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Packaging Lines Control and Validation

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Packaging Lines – Control and Validation

- Computers are more and more widely used during development and manufacturing of drugs and medical devices. Proper functioning and performance of software and computer systems play a major role in obtaining consistency, reliability and accuracy of data.
- Therefore, computer system validation (CSV) should be part of any good development and manufacturing practice.
- It is also demanded by groups like FDA with regulations and guidelines through the overall requirement that ‘equipment must be suitable for its intended use’.
- Lesson: Quality cannot be tested into the product: it has to be built into the system from the beginning.
- Need: To prove beyond reasonable doubt that equipment has been designed, built and is monitored to ensure that it is in consistent compliance with regulatory requirements.

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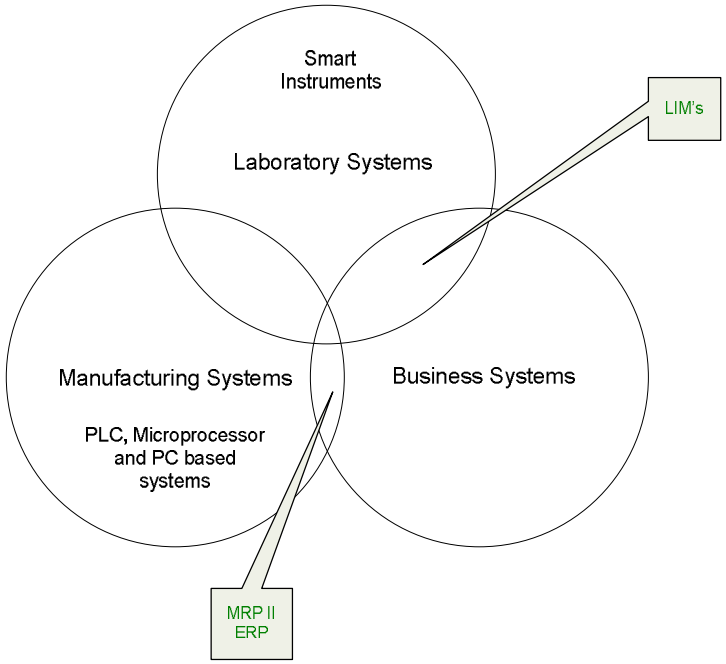
- Computer systems are becoming more integrated, the trend today is to directly send production information to the packaging line to configure the manufacturing equipment directly for example. The computer her will not work in isolation, more often than not the system will by a part of a network of computers exchanging data to provide the required services.



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- Therefore it is important to define the topology of the system as the first step in the validation strategy; this defines the scope of the project.

- Detail the system within a separate document, this can be the URS
- Identify and list the system functionality as it relates to the end **Product**, the **Process**, the **Plant,** its **People** and its **Procedures** (the five P's)
- Identify the **Software** and **Hardware** of the system
- Identify the **Scope** of the system
- Identify the **Interfaces**

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- Now assess the system in the following way:
- Carry out a risk assessment in the following way. Define any Ethical or GMP Risk (Items that would cause a product recall), define Business and Operational Risk, finally any Safety or H&S Risk
- In the GMP assessment define if the system has the capability to impact on the Product in terms of Quality, Strength, Identity or Purity?
- Does the system keep records and data that are to be provided to regulators? Does the system create, retain, modify, report or approve GMP related data? - 21 CFR part 11

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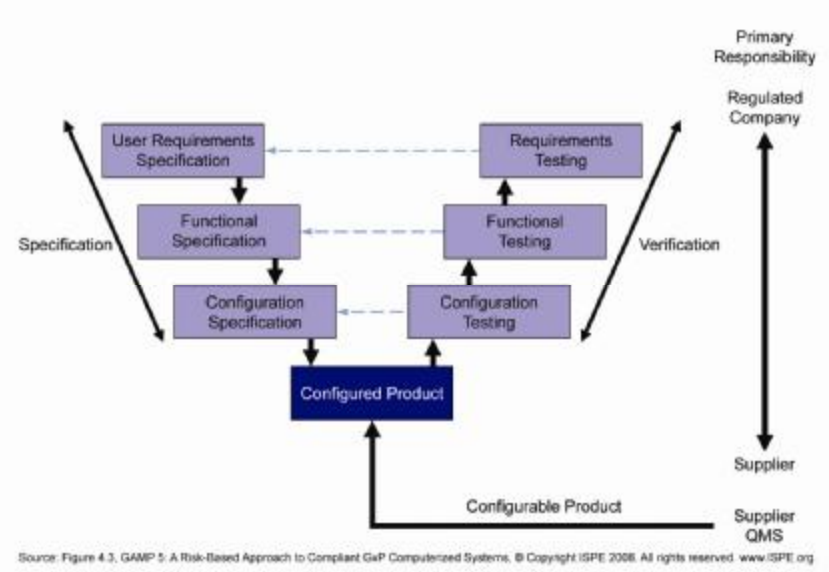
GAMP 5

- URS – User requirement Specification
- FS – Functional Specification
- CS – Configuration Specification (reference the manuals)
- Configuration Testing (was IQ)
- Functional Testing (was OQ)
- Requirements Testing (was PQ)



- We will be working through these phases
- How does this relate to our testing at the FAT and the SAT?

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- The more that standard software is used and the less customisation made for such software the less testing is required by individual users. GAMP has developed software categories based on the level of customisation. In total there are four categories defined in GAMP 5. We are usually concerned with three of them

Category	Description
3	Standard software package. No customization. Examples: MS Word (without VBA scripts). Computer controlled spectrophotometers. Temperature and Humidity controllers. Older barcode readers.
4	Standard software package. Customization of configuration. Examples: LIMS, Excel spreadsheet application where formulae and/or input data are linked to specific cells. Networked data systems. PC Based Machine Control systems. Machine vision systems.
5	Custom software package. Either all software or a part or the complete package has been developed for a specific user and application. Examples: Add-ons to GAMP Categories 3 and 4, Excel® with VBA scripts. Dedicated and unique Machine control system using Industrial PC hardware. Vision systems having PLC functionality.

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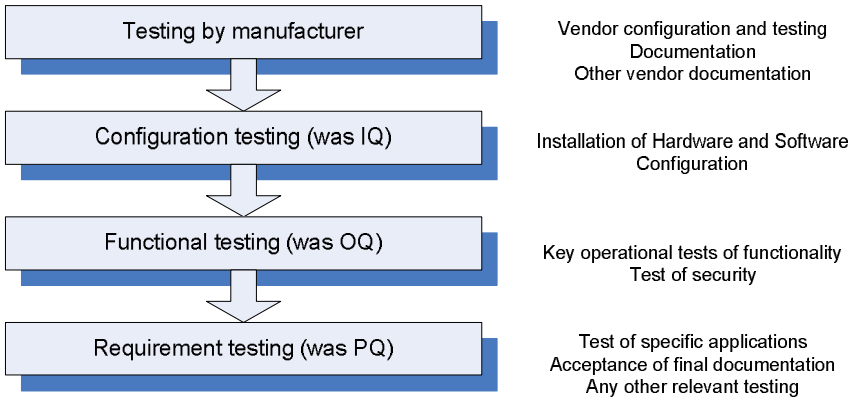
- A **GAMP5 level 4** category system, where the system is a standard Hardware and Software product that is in serial production and only configuration is needed to make it operational.
- Phases like design specification or code development and code testing are not necessary provided that adequate design and testing documentation exists for the system.



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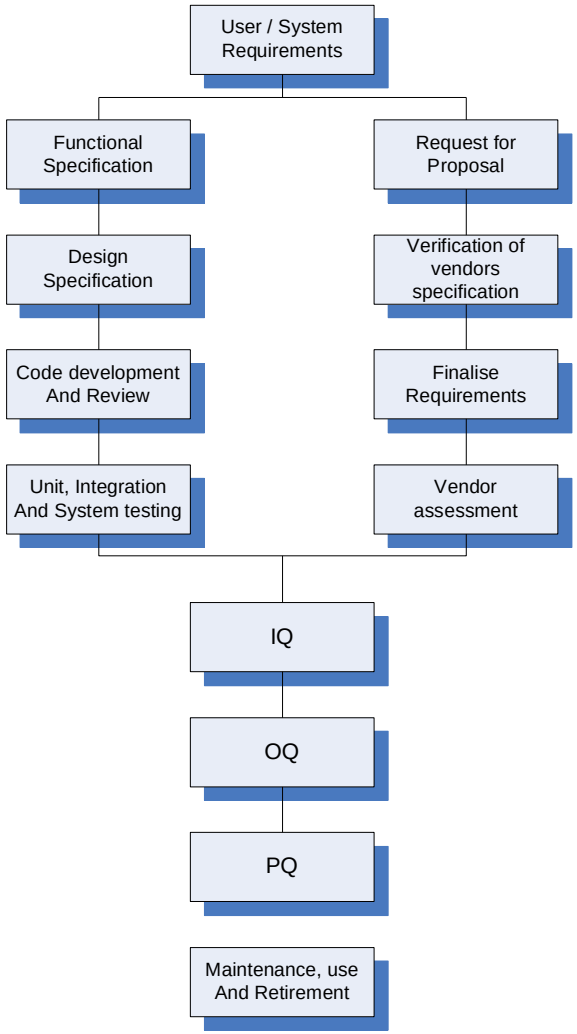
- The 4 Step model is not suitable when systems need to be programmed for specific applications or when additional software is required that is not included in the standard product and is developed by the user's firm or by a 3rd party

- This means that the system immediately moves into a **GAMP5 level 5** category system. In this case a life cycle model that combines system development and system integration is preferred



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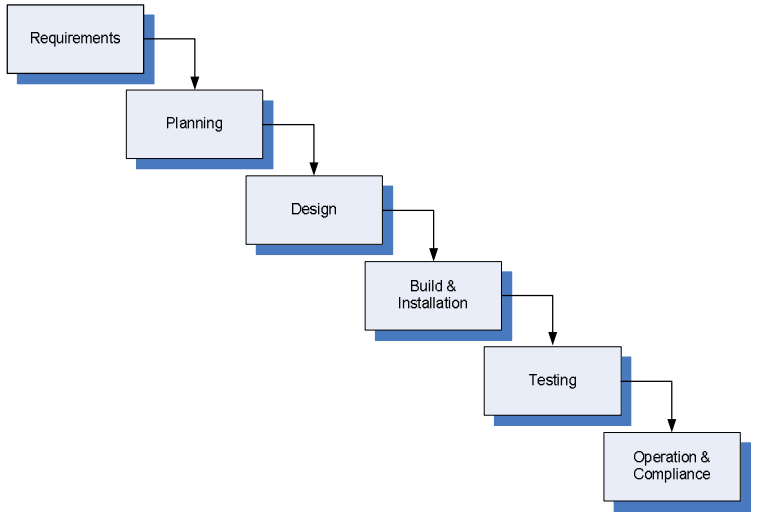
When considering category 5 system the following must be in existence.

- The existence (and use) of an appropriate quality system during the original development of the computerised system
- Thorough design review during development and manufacture and thorough testing against requirements specifications
- Comprehensive documentation of the full development life-cycle
- Controlled and documented procedures and records for the system's operational life
- Controlled and documented phase-out and data archival/migration at the end of the system's life



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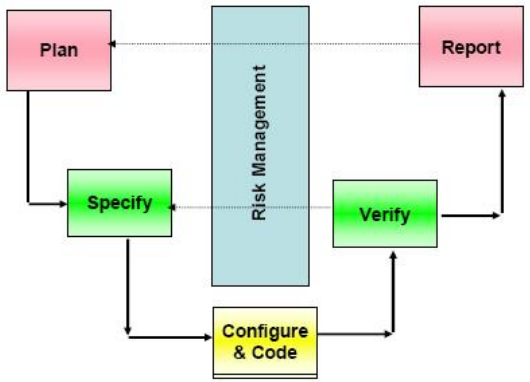
RISK – GAMP 5 places large emphasis on the use of risk analysis

- The first question then is - What tests do we complete to validate the Computer system?
- The easiest approach is to rule out the things we do not need to test in order to complete the validation.
- Complete a Machine and Computer System Risk Analysis, divided into three areas.



1. Ethical or GMP Risk (Items that would cause a product recall).
2. Business and Operational Risk (for example cosmetic defects and throughput of machine).
3. Safety or H&S Risk (injury to personnel, usually covered when the machine is CE marked).

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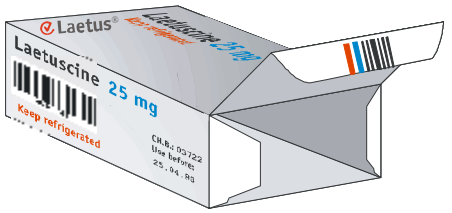
RISK

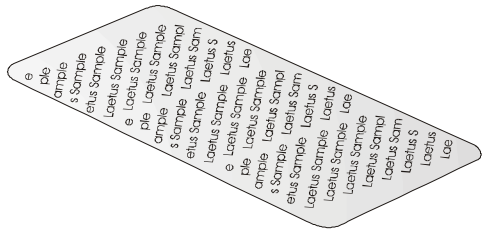
GMP risk

- Incorrect or contaminated pharmaceutical product
- Incorrect assembly of the ‘unit of dose’ carrier (blister, bottle, vial...)
- Incorrect packaging component in the final assembly (incorrect carton, missing or incorrect label, missing or incorrect leaflet…)
- Incorrect or illegible lot or batch identification



2. Business and operational risk

- Poor packaging quality (cosmetic defects)
- Excessive machine down time
- Machine damage or wear
- Excessive change-over times
- Slow speed of operation



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RISK

3. H&S Risk

- Guards not operating correctly
- Exposed mechanisms causing human harm
- Open electrical connections
- Human contamination by API's

- We must make tests 100% for all aspects of potential GMP risk!
- We can include such Business and Operational Risk as we see fit.

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RISK MITIGATION

- Avoidance - Change Process or Approach - Look at modifications to design to prevent an occurrence of the GMP risk.
- Prevention - Eliminate, Warning, Testing – Like avoidance, seek to remove the risk or warn of its occurrence.

- Control - Technical, Physical, Procedural – Prevent the occurrence of the risk by procedural or operational controls.
- Deflection - Dependency on other systems – isolate dependencies to 'shield' the system.

- Absorption - Proof of negligible probability – analysis of the risk to prove it is of little or no concern.

PREVENT

CONTROL

ANALZSE

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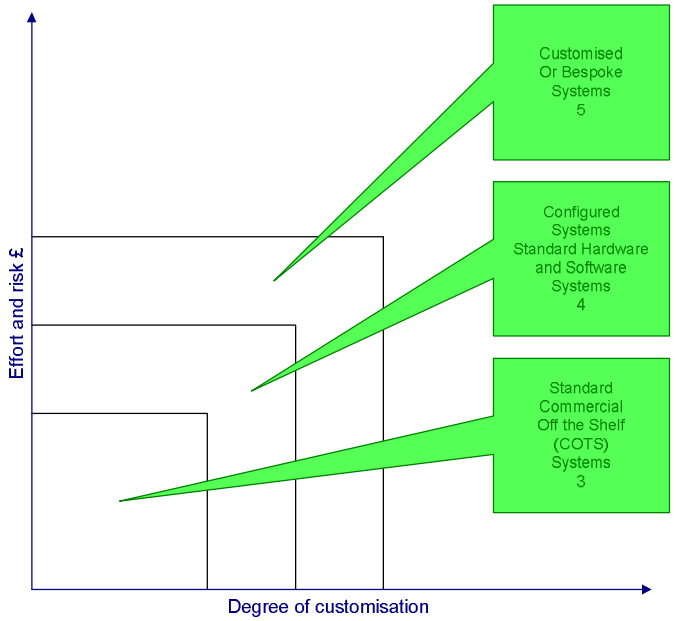
RISK MITIGATION

- Another method of preventing risk is to limit the type of system you consider, the degree of effort and the exposure to risk is much reduced if a standard system can be configured to meet the needs of the company.



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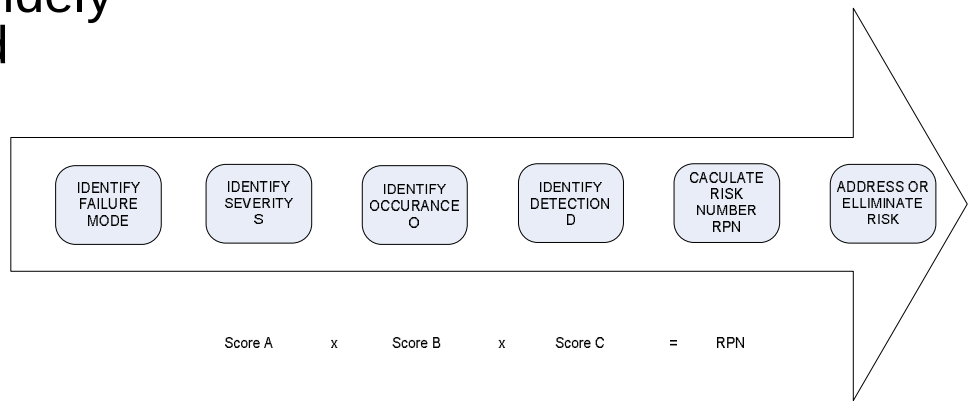
RISK ANALYSIS

- The use of Failure Mode and Effects Analysis (FMEA) widely used in the electronics and medical device industries
- There are three areas of a potential risk to consider Severity, Occurrence and Detection
- After ranking the severity, occurrence and detectability the RPN can be easily calculated by multiplying these 3 numbers: RPN = S x O x D
- RPN do not play an important part in the choice of an action against failure modes. They are more of a threshold values in the evaluation of these actions



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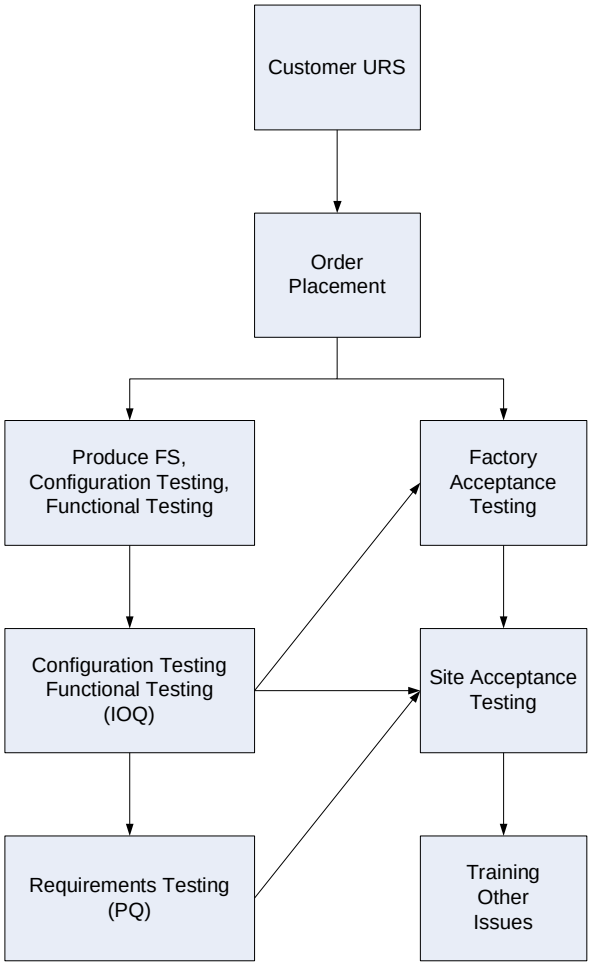
TESTING

- During factory acceptance testing most of the Configuration Testing (was IQ) can be completed if required. Also, some of the Functional Testing (was OQ) can be completed as required
- The System Acceptance Testing FAT and SAT should be fully documented.
- The completion of Functional Testing for a system confirms that it is ready for use in the manufacturing process
- The Requirements Testing step verifies system performance (was PQ). Requirements Testing is conducted under actual running conditions across the anticipated working range. Such testing documentation is usually created by the end customer



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TRACABILITY

- Traceability may be achieved in a number of ways, including a Requirements Traceability Matrix (RTM), automated software tools, spreadsheets, or embedding references directly within documents.
- An RTM may be generated as a separate deliverable or as part of an existing deliverable, such as the requirement document URS or Functional Specification FS.

Requirements URS	Design Functional Specification	Testing Functional Testing
U1 1.1	**F2 4.1**	T1.1
U1 1.2	**F2 4.5**	T1.2
U1 1.3	**F3.1**	T1.3
U2 1.1	**F3.2**	T1.4
U2 1.2	**F3.3**	T1.5

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COMPANY AUDITS

Company audits will fall usually into the following categories:

- Supplier Organisation
- Viability
- Quality Management System
- Systems Lifecycle Procedures
- Document Control
- Requirements and Design
- Electronic Record and Electronic Signature
- Programming
- Security
- Testing
- Change Control
- Support

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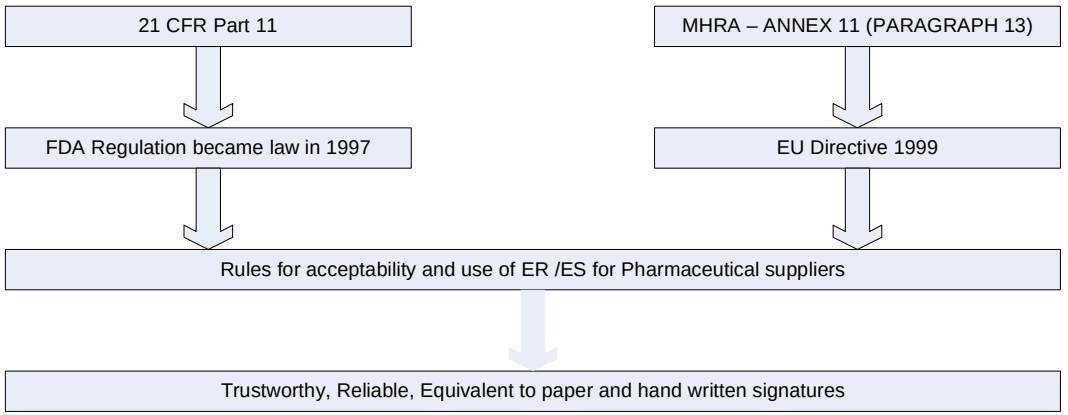
21 CFR PART 11

- The Food and Drug Administration (FDA) in 1997 issued regulations that provide criteria for acceptance by FDA, under certain circumstances, electronic records and electronic signatures, recorded electronically, to be equivalent to paper records and hand written signatures executed on paper.
- This is known as 21 CFR part 11.
- So what's new in the rule?
- Electronic Records = Paper Records.
- Electronic Signatures = Hand Written Signatures.
- These are referred to as ER/ES systems



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21 CFR PART 11

- Data Security – Files on computers are not as secure as printed files locked away. The requirement is to apply the same security to a networked data file as to a printed document, the prevention of unauthorised access.
- Data Integrity – To alter an electronic document and to hide this alteration is easy compared to a printed document. The requirement is to show that an electronic networked document has not been altered, affording the prevention of unauthorised alteration.
- Audit Trail Integrity – Where alteration is permissible by an authorised person, the emphasis here is to show a historical trail of – Who? altered the document, When? was it altered, What? was altered. Please note that not a consideration here is Why? Legitimate reasons are assumed for legitimate users.
- Electronic Signature – The requirement to show a connection between the stated user and his legitimate identity.

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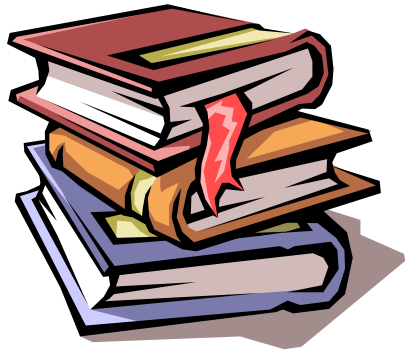
TRAINING

- The supplier should identify training needs and provide appropriate training. They should consider the specific methods, tools, techniques, and hardware to be used. Records of relevant training and experience should be maintained and should be available as part of the project documentation.
- The requirement is for classroom training with notes and a test to be made at the end, in both theory and practice.



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MAINTENANCE

- Procedures must established to ensure that backup copies of all software and other relevant data are taken, maintained, and retained within safe and secure areas. Backup and recovery procedures should be verified.
- Identify and define system components. Record and report the status of items and modifications to items. Ensure the completeness, consistency, and correctness of items of the machine. Control storage, handling, and delivery of items.

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MAINTENANCE

- All changes proposed during the operational phase of an automated system should be subject to a formal Change Control process, and should be reviewed, impact and risk assessed, authorised, documented, tested, and approved before implementation.
- Consider that some elements of the machine must require routine maintenance - This is a planned activity.
- Periodic review – at routine intervals, once per year, review the status of the above.
- Document the review.

Thank you for your attention.

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