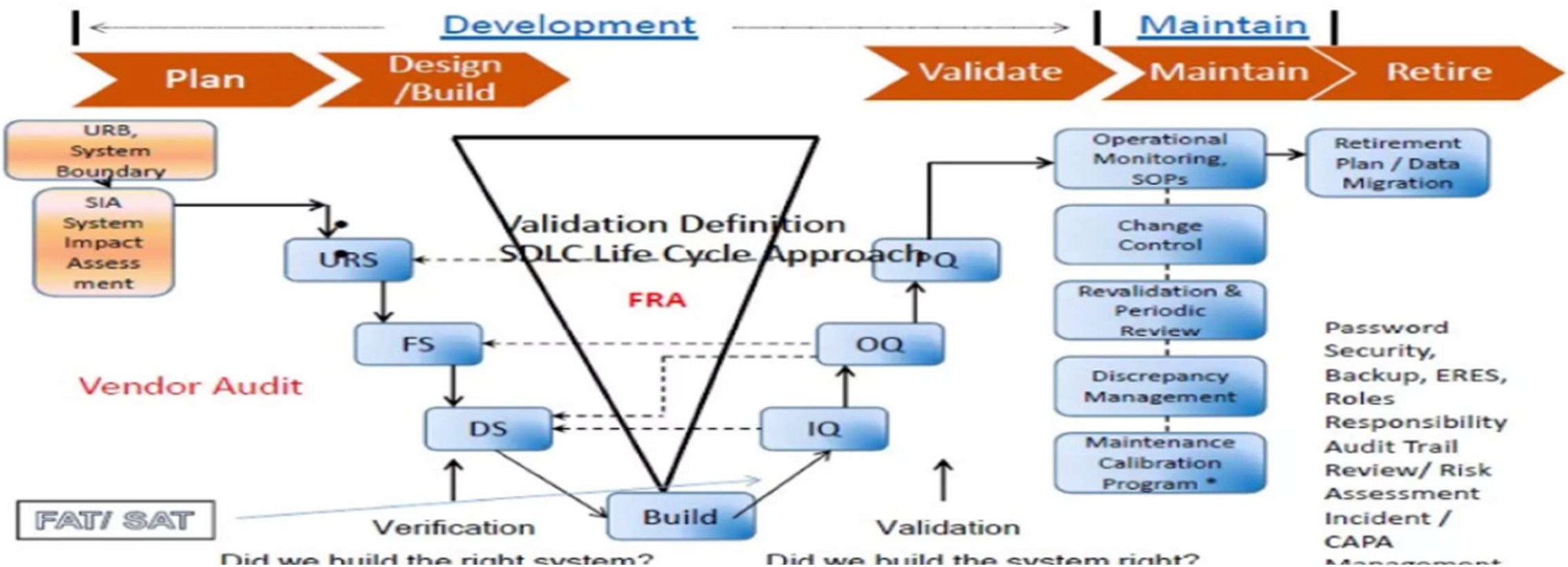
1. Attributable-who performed
2. Legible-readable
3. Contemporaneous-recordable
4. Original-source match
5. Accurate-signed
6. Complete-finished
7. Consistent-sequential
8. Enduring-permanent/Controlled
9. available-accessible

Computerized system validation

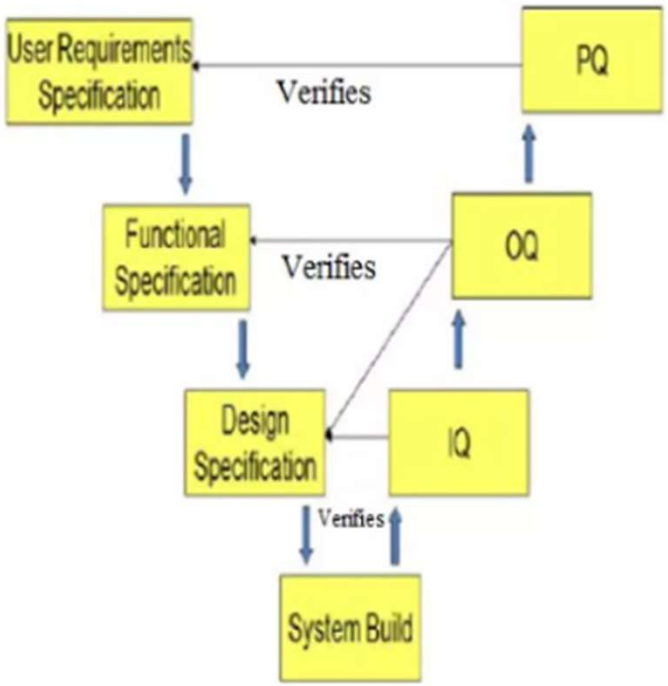
Computerized system validation

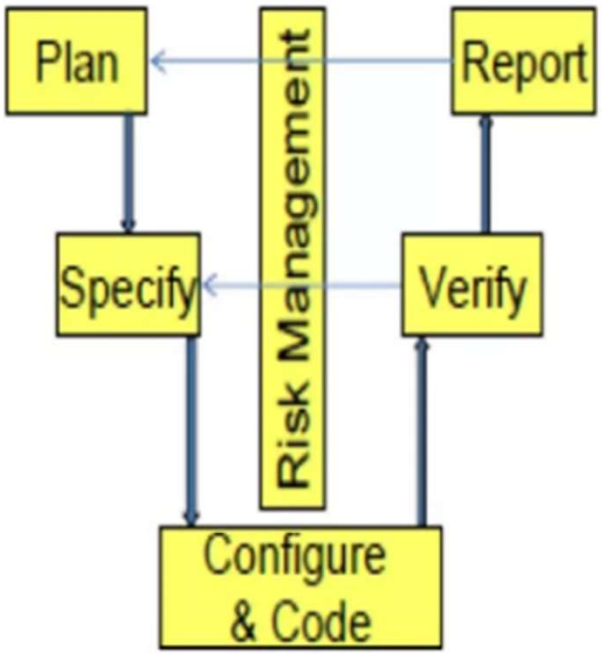
V- model approach for computerized software system validation

Validation approach- Validation approach of **computerized system** is aimed at achieving and maintaining compliance with applicable GxP regulations and fitness for intended use by adoption of principles, Approaches and life cycle activities within the framework of validation plans and reports. The complete validation strategy is explained through below 'V' model approach.



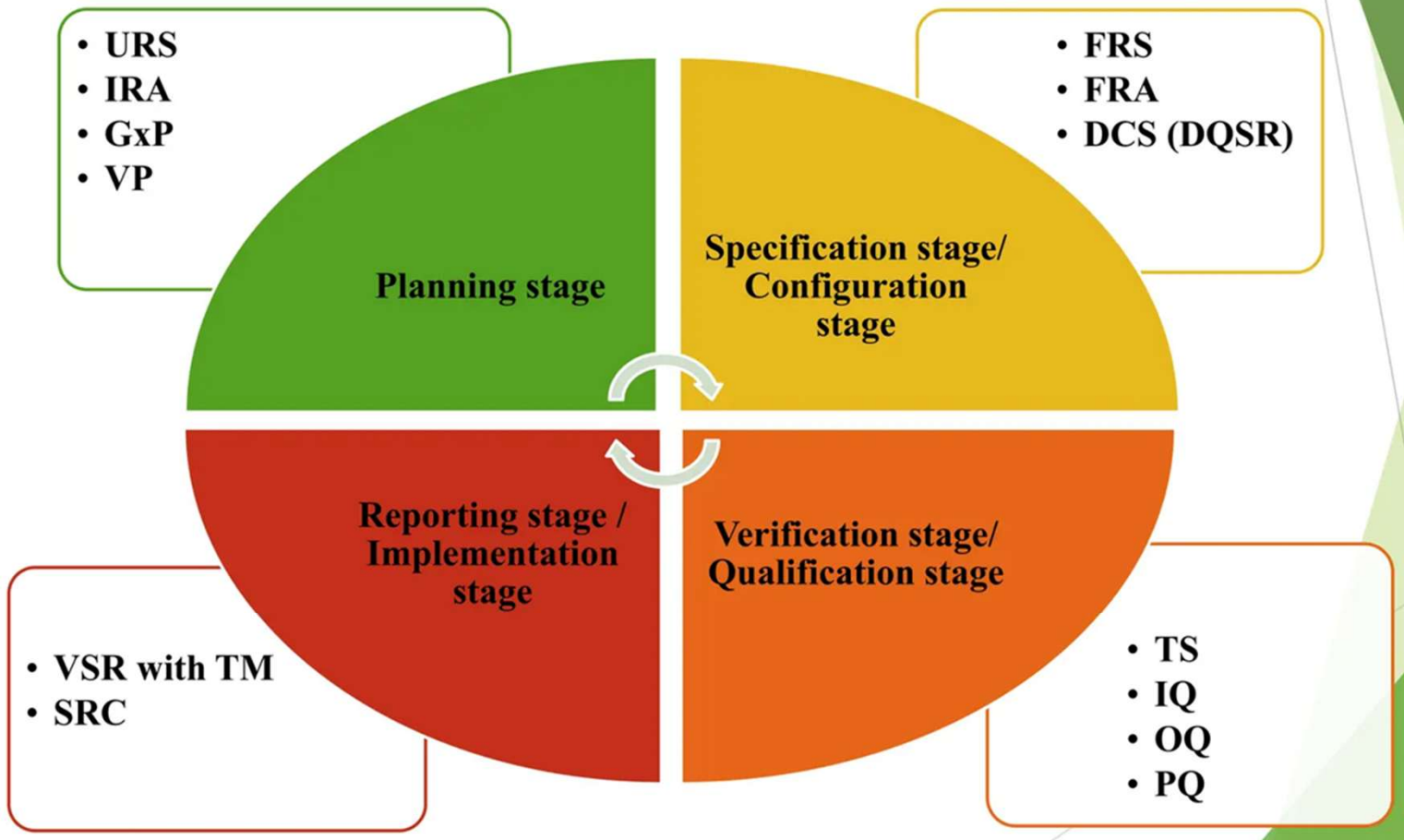
GAMP 5 Model


User Requirements Specification
Verifies
PQ
Functional Specification
Verifies
OQ
Design Specification
IQ
Verifies
System Build


Plan
Report
Risk Management
Specify
Verify
Configure & Code

Computerized system validation

Validation stages:



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"Validation Approach"

Validation of GxP impacting computerized system should be based on the following key steps:

- High Level Risk Assessment
- Implementation of life cycle model for GxP impacting computerized system

Validation deliverables:

1	User Requirements Specification (URS)
2	GxP Assessment (GxP) / (IRA)
3	Validation Plan (VP)
4	Function Specification (FS)
5	Functional Risk Assessment (FRA)
6	Design Qualification Summary report (DQSR)
7	Installation Qualification (IQ)
8	Operational Qualification (OQ)
9	Performance Qualification (PQ)
10	Validation Certificate
11	Reference/Requirement Traceability Matrix (RTM)
12	Validation Summary Report (VSR)

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"Identification of level of Risk"

For GxP relevant system, assess the '**Level of Risk**'

- Assessment regarding GxP relevance (Yes/No).
- Assessment regarding Business relevance (Yes/No).
- Assessment regarding Failure Consequence (High/Moderate/Low).

❖ If system has direct impact on, Product Quality, Patient safety and Data Integrity then system failure consequences shall be **"High"**.

❖ No direct impact then rate as **"Moderate"**.

❖ No impact then rate as **"Low"**.

Computerized system validation

User requirement specifications

- URS should be developed based on the business process
- URS is required for all the GxP computerized systems
- This documents must be prepared by the system owner and reviewed by the process owner and SME and approval by the QA
- The documents shall incorporate the below requirement (Regulatory),

But not limited to

1. **Security and administration**
2. **Functionality**
3. **Electronic records and audit trail**
4. **Backup and restoration**
5. **Environmental conditions**

Initial Risk Assessment/GxP

- IRA shall be performed before or parallel with the development of the user requirement specification.
- The IRA should determine the potential GxP implications arising from the computerization of the process.
- The IRA shall assist in determining the following but not limited to

1. **GAMP software categorization**
2. **Software and hardware categorization**
3. **ER/ES Selection**

Validation Plan

- A validation plan must be produced for each GxP computerized system
- The validation plan will define the activities to be undertaken to demonstrate the system is complaint state and fit for intended purpose
- The validation plan should include the below mentioned areas, but are not limited to:

1. **Project and system overview**
2. **Vendor**
3. **Roles and responsibilities**
4. **Validation strategy**
5. **Supporting process**
6. **Validation deliverables**

Functional risk assessment

- The risk assessment should be done as per the principle of failure mode, effects, and criticality analysis.
- Risk assessment consists of the identification of hazards and the analysis and evolution of risk associated with exposure to those hazards.
- Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk assessment tool and the types of information that will address the risk question will be more readily identifiable.
- Hence the risk assessment will answer the three following questions:

1. **What might go wrong?(Risk identification/ unwanted event)**
2. **What are the consequences? (severity / Impact)**
3. **What are the likelihood (probability and Occurrence) it will go wrong?**
4. **What is the detectability if it goes wrong?**

Installation qualification

- IQ should demonstrate that the correct software and hardware are installed and configured in line with the specification documents in applications environments, (Dev/Quality/Prod.)
- The IQ should include the below mentioned areas, but are not limited to:

1. **Equipment/ Instruments details**
2. **Hardware & Software requirement (Server)**
3. **Hardware & Software Components**

Operational qualification

- OQ verifies that the system is operates according to written and pre approved specifications
- OQ testing should demonstrate correct operation of the functionality that supports specific business process.
- The OQ should include the below mentioned areas, but are not limited to:

1. **Security & Administration**
2. **User Privileges**
3. **Boundary parameters**
4. **Functionality**
5. **Reports & audit trail**
6. **Communication & power failure**
7. **Data Backup & Restoration**

Performance qualification

- PQ verifies that the system is capable of performing the activities of the process according to written and pre approved specifications.
- PQ is carried out in the production environment.
- The testing of the system demonstrates the fitness for intended use.
- PQ shall be performed according to the organization procedure or policy. Like all the OQ test script will be executed in the production environment
- They will use the system for a period of time whether the system works for intended use or not.

Requirements Traceability matrix

- RTM ensures that the requirements are verified and can be traced and shows that requirement has been met.
- The relationship between URS, FS, DS and Verification as applicable shall be mapped.

Validation Summary report

- VSR summarize the validation effort and to assess the associated activities.
- The report should also summarize changes from the validation plan, resolution of the defects and a statement of fitness for intended use.
- Summarize the list of validation deliverables.
- The VSR should include the below mentioned areas, but are not limited to:

1. **Defects**
2. **SOPs**
3. **Training**
4. **Change control and final system validation approval.**

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CSV Regulations

- **21CFR 11,** Electronic record & Electronic Signatures,

  Subpart B-Electronic Records, Sec11.10, Controls for closed systems:-

  a) **Validation of systems** to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

- **21CFR part 211,** Current Good Manufacturing practice for Finished pharmaceuticals

Subpart D, Equipment, Sec. 211.68(b).

Input to and output from the computer or related system of formulas or other records or data **shal be checked for accuracy.**

- **21CFR part 1271,** Human cells, Tissues, Cellular and Tissue based products,

Subpart D, Current good tissue practice, Sec. 1271.160(d)

You must validate the performanceof computer software for the intended use.

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CSV Regulations

- **21CFR 820,** Quality System Regulation,
  - Subpart C-Design Control, Sec. 820.30(g),

  Design validation shall include **software validation** and risk analysis.
  - Subpart G-Production and Process Control, Sec. 820.70(i),

When computer or automated data processing system are used as apart of production or a quality system, **the manufacturer shall validate computer software** for its intended useaccording to an established protocol.

- **Eudralex vol.4,** Good Manufacturing practice, Medicinal product for Human and veterinary Use. Annex11 Computerised systems.

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

- **ICH Q7A,** Good Manufacturing practice for Active pharmaceutical Ingredients

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

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