Validation of Vision Systems used in the Pharmaceutical Industry

A guide to the validation of vision systems used in the pharmaceutical industry using Omron components

SCOPE

The pharmaceutical industry has many standards and guidelines that need to be followed; among these there is a requirement that computerized systems must be validated. This white paper gives an overview on how an automated system can be validated. A specific section with practical examples of vision system applications using Omron products is included. It is expected that the reader already has a basic knowledge of pharmaceutical regulations.

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1 Validation Requirements

1.1 Pharmaceutical legislation (EU and US)

Manufacturing processes in the Life Sciences industries are highly regulated by the so-called GMP (Good Manufacturing Practice). Equipment and systems used in these processes are also regulated by the same rules. cGMP means "current GMP" since the regulations change from time to time.
Regulations exist for other activities performed in these industries, such as the GLP (Good Laboratory Practice), GCP (Good Clinical Practice), GDP (Good Distribution Practice), GVP (Good Vigilance Practice), collectively known as 'GxP' (where 'x' is a placeholder).

Regulations vary across different industry sectors (e.g. pharmaceutical finished products / active ingredients, medical devices, biological products, blood products, vaccines, etc.), each having its own set of regulation, variable country by country.
In this document for simplicity we cover only manufacturing processes in the pharmaceutical industry (finished products) and the regulations applicable in the European Union and United States. Very similar considerations are nonetheless applicable for other regulated industries, processes and countries.

Among the many requirements, almost all regulations worldwide require the validation of processes and the qualification of supporting equipment. This document deals with validation of computerized systems used in pharmaceutical processes. It refers to the entire equipment for completeness, but is focused on the control system and is further specialized on vision systems as application examples.
The main objective of this document is to provide a guide for final users and integrators, to help them understand their regulatory burden and achieve compliance with the applicable regulations.
Omron, as a producer of components for the pharma industry, can help customers with documents like this and can also provide specialized support services to help final users to achieve validated systems.

1.1.1 US GMP

The manufacture of Food, Medicines (Drugs) and Cosmetics in the US is governed by the "Federal Food, Drug, and Cosmetic Act" (FD&C Act), this is a set of laws passed by the US Congress in 1938.
Specific rules applicable for the Food, Drug and Cosmetic industries in the US are since then managed by the FDA (Food and Drug Administration), and are covered into the Title 21 of the US CFR (Code of Federal Regulations).

Worldwide producers who export their products to USA are committed to these rules and are therefore subject to periodic FDA inspections. All FDA rules, including those applicable to other industry sectors, can be found on the FDA's web site: *www.fda.gov*
The main rules regarding the manufacture of medicinal products (US GMP) are:

- 21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding Of Drugs; General
- 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

1.1.2 EU GMP

GMP rules in the European Union are known and published as the EudraLex. These rules are then taken into the law of member states together with any other local regulations that may apply. The EU rules have a large overlap with the USA CFR regulations although conforming to one country's regulations does not mean you necessarily conform to another's.

EU Directives are converted into national laws by the specific countries authorities. Each country in the European Union has its own authority, responsible for converting European regulations and directives into laws in each specific country. Pharmaceutical Directives are:

- **Commission Directive 2003/94/EC, of 8 October 2003**, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. The latter was then replaced by the Replacement of Commission Directive 91/356/EC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- **Commission Directive 91/412/EEC of 23 July 1991**, laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

The rules concerning manufacturing in pharmaceutical for human and veterinary use can be found in EudraLex GMP (Good Manufacturing Practice), Volume 4:
http://ec.europa.eu/health/documents/eudralex/index_en.htm
EU GMP include the following sections:

- Part I (Basic Requirements for Medicinal Products) – finished products
- Part II (Basic Requirements for Active Substances used as Starting Materials) - API
- Part III (GMP related documents)

The rules are composed by a main body composed of many Chapters (currently 1 to 9), and several Annexes (currently 1 to 19). The EudraLex also has an "Other documents related to GMP" section which includes a revised version of the "Guidelines on Good Distribution Practice of Medicinal Products for Human Use" (24 November 2013).

1.2 Specific requirements for computerized systems

1.2.1 EU GMP - Annex 11 (Computerized Systems)

Annex 11 of the EU GMP regulates the use of computerized systems. It has been recently updated in 2011 which represented a major change after almost 30 years from its previous edition - dating back to 1992.
This part of the GMP regulation covers many aspects of the computerized system lifecycle:

- Principle
- General
  - 1. Risk Management
  - 2. Personnel
  - 3. Suppliers and Service Providers
- Project Phase
  - 4. Validation
- Operational Phase
  - 5. Data

- 6. Accuracy Checks
- 7. Data Storage
- 8. Printouts
- 9. Audit Trails
- 10. Change and Configuration Management
- 11. Periodic evaluation
- 12. Security
- 13. Incident Management
- 14. Electronic Signature
- 15. Batch release
- 16. Business Continuity
- 17. Archiving

• Glossary

1.2.2 EU GMP - Annex 15 (Qualification and Validation)

Annex 15 covers other aspects of validation that are of relevant for facilities, processes and equipment and may be applicable to automated equipment, such as processing lines, that are critical for the product.
The latest edition of Annex 15, currently in force, is dated 2001, though there is a new edition, still in draft, which is expected to be adopted in 2015 an represents a major change from the previous edition.
The (new) Annex 15 covers the following topics:

- Principle
- General
- Organising and Planning for Qualification and Validation
- Documentation including VMP
- Qualification stages for equipment, facilities and utilities
- Process Validation
- Verification of Transportation
- Validation of Packaging
- Qualification of Utilities
- Validation of Test methods
- Cleaning Validation
- Re-qualification
- Change Control
- Glossary

In this document we will not cover Annex 15 requirements in detail.

1.2.3 US GMP - 21 CFR Part 211

Part 211 includes many requirements regarding automated systems, and in particular the topic is covered in § 211.68 "Automatic, mechanical, and electronic equipment".
Much before the publication of Part 11 the FDA produced the first official guideline about computer systems validation in February 1983, named "Computerized Systems in Drug Establishments" also known as the "bluebook" [11].

1.2.4 US GMP - 21 CFR Part 11

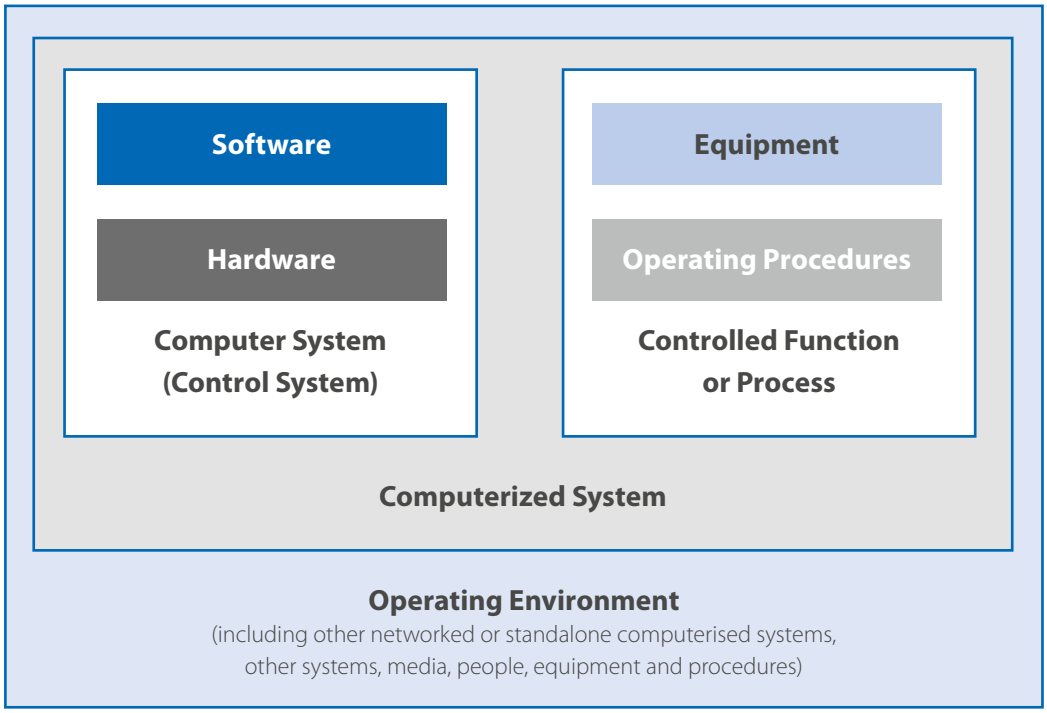
21 CFR Part 11 regulates the usage of Electronic Records and Electronic Signatures in the Life Sciences industries, when they replace the equivalent paper-based records and signatures.

Record keeping rules are defined by the so called "predicate rules" i.e. the GMP themselves; Part 11 does not add requirements on the recordkeeping: it only establishes the rules applicable to the computerized system in order to assure trustworthy records and signatures, so to guarantee at least the same protection of paper based records and handwritten signatures.

21 CFR Part 11 was actually requested to FDA by the pharmaceutical industry to allow paperless operations, and was specifically aimed to address electronic signatures. It contains two main sections: electronic records and electronic signatures, recognizing that electronic signatures are just a specific type of electronic record. Part 11 regulation caused some confusion since its introduction in 1997, because the scope was initially thought to be very broad. In 2003 FDA issued a guidance that helps final user to focus the scope in a narrower manner.

1.3 Computer systems – computerized systems

Before entering into more details, it's useful to better focalize the terminology and architecture of computerized systems used within a manufacturing process.
A scheme derived from a document from PIC/S can help us in this effort:



Source: PIC/S Guidance PI-011 - Good Practices for Computerised Systems in Regulated "GxP" Environments

1.4 Validation

Computerized systems used in regulated industries such as pharmaceuticals must be "validated". The term "validation" is well known in the software engineering world and has been reused in the pharmaceutical industries.

1.4.1 Definition of validation – an historical perspective

A well-known definition started from FDA in 1987 with the definition of process validation, as follows:

- *"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes."*
  [FDA Process Validation Guidelines, 1987].

Computer validation was defined by FDA in 1983 in a guidance document:

- *"The assurance, through testing, that hardware or software produces specified and predictable output for any given input."*
  [FDA Computerized Systems in Drug Establishments (February 1983) – aka the bluebook]

Initial definition of process validation was slightly modified by the PDA in 1995 for a computerised system:

- *"Establishing documented evidence which provides a high degree of assurance that a specific computer-related system will consistently produce a product meeting its predetermined specifications".*
  [PDA Technical Report 18, Validation of Computer-Related Systems, 1995].

FDA further redefined "software validation" in a guideline document of 2002 that is targeted to medical devices but is also useful in other areas:

- *"FDA considers software validation to be "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."*
- *"In practice, software validation activities may occur both during, as well as at the end of the software development life cycle to ensure that all requirements have been fulfilled. Since software is usually part of a larger hardware system, the validation of software typically includes evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. A conclusion that software is validated is highly dependent upon comprehensive software testing, inspections, analyses, and other verification tasks performed at each stage of the software development lifecycle."*
  [FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff, 2002]

Another recent definition can be found in the PIC/S Guidance PI-011 - Good Practices for Computerised Systems in Regulated "GxP" Environments (latest edition is dated 2007):

> *14.2 For the validation of computerised systems there should be a system in place that assures the formal assessment and reporting of quality and performance measures for all the lifecycle stages of software and system development, its implementation, qualification and acceptance, operation, modification, re- qualification, maintenance and retirement.*
> *This should enable both the regulated user, and competent authority, to have a high level of confidence in the integrity of both the processes executed within the controlling computer system(s) and in those processes controlled system(s), within the prescribed operating environment(s).*

1.4.2 Computer Systems Validation requirements

Validation requirements are integral part of any GxP regulation.

EU GMP, Annex 15 (Qualification and Validation):

- *This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products.*
- *It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the lifecycle of the product and process.*
- *Computerised systems used for the manufacture of medicinal products should be validated according to the requirements of Annex 11". [draft new Annex 15, May 2014].*

EU GMP requirements on Qualification and Validation apply to facilities, equipment, utilities and processes. When a computerized system is used, Annex 11 will (also) apply. Annex 15 does not explicitly state that there are cases in which both the equipment and the computer system must be qualified/validated.
Equipment Qualification is beyond the area of interest of this document and will not be covered in detail.

EU GMP Annex 11 (Computerized Systems):

- *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 fulfil certain functionalities.*
- *The application should be validated; IT infrastructure should be qualified.*
- *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.*

Annex 11 requires that the (software) application must be validated using a risk-based approach, while supporting hardware such as the IT infrastructure must be qualified.
The explanation of the terms "qualification" and "validation" can be found in the more general Annex 15. In a simplistic manner "validation" refers to the verification of processes (including software ones) while qualification refers to the verification of supporting elements.

21 CFR Part 211 (211.68: Automatic, mechanical, and electronic equipment)

- *(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.*

FDA Blue book guidance

- *C. Validation of Hardware. The suitability of computer hardware for the tasks assigned to pharmaceutical production must be demonstrated through appropriate tests and challenges. The depth and scope of hardware validation will depend upon the complexity of the system and its potential effect on drug quality.*
- *D. Validation of Software. It is vital that a firm has assurance that computer programs, especially those that control manufacturing processing, will consistently perform as they are supposed to within pre-established operational limits. Determine who conducted software validation and how key programs were tested ...*

21 CFR Part 11 - Electronic Records, Electronic Signatures

21 CFR Part 11 contains specific requirements for:

- Electronic Records (Subpart B)
- Electronic Signatures (Subpart C)

Due to their importance these requirements and the relevant interpretation will be covered in more detail in the subsequent part of this document (Chapter 1.7).

1.4.3 Summary of applicable GMP rules (EU and US)

	EU GMP		US GMP (FDA)		
	Annex 15	Annex 11	21 CFR Part 211 §68	21 CFR Part 11 (ER)	21 CFR Part 11 (ES)
Automated systems not related to product quality	-	-	-	-	-
Simple automated systems (related to product quality in regulated industries) [1]	•	-	•	-	-
Complex automated systems not maintaining GMP ER/ES [2]	•	•	•	-	-
Complex automated system maintaining GMP electronic records [2]	•	•	•	•	-
Complex automated system maintaining GMP electronic signatures [2]	•	•	•	•	•

(1) Simple automated systems may include a programmable controller (such as a PLC), a human machine interface (HMI) and a range of simple devices (sensors and actuators). Such systems do not normally maintain electronic records, and may not perform complex tasks requiring complex processing of information. Though they contain a small computer system, full compliance with EU GMP Annex 11 may not be required, while compliance with Annex 15 still applies: the equipment containing the computer system must be validated if it controls quality related activities or processes. During equipment qualification / validation the few applicable principles of Annex 11 can be easily covered even without explicit reference to Annex 11 itself. Under US regulations these systems are subject to 21 CFR Part 211 and specifically to § 68, so software must be validated as part of the automated system validation.

(2) Complex automated systems may include a more powerful programmable controller (such as a PLC or an industrial PC), a human machine interface (HMI, that can be included in the process control PC) and a range of complex devices (such as smart sensors and actuators). Control system may be connected to a remote supervisory / data acquisition system (such as a SCADA) to achieve a full range of functionality. Such systems usually perform complex tasks, requiring complex processing of information, while they may maintain electronic records and may use electronic signatures. Annex 11 is explicitly applicable to these systems and formal validation is required. 21 CFR Part 211 is applicable, while 21 CFR Part 11 may not be applicable at all or can be applicable only in part, depending on the level or recordkeeping.

1.5 Applicable Guidelines for software validation

To properly manage regulatory requirements on computer systems and achieve compliance, several guidelines were made available from a number of different sources, including the regulatory authorities themselves and industry associations, such as:

- PIC/S (Pharmaceutical Inspection Convention / Cooperation Scheme)
- FDA (Food and Drug Administration)
- GAMP® (Good Automated Manufacturing Practice)
- PDA (Parenteral Drug Association)
- APIC/CEFIC (Active Pharmaceutical Ingredients Committee) and many others.

Regulated companies may decide to follow one or more of these guidelines, and/or they may have their own compliance policies and standard operating procedures (SOPs).

1.6 Documents and records

GMP rules establish the documentation that must be produced and maintained in the long run, to demonstrate compliance of regulated manufacturing operations.

1.6.1 EU GMP

EU GMP requirements are defined in Chapter 4 "Documentation", which allows full equivalence of electronic documents with paper-based ones:

> *"the term 'written' means recorded, or documented on media from which data may be rendered in a human readable form."*

Chapter 4 describes two main types of documents: Instructions and Records.

Instructions (directions, or requirements) type:

- Specifications
- Manufacturing Formulae, Processing, Packaging and Testing Instructions
- Procedures
- Protocols
- Technical Agreements

Record/Report type:

- Records
- Certificates of Analysis
- Reports

Further details and regulatory requirements on records are defined in Chapter 4:

- *"Records: provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution.*
- *Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data."*

1.6.2 US GMP

US GMP requirements for records retention are defined in 21 CFR Part 211 Subpart J--Records and Reports, which includes:

- 211.180 General requirements.
- 211.182 Equipment cleaning and use log.
- 211.184 Component, drug product container, closure, and labelling records.
- 211.186 Master production and control records.
- 211.188 Batch production and control records.
- 211.192 Production record review.
- 211.194 Laboratory records.
- 211.196 Distribution records.
- 211.198 Complaint files.

1.7 Electronic Records and Signatures - 21 CFR Part 11 compliance

1.7.1 Electronic Records

Most complex control systems manage some sort of electronic records. The users are required to evaluate and justify the applicability of Part 11 to these records.

FDA's Guidance for Industry "Part 11, Electronic Records; Electronic Signatures — Scope and Application" [14], published in 2003, gives the most updated official guidance about the interpretation of Part 11 (that remains unchanged).

http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm

The major changes or clarifications FDA made in the guidance document are:

- **Narrow Interpretation of Scope.** Clarifying that fewer records will be considered subject to part 11. It brought to a new definition of Part 11 Records and Part 11 Signatures, as opposed to the previous definition of generic Electronic Records and Electronic Signatures.

- **Enforcement discretion** for those records that remain subject to Part 11, regarding Part 11 requirements for:
  - validation,
  - audit trails,
  - record retention,
  - record copying.

- **Enforcement of all predicate rule requirements** (including predicate rule record and recordkeeping requirements).

Definition of Part 11 Records

"Under this narrow interpretation, FDA considers Part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- *Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records. We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.*

- *Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities.*

- *Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format."*

It should be noted that many electronic records generated by the computerized system during a manufacturing process, are not necessarily retained on the system itself. For instance records may be printed on paper, converted to another electronic format, or transferred to another system for long-term retention. Part 11 does not apply to the records temporarily maintained on such systems (while it may apply on the other systems where the records are then maintained).

However it must be clear that:

- *"In some cases, actual business practices may dictate whether you are using electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be using the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.*

- *Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document)."*

It's common sense to consider therefore as Part 11 records only those electronic records that are retained on the system in the long terms, i.e. for the entire retention period mandated by the predicate rules. Data that is intended to be erased or overwritten by design are not in general Part 11 records.
In other words a GxP computer system may contain different kinds of electronic records:

- *Non-GMP records,* not related to product quality (not subject to any predicate rule). These records do not need to be formally considered during validation. It is however recommended to identify such records and justify the reason why they are not considered GMP relevant.

- *GMP records,* related to product quality but not expressly mandated by the predicate rules and / or not retained in electronic format for the entire retention period. These records need to be dealt with during validation, but aren't subject to 21 CFR Part 11.

- *Part 11 records,* related to product quality, mandated by the predicate rules and retained in the long terms. These records should be covered in the validation and in addition they must comply with Part 11 requirements.

1.7.1.1 Specific requirements for electronic records

Typical attributes / requirements for GMP electronic records are:

- Integrity: data must be protected against wilful and involuntary alterations
- Availability: data must be readily available
- Confidentiality (where applicable): confidential data must not be disclosed to unauthorized people
- Audit trail: change to critical data must be permanently documented
- Long-term retention: data must be made available for the required time mandated by the predicate rules and be available for inspection during the entire retention period.

1.7.1.1.1 Integrity

Data integrity can be assured by several means:

- Security: critical data must only be accessible to authorized personnel, especially for modifications
- SOPs: data entry / modification / deletion must be performed according written Standard Operating Procedures.
- Backup: critical data must be protected with a backup process (manual or automated) and restored in case of problems.

Records can be transformed into another format, preserving the entire record content and meaning.
A useful reference about data integrity has been recently made available in EU through MHRA the British Medicines and Healthcare Products Regulatory Agency, published in January 2015:
MHRA GMP Data Integrity Definitions and Guidance for Industry
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397853/Data_integrity_definitions_and_expectations_v3_4__ack.pdf
This document provides MHRA guidance on GMP data integrity expectations for the pharmaceutical industry, and is intended to complement existing EU GMP published in EudraLex Volume 4.

1.7.1.1.2 Availability

GMP records must be readily available, not only during system use but even much later (e.g. during GMP inspections), for all the retention period (see below). A specific requirement of Part 11 is the ability to extract electronic records from the system in a human readable format, and provide a copy to the inspector if requested, preserving the entire record content and meaning (e.g. copying or converting the records in another format).

1.7.1.1.3 Retention period

GMP records [i.e. those mandated by the predicate rules] must be maintained for a specified period of time, depending on the nature of the record. The retention period definition may be refined according to a risk assessment process. For instance EU GMP (Chapter 4 "Documentation" § "Retention of Documents") requires that:
4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. […]

4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. […]

Record retention period may span tens of years. The definition of the retention period for the various records types related to the system, is part of the validation process.
US GMP requirements for records retention are defined in 21 CFR Part 211 Subpart J--Records and Reports.
Among the general requirements:

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch.

It is quite often difficult to maintain electronic records in the long term. For example, PLCs in most cases do not have sufficient storage capacity, controls, and/or procedures in place to ensure reliable retention of data in the long terms. This would normally require adequate storage, plus data backup/restore procedures as well as adequate data retrieval and analysis functions, normally available only on more complex / powerful systems.
Note again that not all GMP ERs are subject to long term retention. Raw data can be processed and only processed data can be retained to demonstrate compliance. A risk assessment process may help to decide the approach, taking into account the applicable rules (as ERs kept in GLP or GCP applications are typically regulated in a more stringent way).
Examples of raw data could be represented by the images before their processing, in the case of a Vision system and/or data log files related to production.

Ref. to ISPE white paper Risk based Qualification for the 21st Century [23]

When data is to be retained for a long period of time, a practical approach would be to transfer those ERs to another system for long term storage in electronic format, or to print them on paper.

1.7.1.1.4 Audit trail

Fully automated "system generated" audit trail is necessary for critical (GMP) data. This requirement is present in both EU and US GMP. Part 11 requires audit trail to automatically and permanently record the following actions on ER:
- creation
- modification
- deletion

For each event above the system should automatically record:
- previous and new values
- identity of the person who made the change
- date and time of the operation

- reason why the change was done (Annex 11 requirement / GLP, GCP applications, laboratory systems).

Audit trail is necessary for critical records, defined on sound and scientifically based risk assessment (i.e. based on GMP requirements / predicate rules and potential quality issues on the patient safety and product quality).
Audit trail can be applied on:
- Master data (e.g. product recipes, vision systems "scenes", general settings – product related)
- Production data (Batch record). E.g. measurement values and /or results, actual images collected by the vision system, etc.

Other software related elements can be critical and may need precise change management procedures (not necessarily an automated audit trail), such as:
- software (i.e. the actual code)
- software parameters (i.e. software configuration)
- user related parameters (user profiles and access rights to the systems).

Audit trail may not be necessary for records that are preserved in protected read-only state for the entire retention period.

1.7.2 Electronic Signatures

Process control computerized systems may be used with electronic signatures.
ES that are considered subject to Part 11 are specified by the FDA's guidance document:

Definition of Part 11 Signatures

"Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- *Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. approved, reviewed, and verified)."*

It should be noted that many activities performed during a manufacturing process may be properly recorded by means of a simple identity check and do not require an electronic signature. Records may be kept under audit trail if necessary, to keep track of changes in the data.

Ref ISPE White Paper on Risk Based Approach to 21 CFR Part 11 [22]

1.7.2.1 Specific requirements for electronic signatures

Both EU GMP and Part 11 allow electronic signatures in lieu of handwritten signatures.
Part 11 specifically allows different forms of ES:
- using a traditional non-biometric approach with at least two components (such as an ID and a Password)
- using a token (i.e. an identification device)
- using a biometric system (such as a fingerprint)

Electronic signatures maintained on a computer system are just a special kind of electronic record. All requirements applicable to ERs are therefore also applicable to ES, including data integrity and retention period.
Based on the very definition of ES, FDA and other GMP inspectors should inspect the ES directly on the

manufacturing equipment / control system, which may prove unsuitable in many cases, especially for automation systems in the shop floor.

For this reason, GMP Electronic Records are quite often printed on paper documents and then signed with a traditional handwritten signature. Please note that Handwritten Signatures executed to Electronic Records are subject to a specific Part 11 requirement (Sec. 11.70 - Signature/record linking), that mandates a permanent link to their respective electronic records to ensure that the signatures cannot be copied, or otherwise transferred to falsify an electronic record by ordinary means.
A different approach to overcome issues about ES is to transfer ERs on a different system, suitable for long term storage, and then print or sign electronically these records on the remote systems.

2 Validation Approach

2.1 GAMP® Guidelines

Validation include coverage of the entire manufacturing process and supporting equipment and control systems. Computer systems validation includes the software application and supporting hardware.
The equipment and the relevant control systems may be conveniently structured into different portions. For instance a production machine using a vision system may be structured into:

- Equipment (mechanical, electrical and pneumatic components)
- Equipment control system (including hardware & software)
- Vision system (including hardware & software)

One of the most commonly used guidance for computer systems validation is the GAMP® Guide, current version 5 [16]. GAMP® Guide is officially acknowledged by most regulatory authorities including EMA, PIC/S and FDA. Other approaches are however acceptable and the pharmaceutical industry is ultimately responsible for the definition of the approach and extent of validation, using a justified and documented risk assessment of the computerised system.

A useful reference document, specifically targeted at the validation of process control systems, is the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (Second Edition):
http://www.ispe.org/GAMP-good-practice-guide/risk-based-gxp-process-control-systems

Another reference document is the GAMP® Good Practice Guide: Risk-Based Approach to Electronic Records and Signatures:
http://www.ispe.org/gamp-good-practice-guide/electronic-records-signatures

2.2 Software Categories (GAMP®)

GAMP Software Categories for process control systems:

CATEGORY	DESCRIPTION		RANGE OF APPLICATIONS	TYPICAL EXAMPLES
5 Custom Software	Software custom designed and coded to suit the business process.	↑	Complex application, coding language requires consideration of program level decisions/timing/looping as well as process level decisions/timing/looping.	VB or C++ Application DCS or SCADA scripting IEC61131-3 IL or ST application IEC61131-3 LD or SFC application
4 Configured Software	Software (often very complex) which can be configured by the user to meet the specific needs of the user's business process. Software code is not altered.	↑	Library functions selected, parameterized and connected with branches and decisions. Increasing complexity of configuration. Library functions selected, parameterized, and connected in linear fashion.	IEC61131-3 FBD application Vision system software DCS/SCADA Databases **Smart camera software**
3 Non-Configured Software	Runtime parameters may be entered and stored but the software cannot be configured to suit the business process.	↑	Standard item needs a large parameter file loading before it will work. Increasing complexity of parameterization (works 'out of the box').	Electronic Chart Recorder PID Controller Smart Transmitter
1 Infratructure Software	Software used to manage the operating environment. Layered software upon which applications are built.		Refer to GAMP 5 and the GAMP Good Practice Guide: IT infrastructure Control and Compliance for further details.	Version Control Tools Programming Languages Underlying Operating System

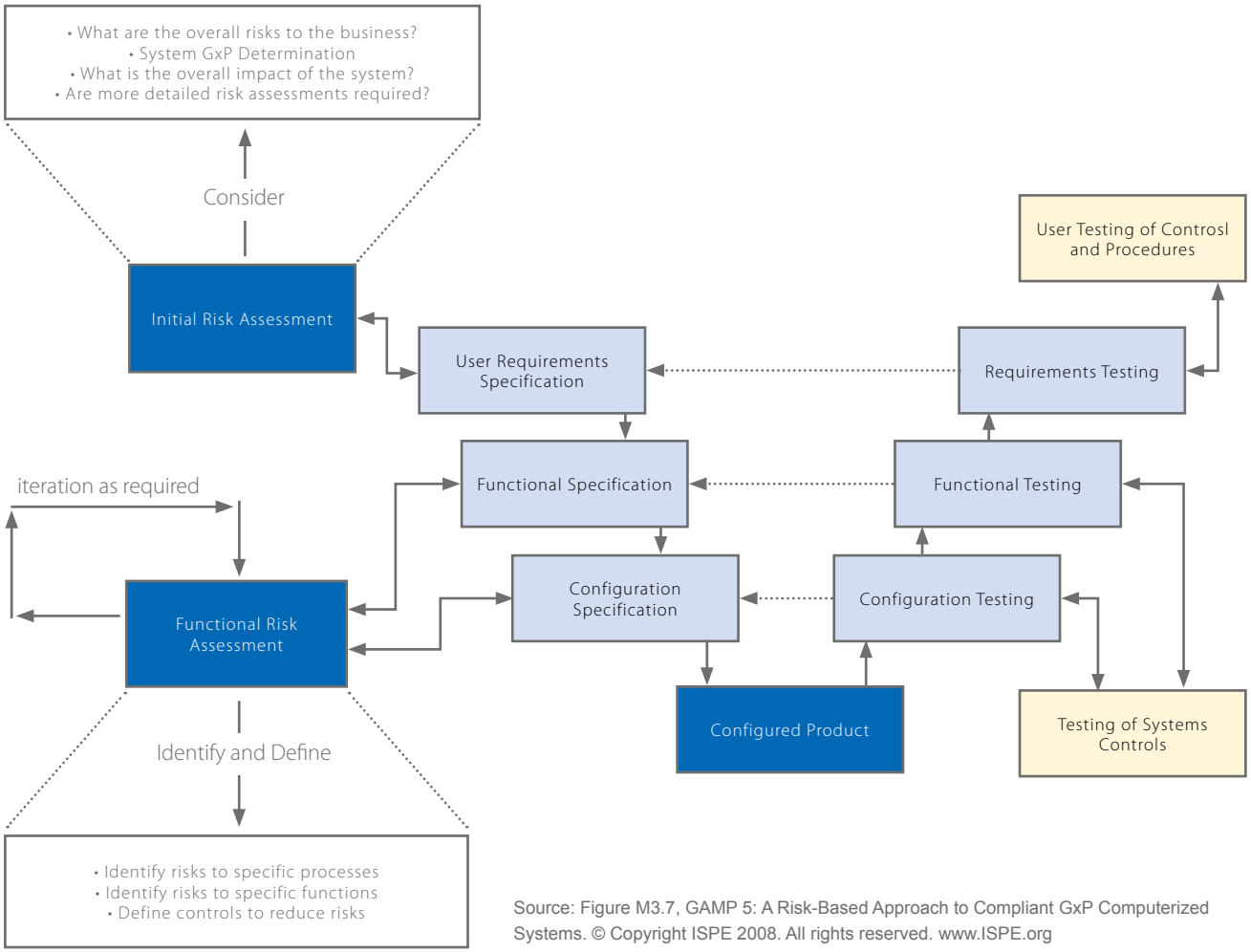
Source: GAMP® Good Practice Guide: A Risk-Based approach to GxP Process Control Systems Figure 4.8.: illustrative examples of software categories.

GAMP Hardware Categories for process control systems:

CATEGORY	DESCRIPTION	RANGE OF APPLICATIONS	TYPICAL EXAMPLES
2 Custom Built Hardware Components	Bespoke software components designed specifically for the application.	Complex bespoke item - typically defined by a large set of drawings and/or a design specification. Increasing complexity of functionality. Simple bespoke item - typically defined by a single drawing.	Safety Shutdown Relay System Control cubicle Control loop
1 Standard Hardware Components	Standard hardware components bought 'off the shelf' using a standard order code from the supplier and covered by manufacturer's specification details.	Complex standard item- typically requires many elements specifying within order code. Increasing complexity of functionality. Simple standard item - single element order code.	PLC Vision system hardware Control System I/O Module Smart camera hardware PT 100 Temperature sensor

Source: GAMP® Good Practice Guide: A Risk-Based approach to GxP Process Control Systems Figure 4.9.: illustrative examples of hardware categories. ©Copyright ISPE 2010. All Rights reserved. www.ISPE.org

2.3 Standard configurable applications (GAMP® category 4)



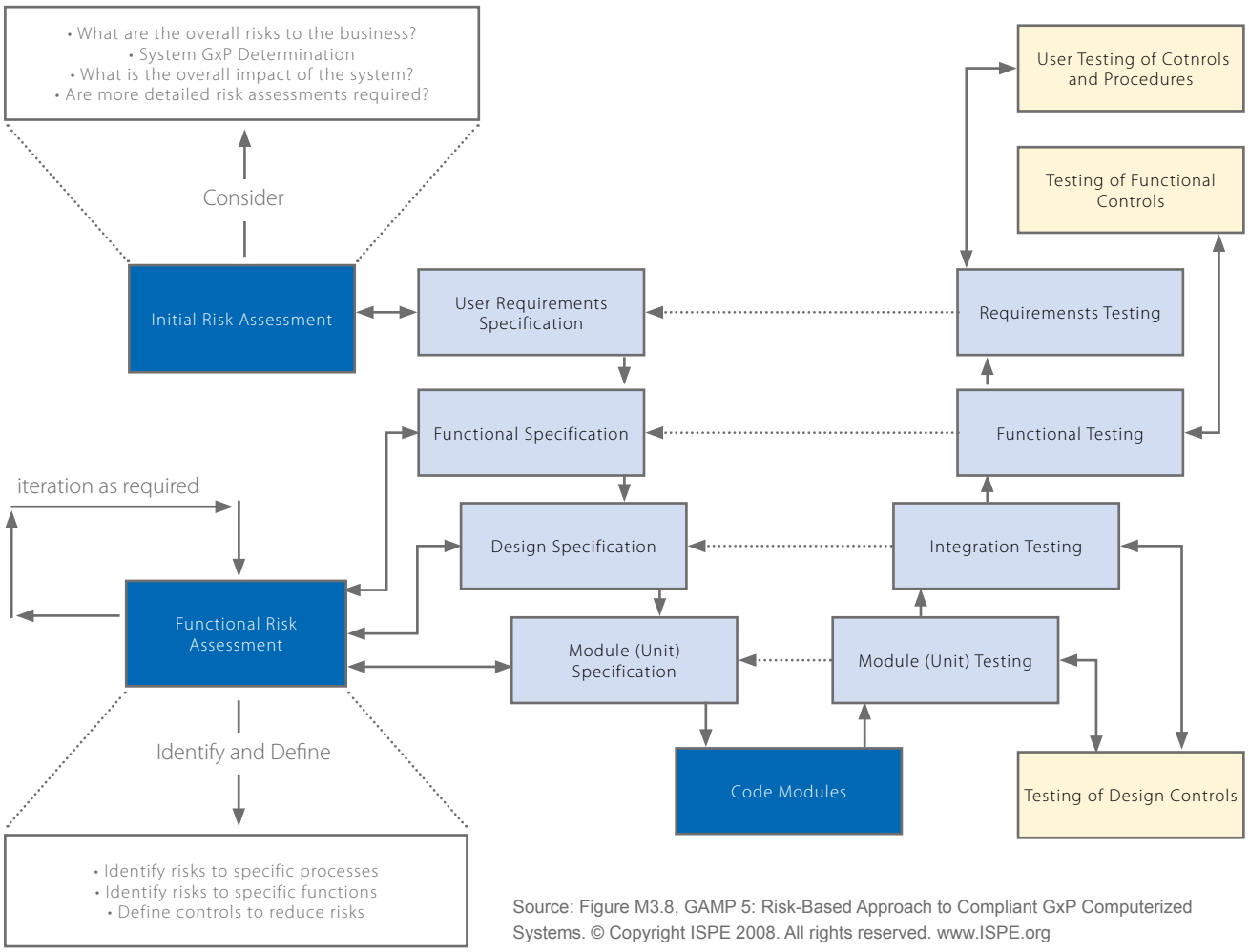
Source: Figure M3.7, GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems. © Copyright ISPE 2008. All rights reserved. www.ISPE.org

Further suggestions and details for the validation of process control systems may be found in the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems [19]. This GAMP® GPG covers in more detail the following aspects:

- *Process Validation*
- *Equipment validation*
- *Control System validations*

In this document we only deal with the control system validation, with focus on the vision system.

2.4 Bespoke applications (GAMP® Category 5)



Source: Figure M3.8, GAMP 5: Risk-Based Approach to Compliant GxP Computerized Systems. © Copyright ISPE 2008. All rights reserved. www.ISPE.org

Further suggestions for process control systems may be found in the GAMP Good Practice Guide: A Risk-Based Approach to the GxP Process Control Systems (19). This guide covers in more detail the following aspects:

- *Process validation*
- *Process Equipment validation*
- *Control System validation*

In this document we only deal with the control system validation.

2.5 Validation Documents

Documents refer to the computer control system only. Additional documents may also be required to properly describe and qualify the equipment (e.g. equipment, machinery). A typical case of a configurable system is assumed (category 4 with some ad hoc developments). Some more documents may be appropriate for a bespoke system (e.g. a complex, non-packaged system). Not all documents are always required. In the case of a simple systems documents may be grouped together.

PHASE	ACTIVITY / DOCUMENT	Description	Details / Responsibilities
Planning	Supplier(s) Audit	The supplier should be evaluated during the selection of the product. The formal assessment can be performed through a general audit questionnaire (Postal Audit) completed by the supplier, prepared according to GAMP® recommendations. Alternatively, an on-site audit may be necessary. This supplier audit identifies any organizational and technical situations to be considered by the end user during the validation and to verify the supplier's suitability to support the validation activity. Consultants (e.g. technical and validation consultants) should also be evaluated).	Supplier assessment is a responsibility of the regulated company. Suppliers may have standard documentation available (such as white papers, or precompiled postal audit questionnaires).
	Validation Plan (VP)	The Validation Plan defines the activities planned for the validation of the system.	The VP is normally issued by the final user (pharmaceutical company).
	User Requirements Specification	The User Requirements Specification describes and analyzed the operational and management requirements that the system shall possess.	This document is prepared and approved by the end user with the contribution of the key users and with the support of the consultants. This ensures the complete coverage of all actual requirements for the system being implemented, including any customizations. The GxP relevance of each requirement is evidenced in the document (this is a preliminary step for the risk analysis).
	Project and Quality Plan	The Project and Quality Plan(s) describe the activities and quality standards that are to be followed.	The document is usually produced by the supplier, and is approved by the end user.
Design & Specifications	Functional Specifications & Configuration Specifications	The Functional Specifications describe in detail the operation of the system, in each component. The content of the documents shall correspond to what is required in the User Requirements Specification. Configuration Specifications may be included in the Functional Specifications or produced as a separate document.	The FS / CS documents may be provided by the supplier on the base of a standard model and are customized according to client's requirements. CS are normally specific for the applications. The documents are reviewed and approved by the customer.

PHASE	ACTIVITY / DOCUMENT	Description	Details / Responsibilities
	Design Specification	The following technical documents are foreseen: • Hardware & Software Specifications. The document defines the hardware and software specifications for the server and the client workstations.	These documents are based on the supplier's specifications and on the technical choices performed by the client and is used as reference for IQ tests.
		• Software Design Specifications. These documents describe in detail any developments and will include also the source code of such developments.	These documents are normally prepared ad-hoc based on the on the supplier's templates and are used as reference for FAT, SAT and OQ tests.
	Risk Analysis & Management	The Risk Management document is intended to identify GxP critical functions, records and parameters, and define in detail the validation approach. It allows managing the potential threats and ensuring that residual risks are acceptable.	These documents are normally prepared ad-hoc based on the on the supplier's templates and are used as reference for FAT, SAT and OQ tests. This document is produced under the responsibility of the final user. The supplier may provide substantial support. It usually refers to the ICH Q9 (Quality Risk Management) approach.
	Traceability Matrix	The Traceability Matrix is intended to document the complete coverage of the user requirements, through all lifecycle phases. A first version is prepared to connect URS, FS and OQ tests. Subsequently the Traceability Matrix is completed (issued new version) to also connect PQ tests.	This document is produced under the responsibility of the final user. The supplier may provide substantial support.
	User Manual	The User Manual will describe the system operating instructions and is included in the supplier documentation. The document is aligned to the actual version of the installed software.	THE DOCUMENT IS NORMALLY PRODUCED BY THE SUPPLIER.
Testing	Test Plan	The Test Plan will describe the test strategy and details on the test methodology adopted. The decision on which tests are to be performed is based on the evaluation of critical items emerging from the risk analysis.	This document is optional and is produced under the responsibility of the final user. The supplier may provide support in the definition of the qualification & validation activities.
	Factory Acceptance Test (FAT)	Tests performed at the supplier's premises, usually to authorize delivery of the system to the final user. Covers most system features, hardware and software, GMP and non GMP.	FAT is a common contractual step in the supply of automated equipment, and is normally agreed between supplier and final user. The document is normally prepared by the supplier and approved by the final user. It's now covered in the new Annex 15 (draft).

PHASE	ACTIVITY / DOCUMENT	Description	Details / Responsibilities
	Site Acceptance Test (SAT)	Tests performed at the final user's premises, to confirm proper operation of the system in the actual operating environment. Covers many system features, GMP and non GMP, focused on those not previously covered during FAT.	SAT is a common contractual step in the supply of automated equipment, and is normally agreed between supplier and final user. This document is normally prepared by the supplier and approved by the final user. It's now covered in the new Annex 15 (draft).
	Installation Qualification Protocol	The Installation Qualification Protocol defines the verifications necessary to ensure that the specified components are installed in conformance with the design specifications and the supplier recommendations. The IQ tests confirm that system components are properly identified, installed and configured. The IQ activity is considered a prerequisite for the subsequent OQ phase. The areas to be covered for the h/w and s/w verifications, as applicable, can be: • Servers • Clients • Critical Peripherals • Networks (where necessary or applicable) • Documentation • SOPs When the system is based on a qualified common platform (infrastructure), IQ protocol will only cover those parts not already covered by the Infrastructure Qualification.	IQ Protocol is prepared by the regulated company with the support of the supplier / consultants as needed and is approved by the end user. It may be separated into different sections (e.g. equipment, control system).
	Operational Qualification Protocol	The objective of the Operational Qualification Protocol is to demonstrate in advance the correct operation of the system during its intended use, particularly for the functions that manage critical data. The OQ protocol will include, as appropriate and applicable, verifications about custom made functions.	OQ Protocol is prepared by the end user, cooperating with the consultants and with the support of the supplier, and is verified and approved by the customer.

PHASE	ACTIVITY / DOCUMENT	Description	Details / Responsibilities
	Installation Qualification Test Execution	The formal IQ execution verifies the correct installation and configuration of the system hardware and software components. The verifications foreseen in the Test Plan is performed on servers, clients and infrastructure hardware and software as required, according to approved IQ Protocol.	The tests are executed by the end user personnel with optional support from the supplier. A short IQ Summary is usually drawn up at the end of the test activity.
	Operational Qualification Test Execution	The formal OQ execution verifies that the system functionality satisfy user and regulations requirements. Every test performed on the system will include the usage of specified data and test actions. Test results are compared with expected results. Test data and actions, together with expected results and test planning is those specified in the previously approved OQ Protocol.	The tests are executed by the end user's personnel with optional support from the supplier. A short OQ Summary is usually drawn up at the end of the test activity
	System Configuration Verification	System Configuration Verification is usually included in the OQ protocol.	System Configuration Documentation is usually produced with the support of the supplier.
	Performance Qualification Protocol	Performance Qualification Protocol drawing up. The PQ protocol will include, as appropriate and applicable, verifications related to: • System global functionalities and operating flows • SOPs and their correct application.	PQ Protocol is produced by the end user cooperating with the consultants.
	Performance Qualification Execution Test	GxP critical operation flows and SOPs are verified according to previously approved protocols.	The tests are executed by the end user's personnel (possibly by system users) before the go-live. A short PQ Summary is drawn up at the end of the test activity.
Release and Acceptance	Preparation to Operating Start-up	It includes activities of preparation for production. At the end of these operations and the necessary verification the system can be made operational.	This activity is normally performed by the end user with optional support from the supplier.
	GO-LIVE	It is the starting of the operating activities of the system. At the successful completion of all preparation activities the system is started up.	This activity is normally performed by the end user with optional support from the supplier.

PHASE	ACTIVITY / DOCUMENT	Description	Details / Responsibilities
Release and Acceptance	Validation Report	All validation activities specific for a site is described in a Validation Report including any deviations and residual or corrective actions still necessary. To conclude validation, a final verification is undertaken and a Validation Report is issued. This activity is intended to verify that all the activities foreseen in the Validation Plan have been properly executed and completed, and to document any deviations and corrective actions still necessary. The VR authorizes the use of the system for regulated activities and defines the steps needed to maintain the validation.	The Validation Report is normally produced by the regulated company.

2.5.1 GAMP® GPG: A Risk-Based Approach to GxP Process Control Systems

Further suggestions for process control systems may be found in the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems [19]. This guide covers in more detail the following aspects:

- *Process validation*
- *Process Equipment validation*
- *Control System validation*

In this document we only deal with the control system validation.

> *"This Guide distinguishes three types of process control system. These are intended to be used in conjunction with GAMP categories to highlight system scale and complexity (often in terms of the range of suppliers involved), and to allow a common basis for presenting examples across a range of systems."*

Types of Process Control Systems:

- Device
- Packaged systems
- Non-packaged systems

Process Control Device	Single device from a single supplier comprises an entire standalone process control system. Example: smart camera used in a stand-alone application.
Control System Packaged with Process Equipment	Process control elements are embedded within process equipment into a "packaged" product from a supplier where the supplier quality management system provides assurance of the system in effect as though it were a commodity (may comprise multiple instruments, Programmable Logic Controllers (PLCs) and Supervisory Control and Data Acquisition/ Human Machine Interface (SCADA/HMI) components). Example: automated machinery provided with standard control system hardware & software.
Control System Not Packaged with Process Equipment	rocess control system elements are developed independently in order to deliver a specific business process (may involve integrating multiple process control devices or packaged systems). Examples: - bespoke software developed for a prototype equipment used for pharmaceutical processing. - Non-standard retro-fit software supplied for upgrading a previously supplied equipment.

GAMP GPG recommends the following validation approach for process control systems validation:

"For automated manufacturing equipment, separate computer system validation should be avoided. Computer system specification and verification should be part of an integrated engineering approach to ensure compliance and fitness for intended use of the complete automated equipment."

Related facility and equipment topics, including, but not limited to the following, should be considered, but are outside the scope of this document:

- *Environmental Control*
- *Product Contact*
- *Equipment Cleaning and Maintenance*
- *Equipment Calibration*
- *Equipment Identification*

3 Application Examples

The following application examples consider only the computerized system(s), not the entire equipment. Qualification of the rest of the equipment (e.g. mechanical and electrical functions / parts) is required to achieve compliance, but are not covered here.
These examples show that, where possible, the use of standard equipment reduces the lifecycle effort considerably, hence reducing costs. Project risk is also reduced, as a supplier offering a standard package.
The examples given are illustrative only, and are not intended to be neither prescriptive or exhaustive.
Equipment with a vision system is to be implemented. The required functionality could be achieved in one of three ways:

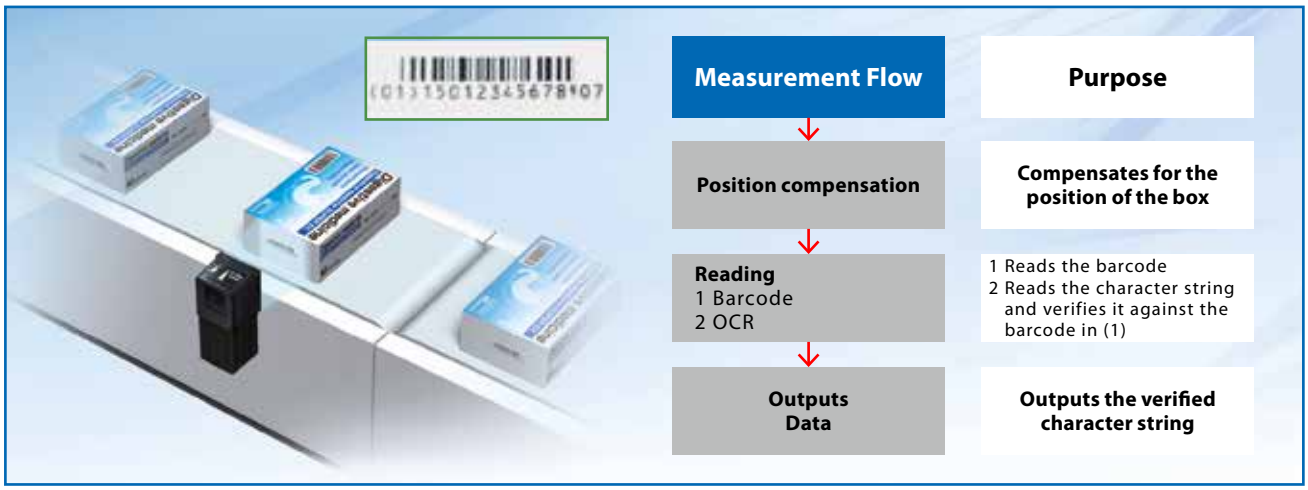
1. a standard product (requiring parameter entry only) from a mature supplier with an adequate Quality Management System (QMS)
2. a highly configured application using library functions that have been linked together for this specific use, produced by a mature supplier with an adequate QMS
3. a custom coded application produced by a mature supplier with an adequate QMS

3.1 Example 1 (simple automation system)

Simple automated systems may include a programmable controller (such as a PLC) performing simple operations, a human machine interface (HMI) and a range of simple devices (such as sensors and actuators).

3.1.1 Vision function: Code and Character Verification

OCR and Code Reading inspection items can be combined to read codes and verify them against character strings all within the smart camera. No programming of external devices is required.

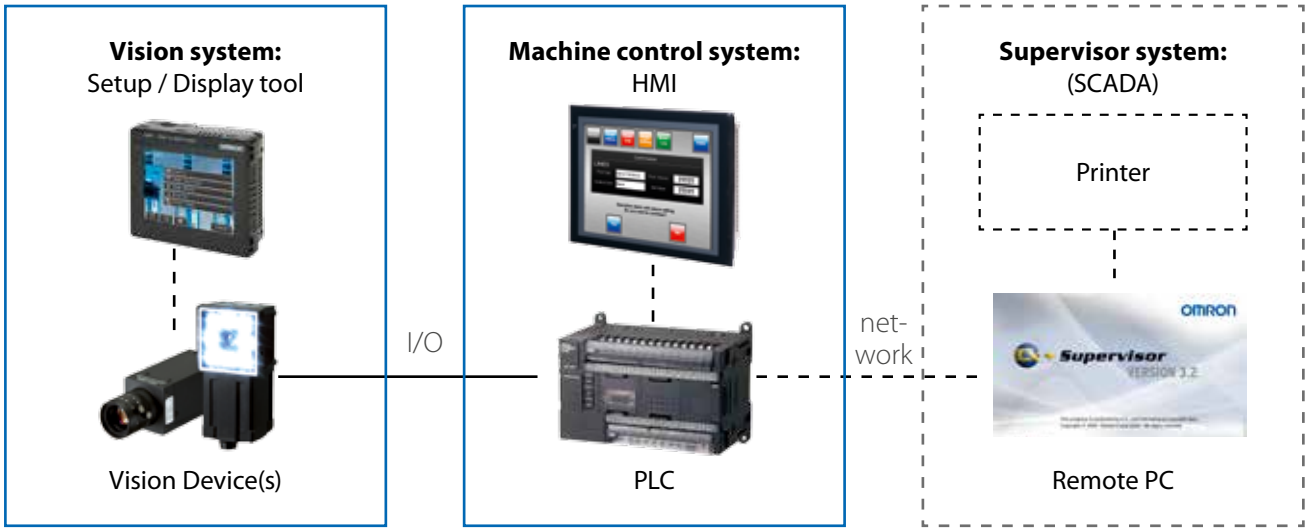


3.1.2 System Components and Architecture

The application example uses a simple vision system (e.g. Omron FQ2 smart camera), a simple PLC (e.g. Omron CP1L family), and a HMI (e.g. Omron NB family).

The smart camera can be programmed using a separate unit (Omron Touch Finder), which may be optionally permanently installed on the equipment and used as a camera display.

Logical Architecture:



3.1.3 System Features

Main features:

- The system is mainly intended for manual data recording, with no permanent electronic data storage.
- Interface between vision system and PLC is through I/O lines (cabling), without data transfer. Ethernet connection, though available on Omron smart cameras, is not used in this example.
- Vision system setup is performed when necessary using the Touch Finder. This is a small monitor with a touch panel, which can optionally be installed on a control panel.
  A PC Tool, that provides the same functions as the Touch Finder, but on a PC, cannot be used because in this case there is no network connection and no local PC.
- The PLC may provide basic data generation and short term recording of vision system activities, such as counting the number of good units and/or defects.

Optional features:

- A remote PC / SCADA system may be optionally available for data collection and analysis, printing of reports and supervisory activities, including upload of process parameters to the PLC where required.
- Optional interface between PLC and remote PC can be through local network. Data transfer may cover equipment data and control results. Vision system information such as images or setup parameters (scenes) cannot be transferred.
- Optional reports can be printed on the remote PC. Signatures, when required, are typically managed through handwritten signatures on printed reports.

Note: Remote PC is out of scope.

3.1.4 Compliance considerations (including ER/ES)

QUESTION	ANSWER
Type of application	Stand-alone Process Control System, optionally connected to SCADA or MES system.
GAMP® Category for software	• Vision Device: cat. 3 (or even 4 in some cases) • PLC: cat. 4 (packaged systems) or 5 (non packaged, bespoke applications) • Remote PC: cat 4 (e.g. commercial SCADA) or 5 (bespoke system)
Typical regulated electronic records maintained in the system	The system has GxP impact but does not maintain any regulated electronic records. Packaging records and alarms are on paper (but electronic records may be retained on a SCADA or MES system if relevant data is transferred to such a system). Note: PLC data are usually temporary (i.e. retained for a short time and then deleted/overwritten, after transfer to a SCADA system and/or printing as required). Critical process parameters will typically be controlled by machine settings. Some critical parameters are kept in the vision device and PLC. No regulated electronic record is maintained (these are controlled by validation, change control, and access control).
Typical hybrid situations for records and signatures	Some records may be generated by the system and would typically be printed out for subsequent review and approval.
Typical regulated signatures maintained in the system	No electronic signatures.
Typical access controls	Physical and procedural controls. PLC and vision device should (but may not) have electronic access controls for users. User-ID and password should be required for access through HMI (or other systems such as SCADA).
Audit trail	Electronic audit trails are not typically provided. Changes to critical parameters should be formally managed by change control procedures.
Typical data or operating parameters are subject to formal change control	Changes to critical parameters (such as vision system parameters) are likely to be made periodically, and such changes should be subject to formal change control.
Typical procedures required	Standard Operation Procedures (SOPs) are required for machine set up and usage, managing access controls, and changes to critical parameters (including vision system parameters).
Special issues	Any interfaces to other systems such as SCADA or MES for transferring batch record information. Some PLCs can "store and forward" data to ensure data is not lost due to temporary network problems.

3.2 Example 2 (intermediate complexity system with ER)

Complex automated systems may include a programmable controller (such as a PLC or an industrial PC), a human machine interface (HMI, that can be based on the control PC), and a range of complex devices (such as smart sensors and actuators). They may be optionally connected to a remote system, such as a SCADA, to achieve a full range of functionality. Such systems normally perform complex tasks requiring complex processing of information and may maintain regulated electronic records.

3.2.1 Tablet / Code Verification

3.2.2 System Components and Architecture

Vision System:

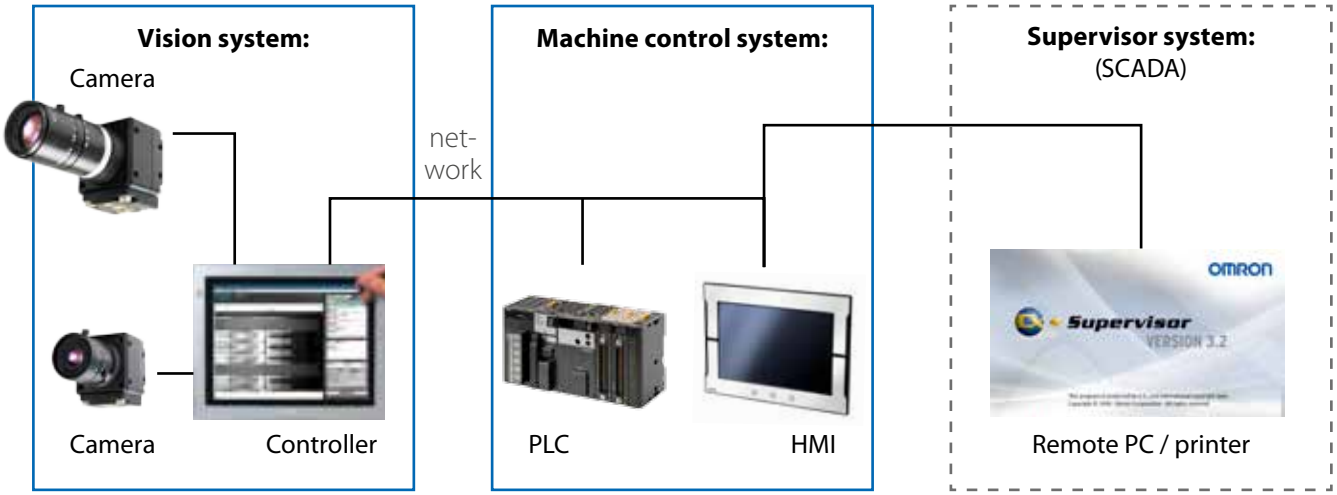
- Omron FZ vision system running FlexXpect Pharma software,
  - Touch screen panel
  - Up to 4 cameras connected

Note: FlexXpect Pharma software requires FZ / FH hardware

Machine Control System:

- PLC: Omron CJ2 family
- HMI: Omron NA family

Logical Architecture:



3.2.3 System Features

Main Features:

- The system is intended for semi-automatic operation and paper recording. Reports can be generated on the vision system.
- Vision system set-up can be performed many times using the vision system screen always connected.
- Interface between vision system and control system is performed through the local network, with optional data transfer (including vision controls).
- Machine control system manages recipes (i.e. set of parameters specific for each product). Recipes are set-up and stored on the PLC.

Optional features:

- A remote PC / SCADA system may be optionally available for data collection and analysis, printing of reports and supervisory activities, including upload of process parameters (recipes) to the PLC where required.
- Optional interface between PLC and remote PC can be through local network. Data transfer may cover equipment data and control results. Vision system information such as images or setup parameters (scenes), in this example, are not transferred to the PLC nor to the supervisor.
- Optional reports can be printed on the remote PC. Signatures, when required, are typically managed through handwritten signatures on printed reports.

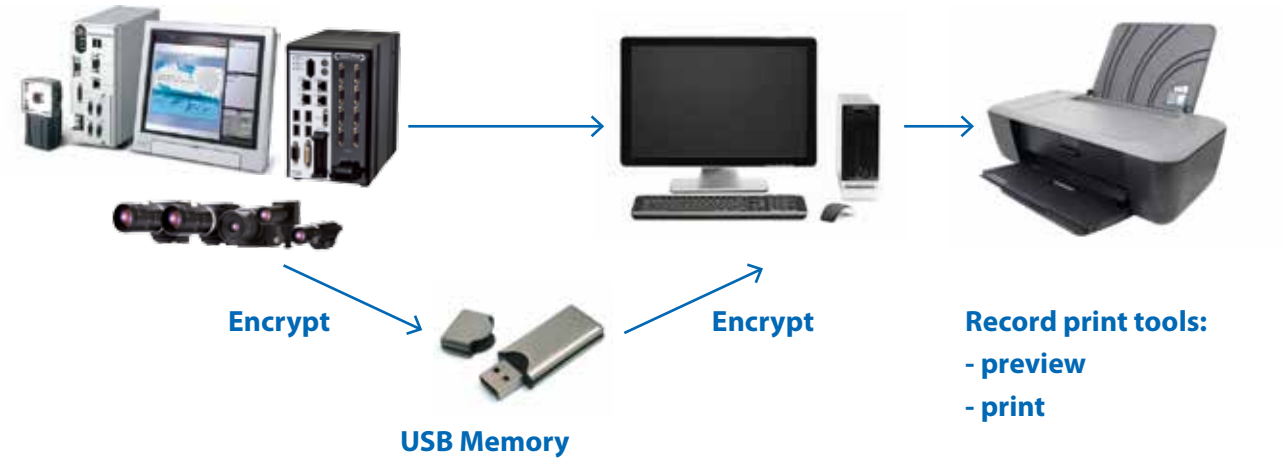
Note: Remote PC (SCADA) is considered out of scope.

3.2.4 Benefits deriving from FlexXpect Pharma software

Using a specialized software (FlexXpect Pharma) in the vision system gives the regulated user several advantages over users of standard software:

- User profile management on vision system (protection of settings, scenes). Three basic user classes are available distinguishing in Administrator level, Engineer level, Operator level, and other 40 different classes can be defined.

- Audit trail. Changes to the scenes are protected and any changes are recorded in the audit trail.
- Production logs. Logs are generated in CSV format and can be optionally printed, or exported to other systems. Logs are related to the Start and the End of the production process.
- Reports. Reports can be generated using FlexXpect Pharma software, if a local / remote printer is made available.
- PC software for external analysis. Records can be transferred / backed up and then analyzed on a separate PC, using a removable USB device or directly though the local network.



3.2.5 Compliance considerations (including ER/ES)

QUESTION	ANSWER
Type of application	Networked Process Control System, optionally connected to SCADA (or MES) system to download batch- and component-specific data. Optional real time data acquisition, control and data processing (SCADA).
GAMP® Category	• Vision System: cat. 4 • Machine Control System: cat. 4 or 5 • Remote PC: cat 4 (commercial SCADA) or 5 (bespoke system)
Typical regulated electronic records maintained in the system	The system has GxP impact and maintains some regulated electronic records, such as vision parameters (scenes). Packaging records and alarms are on paper (but electronic records may be retained on a SCADA or MES system if relevant data is transferred to such a system). Note: PLC data are temporary (i.e. retained for a short time and then deleted / overwritten, after transfer to a SCADA system and/or printing as required). Some critical parameters are kept in the vision system and can be transferred elsewhere through the network or to a removable storage device (such as a USB flash drive), for long-term retention or printing. Other critical parameters managed by the PLC will typically be controlled by machine settings and not maintained in electronic format (these are controlled by validation, change control, and access control).
Typical hybrid situations for records and signatures	Some records may be generated by the control system and would typically be printed out for subsequent review and approval. ER's managed by the vision system (scenes) and audit trails can be copied (in encrypted format), then analyzed and printed on separate PC using specialised Omron software. SCADA (optional): Approval signatures on printed batch records and trends.

QUESTION	ANSWER
Regulated signatures typically maintained in the system	Vision and machine control systems do not use electronic signatures. Any signatures required by the applicable predicate rules can be executed on paper documents. SCADA (optional) may have e-signature functionality for on screen review and approval of trends and handling alarms.
Typical access controls	Physical and procedural controls. PLC may not have electronic access controls for users. User-ID and password should be required for access through another system such as SCADA/HMI. SCADA (optional): Access control may be physical/procedural as system may be permanently switched on if required for real-time process control. Formal change control required for changes to settings and data related to critical parameters.
Audit trail	Audit trail is provided on the vision system (FlexXpect software). Electronic audit trails are not typically provided on the machine control system (PLC). Changes to critical parameters should be formally managed by change control procedures. SCADA (optional): Depends on records being maintained. Use of audit trail to document creation, modification, or deletion of regulated records would be good practice. Key processing steps require signatures, other processing steps require identity checks.
Data or operating parameters typically subject to formal change control	Changes to critical parameters (such as vision and machine control parameters) are likely to be made periodically and such changes should be subject to formal change control. SCADA: Formal change control required for changes to settings and data related to critical process parameters, recipes, and batch record information.
Procedures typically required	SOPs are required for machine set-up and usage, managing access controls, and changes to critical parameters. SCADA: Formal change control for changes to critical processing parameters. Access control procedures.
Special issues to be considered	Any interfaces to other systems such as SCADA or MES for transferring batch record information. Some PLCs now "store and forward" data to ensure data is not lost due to temporary network problems. SCADA: Operators may enter into the system settings and actual values for critical steps of the operation. The system should record the identity, time and date of the operator making such entries. Some process entries may be recorded automatically in which case the validation should ensure that the entry is correct. Some entries are manual, e.g., which operation cycle to select and this will be entered via a keyboard. In this case the entry is subject to validation, procedural control and training. Operator interventions/holds and safety shutdown conditions should be considered as part of a risk assessment. Access control may be physical as system may be permanently switched on in a manufacturing environment.

3.3 Example 3 (complex system, with both ER and ES)

3.3.1 Multiple controls including cross contamination detection, lot code and data matrix (serialization), correct cap closure, anti-mix-up (cap colour detection).

3.3.2 System Components and Architecture

Vision System:

- Omron FH vision system running FlexXpect Pharma software,
  - Touch screen panel (optional)
  - Up to 8 cameras connected (only 4 used in the example)

Connection to a supervisor / data storage system.

Note: As already considered FlexXpect Pharma software requires FZ / FH hardware

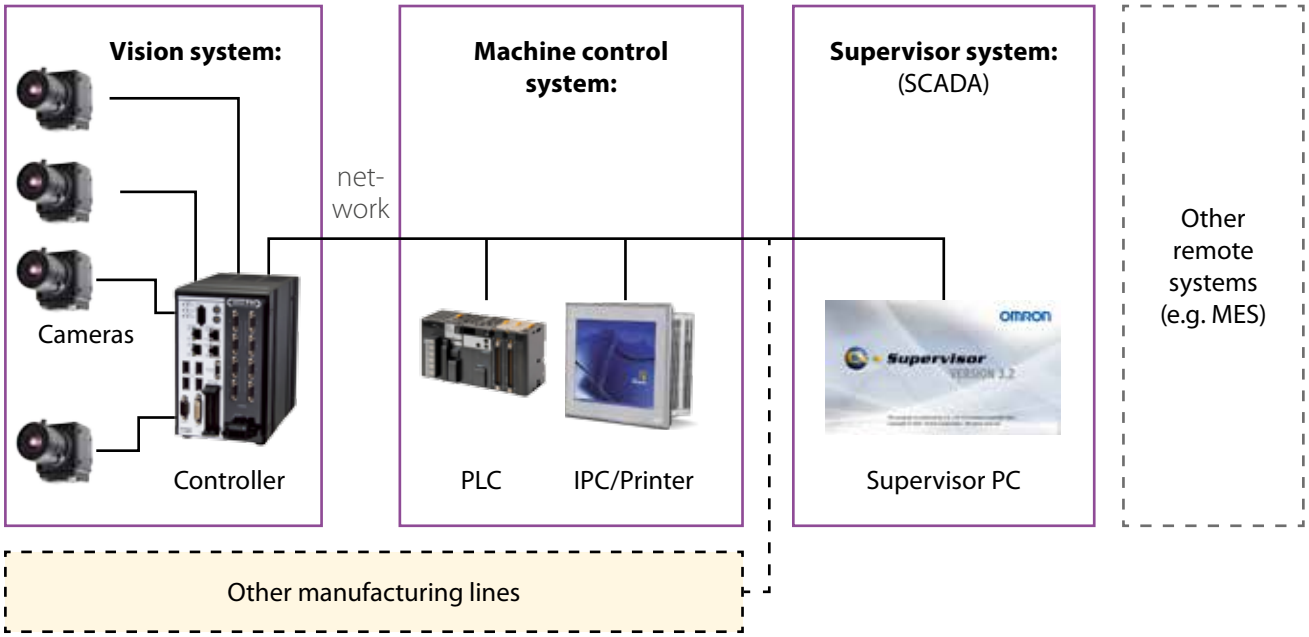
Machine Control System:

- PLC: Omron Sysmac NJ platform
- HMI: Omron Dyalox IPC provided with packaged software from the machine manufacturer

Supervisor (SCADA):

- PC running Omron CX-Supervisor software (or other software platform)

Logical Architecture:



3.3.3 System Features:

Main Features:

- The system is intended for paperless recording, using electronic signatures.
- Local PLC is used for low-level machine control functions.
- Local PC is used for both high-level machine control and human-machine interface, including remote tools of vision system.
- Vision system setup can be performed via the local PC and appropriate Omron software.
- Local IPC makes use of electronic signatures and could be optionally connected to a local printer.
- An external PC (SCADA system) is available for data collection and analysis, printing of reports and supervisory activities, long term data storage, including upload of process parameters to the PLC and vision system as needed. The SCADA may be connected to other equipment in a local manufacturing department.
- Interface between vision system and control system is performed through the local network (including vision controls).
- Additional reports can be printed on the remote system.
- Machine control system manages recipes (i.e. set of parameters specific for each product). Recipes are set-up and stored on the PC, and transferred to the PLC when necessary.
- Optionally the system software may use vision system for product serialization. Requires specific software, either standard or developed by the integrator.

Note: Remote PC (SCADA software) is considered in scope. MES is considered out of scope.

Optional Features:

- Connection to MES.
- Electronic Batch Record (MES).
- Serialization (if requested by the packaging process).

3.3.4 Compliance considerations (including ER/ES)

QUESTION	ANSWER
Type of application	Networked Process Control System, connected to SCADA (and optionally to MES) system to download batch- and component-specific data. Real-time data acquisition, control and data processing (SCADA). Optional connection to MES (e.g. for Electronic Batch Record management).
GAMP® Category	• Vision System: cat. 4 • Machine Control System: cat. 4 or 5 • Supervisor: cat 4 (Omron CX-Supervisor software) with optional cat. 5 software modules (bespoke functionality)
Regulated electronic records typically maintained in the system	The system has GxP impact and maintains a full range of regulated electronic records, including both vision and machine controls. The SCADA system may be used to download parameters and recipes to PC/PLC for critical processes, to record critical parameter data, record calibration data, and produce batch record information and trend information. Packaging records and alarms, critical process parameters and electronic signatures are all retained in electronic format on PC and SCADA (or optional MES) system. Engineering and management information are typically low impact records. Critical parameter data, recipes, batch record information and calibration data may be medium or high impact, depending on the process and the product. Vision system and PLC generate (but do not maintain) regulated electronic records in this example: data are transferred to/from PC/SCADA system. Data generated by PLC/PC are usually retained on the PC for short/medium period, and are transferred to SCADA where they can be retained for a long time so to comply with predicate rules recordkeeping requirements. Back-up and/or archival mechanism are necessary to protect data during the retention period. Additional back-up measures can be on the optional MES where ER's can be transferred.
Typical hybrid situations for records and signatures	Some records may still be printed for subsequent review and approval on paper (e.g. printed batch records and trends).
Regulated signatures typically maintained in the system	Electronic signatures are typically used for critical operations on PC, like creation of recipes, batch opening / closing, and vision parameters setup. ESes are generated and maintained on the PC using standard / packaged or bespoke software provided by the machine control system supplier. Approval of recipes and/or key processing steps require signatures, other processing steps require identity checks (managed with audit trail). SCADA may in some cases have e-signature functionality for on-screen review and approval of trends and handling alarms. Optional MES is usually provided with electronic signatures for Batch Record approval (EBR).
Typical access controls	Physical and procedural controls. PC must have electronic access controls for users. User-ID and password should be required for access through another system such as SCADA / MES. SCADA: Access control may be physical/procedural as system may be permanently switched on if required for real-time process control. Formal change control required for changes to settings and data related to critical parameters.

QUESTION	ANSWER
Audit trail	Electronic audit trails are required and must be provided for changes to critical parameters. Change control procedures should also be available. • Vision systems audit trail is available from FlexXpect Pharma software • Machine control parameters and recipes audit trail must be provided with software from the machine supplier. Packaging records and alarms retained in electronic format are usually saved in read-only format and/or protected against manual changes. Audit trails are not necessary provided with security to ensure that these records cannot be altered after being generated. ER generation and protection is covered by validation. SCADA: Depends on records being maintained. Use of audit trail to document creation, modification, or deletion of regulated records would be good practice.
Data or operating parameters typically subject to formal change control	Changes to critical parameters including vision system are likely to be made periodically and such changes should be subject to formal change control. SCADA: Formal change control required for changes to settings and data related to critical process parameters, recipes, batch record information.
Procedures typically required	SOPs are required for machine set-up and usage, managing access controls, and changes to critical parameters, including vision system. SCADA: Formal change control for changes to critical processing parameters. Access control procedures.
Special issues to be considered	Interfaces between vision systems and PC / PLC and optional interface to MES or other systems for transferring batch record information. Some PLCs now "store and forward" data to ensure data is not lost due to temporary network problems. PC/SCADA: Operators may enter into the system settings and actual values for critical steps of the operation. The system should record the identity, time and date of the operator making such entries. Some process entries may be recorded automatically in which case the validation should ensure that the entry is correct. Some entries are manual, e.g., which operation cycle to select and this will be entered via a keyboard. In this case the entry is subject to validation, procedural control and training. Operator interventions/holds and safety shutdown conditions should be considered as part of risk assessment. Access control may be physical as system may be permanently switched on in a manufacturing environment.

3.3.4 Compliance considerations (including ER/ES)

QUESTION	ANSWER
Type of application	Networked Process Control System, connected to SCADA (and optionally to MES) system to download batch- and component-specific data. Real-time data acquisition, control and data processing (SCADA). Optional connection to MES (e.g. for Electronic Batch Record management).
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Regulated electronic records typically maintained in the system	The system has GxP impact and maintains a full range of regulated electronic records, including both vision and machine controls. The SCADA system may be used to download parameters and recipes to PC/PLC for critical processes, to record critical parameter data, record calibration data, and produce batch record information and trend information. Packaging records and alarms, critical process parameters and electronic signatures are all retained in electronic format on PC and SCADA (or optional MES) system. Engineering and management information are typically low impact records. Critical parameter data, recipes, batch record information and calibration data may be medium or high impact, depending on the process and the product. Vision system and PLC generate (but do not maintain) regulated electronic records in this example: data are transferred to/from PC/SCADA system. Data generated by PLC/PC are usually retained on the PC for short/medium period, and are transferred to SCADA where they can be retained for a long time so to comply with predicate rules recordkeeping requirements. Back-up and/or archival mechanism are necessary to protect data during the retention period. Additional back-up measures can be on the optional MES where ER's can be transferred.
Typical hybrid situations for records and signatures	Some records may still be printed for subsequent review and approval on paper (e.g. printed batch records and trends).
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Typical access controls	Physical and procedural controls. PC must have electronic access controls for users. User-ID and password should be required for access through another system such as SCADA / MES. SCADA: Access control may be physical/procedural as system may be permanently switched on if required for real-time process control. Formal change control required for changes to settings and data related to critical parameters.

3.4 Summary of characteristics

REQUIREMENT	EXAMPLE 1	EXAMPLE 2	EXAMPLE 3	OBSERVATIONS
OVERALL REGULATORY COMPLIANCE				
Validation	☑	☑	☑	All examples perform quality related GMP operations, and therefore all require validations and can be validated if properly designed and managed (each one according to the specific functions it performs).
Annex 11 compliance (EU GMP)	N/A	☑	☑	Example 1 does not need to be validated under Annex 11 (qualification under Annex 15 applies, including automated functions) Example 2 and 3 are subject to Annex 11 requirements and can be implemented in compliance with it, according to the different functionality they offer.
Annex 15 compliance (EU GMP)	☑	☑	☑	All examples can be implemented in compliance with Annex 15, each according the different functionality they offer.
21 CFR Part 211 compliance, incl. § 211.68 (FDA)	☑	☑	☑	All examples can be implemented in conformity with Part 211 (US GMP) and validated according to the specific functions they performs.
21 CFR Part 11 compliance (FDA)	N/A	☑	☑	Part 11 does not apply to example 1, since it doesn't maintain ER/ES. Example 2 can be implemented in compliance with Subpart B only (ER). Subpart C (ES) doesn't apply. Example 3 can be implemented in compliance with both Subpart B and C (ER and ES).
SPECIFIC FEATURES				
Security (Access Control)	☑	☑	☑	All examples should have user profile management and access control. • Example 1 allows only one user profile. • Examples 2 and 3 are more complete and more critical (because of ER / ES).
Electronic Records (GMP)	N/A	☑	☑	Example 1 does not maintain ER. Example 2 and 3 can have GMP ERs. Example 3 also maintain ES, which are a special category of ER.
Backup / Restore	N/A	☐	☑	Example 1 does not require ER backup/restore (backup is still required for system software and settings). Examples 2 and 3 require ER backup/restore (partial or full paperless operation), with additional care and more adequate controls, including remote data transfer.
Audit Trail	N/A	☑	☑	Example 1 does not need AT Example 2 and 3 need AT for GMP ERs. • Example 2 only for settings • Example 3 may also require audit trail for manufacturing data (if modifiable)

REQUIREMENT	EXAMPLE 1	EXAMPLE 2	EXAMPLE 3	OBSERVATIONS
Electronic Signatures	N/A ☒	N/A	☑	Example 1 does not have ES (nor it can have it) Example 2 does not use ES (it is based on paper records). Reports mandated by the rules may be printed and signed, then archived in the (paper based) batch record. Example 3 uses ES. Records and signature are retained in electronic format (paperless system, with Electronic Batch Record).
Electronic Batch management	N/A ☒	☑	☑	Example 1 does not maintain batch data. Example 2 has a limited batch management (single or few batch data can be stored). Example 3 has a complete batch management (many batch data can be stored).
Historical data management and analysis	N/A ☒	☐	☑	Example 1 does not maintain batch data. Example 2 has a limited or no batch analysis capability (production records are not stored on a batch-by-batch arrangement). Example 3 has a complete batch analysis capability (many batch data can be analysed).
Long- term data storage / archiving	N/A ☒	☐	☑	Only example 3 can maintain GMP records in the long term (e.g. 5 years or more, according to the applicable GMP rules). Examples 1 and 2 may optionally maintain historical data if connected to an external system.

LEGEND:

☑	Functionality or characteristics fully implemented.
☐	Functionality or characteristics partially implemented.
☒	Functionality or characteristics not available.

3.5 Validation documents

ACTIVITY / DOCUMENT	EXAMPLE 1	EXAMPLE 2	EXAMPLE 3
Validation Plan	○	●	●
Supplier(s) Audit	-	○	●
User Requirements Specification	●	●	●
Project and Quality Plan	-	○	●
Functional Specifications	○	●	●
Configuration Specifications	-	○	●
Design Specifications	○	○	●
Risk Management	-	○	●
Traceability Matrix	○	○	●
User Manual	●	●	●
Test Plan	-	○	●
FAT (Factory Acceptance Test)	○	○	○
SAT (Site Acceptance Test)	○	○	○
Installation Qualification	○	●	●
Operational Qualification	●	●	●
Performance Qualification	-	○	●
Validation Report	○	●	●

-	Document / activity not required
○	Document / activity recommended. Can be required when using optional features, such as supervision.
●	Document / activity strongly recommended

The document list refers only to the parts considered in scope. External / remote systems may require additional activities and a separate set of documents.

3.6 Other

3.6.1 Revamping / retro-fit

Adding a vision system to existing equipment already validated may lead to additional considerations:

- Vision System can be validated separately from the equipment / control system.
- Equipment qualification / application validation may require a modification, performed under formal change control.
- Interfaces between the new vision system and the existing control system, if any, must be validated.

4 Applicability of 21 CFR Part 11 to Omron vision system

The following table summarizes Part 11 compliance requirements applicable to some Omron vision system products used in pharmaceutical application. It does not cover other parts, developed by the end user or integrators (such as the equipment control system and supervisor).

21 CFR PART 11 REQUIREMENTS	FQ2	FZ/FH STD. S/W 2	FZ/FH FLEXXPECT PHARMA S/W	TECHNICAL / PROCEDURAL REQUIREMENT
Subpart B – Electronic Record				
11.10 Controls for closed systems				
11.10 (a) System validation	●	●	●	P
11.10 (b) Record review, inspection and copy	N/A	○	●	T/P
11.10 (c) Records protection and retrieval	N/A	○	●	T/P
11.10 (d) System access	○	●	●	T/P
11.10 (e) Audit trails	N/A	○	●	T/P
11.10 (f) Operational system checks	○	●	●	T/P
11.10 (g) Authority checks	○	●	●	T/P
11.10 (h) Validity of source of data input	N/A	N/A	N/A	N/A
11.10 (i) Training	N/A	N/A	N/A	P
11.10 (j) Signature policy and prevention of falsification	N/A	N/A	N/A	N/A
11.10 (k) Control over system documentation	N/A	N/A	N/A	P
11.30 Controls for open system	N/A	N/A	N/A	N/A
11.50 (a) Signature manifestations & required information	N/A	N/A	N/A	N/A
11.50 (b) Required controls for signature records	N/A	N/A	N/A	N/A
Subpart C - Electronic Signature				
11.70 Signature/record linking	N/A	N/A	N/A	N/A
11.100 General requirements				
11.100 (a) Electronic signature uniqueness	N/A	N/A	N/A	N/A
11.100 (b) Verification of individual identity	N/A	N/A	N/A	N/A
11.100 (c) Legal notification to FDA	N/A	N/A	N/A	N/A
11.200 Electronic signature components and controls				
11.200 (a) Non-biometric signature	N/A	N/A	N/A	N/A
11.200 (b) Genuine use of biometrics signature	N/A	N/A	N/A	N/A
11.300 Controls for credentials				
11.300 (a) Maintain the uniqueness of user credentials	NA	N/A	N/A	N/A
11.300 (b) Credential maintenance and periodic controls	NA	N/A	N/A	N/A
11.300 (c) Deactivation of lost or compromised credentials	NA	N/A	N/A	N/A
11.300 (d) Prevent unauthorized use of credentials	NA	N/A	N/A	N/A
11.300 (e) Testing of identification code devices	NA	N/A	N/A	N/A

Legend: ● = Fully applicable; ○ = Partially applicable; N/A = Not Applicable to the system (e.g. procedural requirement)
T = Technical requirement; P = Procedural requirement (usually covered by a specific SOP)

Observation about Electronic Signatures:

- Part 11 requirements regarding electronic signatures are not applicable to Omron vision systems products. In case predicate rules require record signature, these can be implemented on paper (handwritten signatures, eventually executed to electronic records – see 11.70).

Further details are available in Appendix 2, with the detailed 21 CFR Part 11 analysis for the FlexXpect Pharma software.

5 References

5.1 Pharmaceutical Regulations

[1] EU Commission Directive 2003/94/EC of 8 October 2003

[2] EU Commission Directive 91/412/EEC of 23 July 1991

[3] EU GMP: EudraLex, "The rules governing medicinal products in the European Union", Volume 4 - Good Manufacturing Practice (GMP) Guidelines.

[4] EU GMP Annex 11 "Computerized Systems" (January 2011)

[5] EU GMP Annex 15 "Qualification and Validation" (December 2000). New edition (still draft): February 2014.

[6] EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use (24 November 2013)

[7] US Federal Food, Drug, and Cosmetic Act (FD&C Act), 1938

[8] FDA: 21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding Of Drugs; General

[9] FDA: 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

[10] FDA: 21 CFR Part 11 "Electronic Records, Electronic Signatures", March 20, 1997

5.2 Validation Guidelines

[11] FDA: Process Validation Guidelines, 1987

[12] FDA: "Computerized Systems in Drug Establishments" aka the "bluebook", February 1983.

[13] FDA: "General Principles of Software Validation; Final Guidance for Industry and FDA Staff", January 11, 2002.

[14] FDA: Guidance for Industry "Part 11, Electronic Records; Electronic Signatures — Scope and Application", August 2003

[15] HMRA: "GMP Data Integrity Definitions and Guidance for Industry", January 2015

[16] ISPE: GAMP® 5 "A Risk-Based Approach to Compliant GxP Computerized Systems", February 2008

[17] ISPE: GAMP® Good Practice Guide "A Risk-Based Approach to Electronic Records and Signatures", February 2005

[18] ISPE: GAMP® Good Practice Guide "IT Infrastructure Control and Compliance", September 2005

[19] ISPE: GAMP® Good Practice Guide "A Risk-Based Approach to GxP Process Control Systems" (2nd edition), February 2011

[20] ISPE: GAMP® Good Practice Guide "A Risk-Based Approach to Testing of GxP Systems" (Second Edition), December 2012.

[21] ISPE: GAMP® Good Practice Guide "Electronic Data Archiving", July 2007

5.3 Other documents

[22] ISPE: White Paper "ISPE – Risk-Based Approach to 21 CFR Part 11" (2002)

[23] ISPE: White Paper "Risk based Qualification for the 21st Century" (2005)

[24] Omron: White Paper "Automated Manufacturing in the Pharmaceutical Industry (An Introduction to the Regulations)" - Andy Avery. (2011).

6 Glossary

Application program	A complete, self-contained program that performs a specific function for the user. Applications use the services of the computer operating system and other supporting applications.
Audit trail	An electronic or paper log used to track computer activity.
Biometric	A method of verification of an individual's identity based upon measurement of the individuals physical features or repeatable actions that are both measurable and unique to that individual.
CFR	Code of Federal Regulations.
Closed system	An environment where system access is controlled by persons who are responsible for the content of electronic records that are on the system.
Database	A database is a collection of data that is organized so that its contents can easily be accessed, managed, and updated.
Digital signature	An electronic signature based upon cryptographic methods or originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and integrity of the data can be verified.
Electronic records (Part 11)	Any combination of text, graphics, data, audio, pictorial or other information representation in digital form that is created, modified, maintained, archived, retrieved or distributed by a computer system. Part 11 Records: • Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format. • Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities. • Records submitted to FDA under predicate rules in electronic format.
Electronic signatures (part 11)	A computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual to be the legally binding equivalent of the individual handwritten signature. Part 11 Signature: • Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.
Encryption	The conversion of data into a form, called a cipher text, which cannot be easily understood by unauthorized people.
FDA	Food and Drug Administration.
Functionality	The sum or any aspect of what a product, such as a software application or computing device, can do for a user.
GXP	Incorporates GMP (good manufacturing practice), GCP (good clinical practice), GLP (good laboratory practice), GDP (good distribution practice), GVP (good vigilance practice – pharmacovigilance). NB: GDP is also used for Good Documentation Practice. GDocP is a preferred form to avoid ambiguity. GEP is used for Good Engineering Practice.

Infrastructure	The physical hardware used to interconnect computers and users. Infrastructure also includes the software used to send, receive, and manage the signals that are transmitted.
Metadata	Data about data. In data processing, metadata is definitional data that provides information about or documentation of other data managed within an application or environment.
Open system	An environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.
Operating system	The program that, after being initially loaded into the computer by a boot program, manages all the other programs in a computer.
System	The entire computer system, including input/output devices, the operating system and possibly other software
Validation	The process where software is evaluated to ensure that it complies with the requirements.
IQ	Installation Qualification
OQ	Operational Qualification
PQ	Performance Qualification. Sometimes also used to address Process Qualification (FDA)
PV	Process Validation
FAT	Factory Acceptance Test
SAT	Site Acceptance Test

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Luca Fraticelli joined Omron in 2004 as Field Application Engineer for Advanced Sensors, Safety, Temperature Controllers. In the previous experiences he commissioned works in the application area of industrial automation for Automotive, Pharmaceuticals, Tobacco, and other market segments. In Omron Electronics Luca then became an Application engineer Vision Specialist improving his knowledge starting on the Omron White Box and latest Omron vision solutions. This activity focused on Pharmaceutical issues, with special attention on validation matters related to automation applications. As member of ISPE Gamp association - Italy affiliate since 2012 - he worked with the GAMP Italy Chairman, Sandro De Caris, in defining criteria and a valid approach in using Omron vision systems in the Pharmaceutical Industry. This document collects the summary of this work and can represent a first support document for End Users, OEMs and System Integrators interested to use Omron validated solutions in Pharma. Recently Luca Fraticelli is in charge of the Omron solution Partners and System Integrators project in Italy. He joined the Panel Solutions Marketing team in Europe in 2013 up to present day.

Omron Corporation

- 50 years in industrial automation
- Over 37.500 employees
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- Over 1.800 employees in 19 European countries
- 800 Specialised field engineers
- 6% of turnover invested in R&D
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Headquartered in Kyoto, Japan, Omron Corporation is a global leader in the field of automation. Established in 1933 and headed by President Yoshihito Yamada, Omron has more than 37,500 employees in 35 countries working to provide products and services to customers in a variety of fields including industrial automation, electronic components industries, and healthcare. The company is divided into five regions and head offices are in Japan (Kyoto), Asia Pacific (Singapore), China (Shanghai), Europe (Amsterdam) and US (Chicago). The European organisation has its own development and manufacturing facilities, and provides local customer support in all European countries. For more information visit Omron at www.omron.com.