ISSN: 2573-9565

Review Article

Journal of Clinical Review & Case Reports

GxP/GMP and its Consequences for Documentation and Information Technology Systems

Eleonora Babayants*

Founder and President of Galaxy Consulting, San Francisco Bay Area, Information Services, USA

***Corresponding author**
Eleonora Babayants, Founder and President of Galaxy Consulting, San Francisco Bay Area, Information Services, USA, E-mail: Eleonora@galaxyconsulting.net

Submitted: 11 Jan 2018; **Accepted**: 18 Jan 2018; **Published**: 08 Feb 2018

Abstract

Documentation is a critical tool for ensuring GxP/GMP compliance. In the regulated environment which must be GxP/GMP compliant, document control is the cornerstone of the quality system. It is so important that if an external audit identifies deficiencies in the document control system, the entire organization can be shut down.

There are also GMP requirements for information technology. For a drug to be produced in a GxP/GMP compliant manner, some specific information technology practices must be followed. Computer systems involved in the development, manufacture, and sale of regulated product must meet certain requirements.

Change control within quality management systems (QMS) and information technology (IT) systems is a formal process used to ensure that changes to a product or system are introduced in a controlled and coordinated manner. In the regulated industries, manufactures are required to use a change control procedure.

In this article, the connection between GxP/GMP and document control is discussed. Details of document control procedures and the role of Quality Assurance in the documentation systems are described. GMP requirements for information technology and how computer systems including documentation management systems must meet GxP/GMP requirements are reviewed. There is also a review of change control procedure and how it should be used in GxP/GMP environment.

GxP/GMP and Documentation

GxP/GMP is about Quality Management System **(QMS)** where an organization needs to demonstrate its ability to consistently provide product that meets customer and applicable statutory and regulatory requirements.

General philosophy of any quality system is: say what you do, do what you say, prove what you say and do. In other words, if it is not written down, it did not happen is FDA statement

Documentation is the key to GMP compliance and ensures traceability of all development, manufacturing, and testing activities. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product.

Documentation is a critical tool for ensuring GxP/GMP compliance. A cornerstone of the QMS is document control.

This is what GMP regulations state about document control:

"Each manufacturer shall establish and maintain procedures to control all documents that are required."

GMP documentation requirements are aligned with GDP or GDocP - Good Documentation Practice. GDP is the systematic procedure of preparation, reviewing, approving, issuing, recording, storing, and archiving documents.

Auditors pay particular attention to documentation to make sure that it complies with GMP and GDP.

Therefore, in order for an organization to meet GxP/GMP requirements, it must have a document control system in place.

Purpose of Document Control

The primary purpose of document control is to ensure that only current documents and not documents that have been superseded are used to perform work and that obsolete versions are removed.

Document control also ensures that current documents are approved by the competent and responsible for the specific job people and documents are distributed to the places where they are used.

Document control is an essential preventive measure ensuring that only approved, current documents are used throughout the organization.

Inadvertent use of out-of-date documents or not approved documents can have significant negative consequences on quality, costs, customer satisfaction, and can even cause death. Here are couple of examples.

Example 1

In 1972 Devonport, UK, incident resulted in at least five deaths when drug products designed to be sterile became contaminated and recipients developed infections. An unwritten change to autoclave operation, communicated orally between operators, resulted in dextrose intravenous solutions that were not uniformly sterile.

Investigation, which examined the causes and contributing factors, identified several violations of what we now consider basic good manufacturing practice (GMP).

The chain of events that compromised the safety of the drug product included inadequate maintenance, inadequate understanding of autoclave operations and regular deviations from the written production instructions which was due to the lack of proper documentation about autoclave operations.

Together, these factors resulted in a sterilization cycle that did not assure that all vials in the autoclave were sterilized; thus, some doses were safe, while others led to sepsis in patients who received them.

Example 2

This is the more recent incident. In 2014 in Redwood City, California, United States, a woman was infected with Hepatitis B during blood transfusion which resulted in liver damage and further necessity of liver transplant.

Investigation revealed that the root cause was that proper documentation was not followed.

Controlled Documents - Types and Identification

Let's define controlled documents.

Controlled document is any document that is used to perform work and not for reference. Furthermore, GxP/GMP states that documents required by the QMS should be controlled.

The most important rule of document control is that only current documents must be used for work. Other documents are less vital and it may not be worth the effort of controlling them.

The format and storage of documents must protect a document from being rendered unreadable due to wear or damage.

The first task is to identify which documents need to be controlled.

The typical controlled document types include:

- policies - the company's position or intention for its operations;
- procedures - responsibilities and processes for how the company operates to comply with its policies;
- work and/or test instructions - step-by-step instructions for a specific job or task;
- forms and records;
- drawings - those that are issued for work;
- process maps, process flow charts, and/or process descriptions;
- specifications;
- internal communication;
- production schedules;
- approved supplier lists;
- test and inspection plans;
- quality plans.

QMS Documents

According to GMP requirements, QMS documents must be controlled. QMS documents include the following documents:

- Quality Manual
- Company quality policy and quality objectives
- Standard Operating Procedures (SOPs)
- Batch Records, Test Methods, Specifications, Validation Documents, Equipment Records, Packaging Instructions
- Records determined by the organization to be necessary to ensure the effective planning, operation, and control of its processes.

The format and structure of the quality policy, quality objectives, and quality manual is a decision for each organization, and will depend on the organization's size, culture and complexity.

A small organization may find it appropriate to include the description of its entire QMS within a single manual, including all the documented procedures required by the standard.

Large, multi-national organizations may need several manuals at the global, national or regional level, and a more complex hierarchy of documentation.

Identification of Controlled Documents

- Controlled documents must be legible.
- Controlled documents need to be clearly and readily identified through a title and document number which should be unique for each document.
- Current version of a document must be identified on the document.
- All master documents should have the effective date and approval date.
- Hard copy documents need to be stamped.
- Electronic documents need to be watermarked so that when they are printed so that they could be identified as controlled documents and a user can be alerted to verify an electronic version prior to use of this document.

Role of QA in Document Control

The role of QA, in regards to the document control system is one of management and overview.

QA ensures that all documents are maintained in a controlled fashion and that all controlled documents are approved by the appropriate subject matter experts, are consistent with other documents, and are the most current version.

One way that QA ensures this is by being the last signature on all approved documents. All documents: current, obsolete, superseded, as well as all the history on the creation and revision of the document should be kept in Quality Assurance.

Document Control Procedures

These are document control procedures:

- Documents Creation
- Documents Revising
- Documents Routing
- Documents Approval
- Documents Distribution
- Documents Archiving

Let's look at these steps more closely.

Documents Creation

- Any knowledgeable employee should be able to write or revise documents as needed.
- Documents must be clear and legible.
- Clear and concise titles should be used.
- Full text spelling with abbreviation in brackets should be used for the 1st time. Abbreviation may be used for the remainder of the document.
- Current date must be used. Backdating is not allowed.
- Newly created documents need to be approved.

Documents Revising

GMP Requirements – "Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the review and approval of original documents, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective."

- All documents must be periodically reviewed, updated and re-approved.
- This review can be tied to a company's internal audit process, management review or scheduled on some periodic (annual) basis.
- A record of such reviews must be kept.
- Usually, the change process starts when someone identifies an issue that may need to be addressed with a change to the product. It ends when the agreed-upon change is implemented.
- Ensure that changes and the current revision status of documents are identified.
- When a document is updated, a record and history of changes must be kept of the change, including the reasons for and nature of the change.

Documents Routing

The document control function of QA is responsible for routing documents for review and approval.

It is suggested that a pre-route be done to ensure that all affected parties are in agreement with the document before it is submitted to QA.

There should be a documented process detailing how documents are submitted for review and approval.

A controlled form listing all the changes made to the document, justification for the changes, and a list of personnel who need to review the document needs to be routed along with the document.

Documents Approval

GMP requires that documents are approved for adequacy prior to issue.

GMP Requirements – "Each manufacturer shall designate an individual(s) to review for adequacy and approve prior to issuance all documents. The approval, including the date and signature of the individual(s) approving the document, shall be documented. Documents shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use."

An approval system ensures that controlled documents are appropriate for people receiving them and that they are correct. Document approvals are mandatory and must be kept as a record as well.

Once all affected parties agreed to the changes, document control should prepare the document for approval. All changes have to be incorporated into the document.

A master document should be routed for approval signatures.

When determining who should approve a particular document, limit approvals to those with direct knowledge or responsibility for the document. Typically the approval people are the Author, the Department Head, all affected department heads, and QA. Other Subject Matter Experts can be included. QA must be the last signature on all documents.

Approvals may be in the form of a written signature on a paper document or a password-protected electronic approval record. If there is no electronic signature, the approval usually can be verified through electronic workflow the document went through to get approved.

Approval signatures must be recorded prior to the release and use of the document. Approval signatures only appear on the first page of the document. No scanned signatures, duplicated signatures, or stamps in lieu of signature should be used. Signature should be handwritten and original. Signing for other people is not allowed.

For new documents the version # will be 00. For each revision of a document the version number will increase (01, 02, 03, etc.)

The date of all approvals must precede the document's release date. Once the master document has been signed, the effective date should be stamped onto each page of the document. The effective date must be far enough in advance to allow for the document to be trained on before it becomes effective (typically this is 5 days).

Documents Distribution

Need to ensure that current versions of applicable documents are available at points of use. On the effective day copies of the signed master document are distributed to the affected departments. Distribution may be physical (paper documents) or electronic. When posting the document on electronic systems, ensure that everybody who needs to have the new document knows about the posting (e.g. through an email or workflow notifications).

When paper documents are distributed, documents need to be stamped to identify that this is a controlled document and users of this document need to verify that this is the most current version before starting work.

The departments should remove the old version and replace it with the new version (for revised documents). If the document is new, there will be no replacement document.

The old versions must be returned to document control. On a periodic basis document control personnel should audit the binders to determine if they contain the correct versions. Each document binder should contain a table of contents and only those documents that the department is responsible for.

A full set of all approved documents should be in the QA department as well as in a central company location.

An inventory of controlled documents should be created with the exact location of each controlled document.

Consider where designated controlled locations of your documents will be established. The storage and access of documents must easily allow individuals to find the current version of a document to use where needed.

Typically, the easier it is for employees to access controlled copies when needed, the fewer times they will feel the need to use an uncontrolled copy of a document. Inability to quickly find documents is frequently the source of high costs and repeated discrepancies. Ensuring timely and convenient access to documents is very important.

External Documents Distribution

GMP Requirements – "Ensure that documents of external origin determined by the organization to be necessary for the planning and operation of the Quality Management System are identified and their distribution is controlled."

Documents that do not originate within the organization but are necessary for ensuring quality and meeting customer requirements must also be controlled. These can include customer, supplier or industry documents. However, the extent of control is limited to clear identification and controlled distribution. A log or other records would suffice to track external documents.

Documents Archiving

GMP Requirements – "To prevent the unintended use of obsolete documents, and apply suitable identification to them if they are retained for any purpose. Old revisions of documents should be stamped as superseded. No document revisions should be discarded or altered. A file should be maintained within QA that contains all the superseded documents and the signature approvals of personnel who agreed to the revisions."

Out-of-date documents or older versions of revised documents must be protected from unintentional use. Request the receiver of new documents to send back obsolete documents. If for some reason you need to retain obsolete versions of documents, they need to be marked "obsolete" and segregated from other documents to avoid their unintended use. Many organizations use a stamp: "Obsolete Document".

Retention schedule should be established. Establish the period of time during which a document remains active and at what point in time it should be reviewed and edited or reviewed and archived or maybe reviewed and nothing else needs to be done.

Document Management System

GMP regulations require that all documentation be issued, managed, and controlled using a document management system.

Main Objectives of Document Management System

These are some of the main objectives of an organization's document management system:

1. Communication of Information - Documentation is a tool for information transmission and communication.
2. Evidence of conformity - Documentation is provision of evidence that what was planned has actually been done. Remember: If it is not written down, it did not happen.
3. Knowledge sharing - Documentation is used to disseminate and preserve the organization's knowledge. A typical example would be a technical specification, which can be used as a base for design and development of a new product.

Measuring Success of Document Control System

Here are some suggested metrics how you can measure the performance of your document control process:

User Satisfaction

Periodically survey your employees on the usability of your documentation. Use the results to improve the format of your documents and authors' training.

Document Errors

Track the number of document revisions due to mistakes in your documentation. Results will often reveal weaknesses in your review and proofreading processes.

Cycle Time

Measure the time it takes for a document to be developed or revised from initial draft to release.

Cost

Consider tracking the costs associated with your documentation including developing, revising, storing, retrieving, distributing, filing, auditing, reviewing, approving, etc. Of these potential costs, document retrieval is often an expensive hidden cost generated when individuals search endlessly for a document because of inadequate indexing, organization, storage or training.

Results of the performance of your document control processes can help you determine how to drive continual improvements into your entire QMS and document control system.

Change Control Procedure

In GMP regulated industries, manufactures are required to use a change control procedure.

A change control procedure is usually one of standard operating procedures (SOP's). It usually includes a change control form.

In a Good Manufacturing Practice (GMP) regulated environment, change control activities are used in a wide variety of products and systems.

In a case of the regulatory agencies inspection, the change control procedure is usually audited.

Change procedure usually includes the following components:

Identification

The identification of the changed device, assembly, component, labeling, packaging, software, process, procedure, manufacturing material, and any other related item or document.

Effective Date

The effective date of the change which is usually a completion date.

Responsibility

The change procedure should state which department or designee is responsible for each function to be performed.

Revision Number

The change procedure should describe the way the revision level is to be incremented. It is common practice to use sequential numbers for revisions.

Communication

The change procedure should describe the communication of changes to all affected parties such as production, purchasing, contractors, suppliers, etc.

As appropriate, the document might include activities that apply to internal operations. Examples are employee training, rework, or disposition of in-process assemblies, use of revised drawings and/or procedures, and disposition of old documents.

Updating Documentation

The change procedure should cover updating of primary and secondary documentation such as instruction manuals. Usually there are no problems with updating or revising primary documentation - in fact, that is a major reason the given change order is being processed. In contrast, it is rather easy to forget that related secondary documents such as component drawings, instruction manuals or packaging require revision if affected by a given change. The use of a good change control form can alleviate this problem.

Documentation Distribution

Revised documentation should be distributed to persons responsible for the operations affected by the change and old documents removed and filed or discarded, as appropriate. After updated documents have been approved, these documents have to be made available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents have to be promptly removed from all points of use or otherwise prevented from unintended use.

Remedial Actions

Certain changes may require remedial action. Changes of this nature should be addressed in the change control procedure.

Regulatory Submissions

There may be changes may that require a regulatory submission. The change control procedure should specify if regulatory submissions should be considered when making a change.

Business Factors

The change procedure should also cover other factors such as financial impact, modification of sales literature, update of products in commercial distribution, etc.

Quality Assurance Review

The change procedure should cover if the quality assurance review is required for the change.

Change Control Procedure for Document Control

This change control procedure specifically used for document control - as discussed:

Changes to documents have to be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval of these documents unless there is a specific designation that states otherwise. These approved changes have to be communicated to the appropriate personnel in a timely manner. A company has to maintain records of changes to documents.

Change control for documents should include:

- identification of the affected documents;
- a description of the change;
- revision number;
- the signature of the approving individual(s);
- the approval date;
- the date when the change becomes effective.

Change Control Procedure for Information Technology (IT) Systems

It is a formal process used to ensure that changes to a system are controlled and coordinated.

It reduces the possibility that unnecessary changes will be introduced to a system without analysis, introducing faults into the system.

The goals include minimal disruption to services, reduction in back-out activities, and cost-effective utilization of resources involved in implementing a change.

Typical examples are patches to software products, installation of new operating systems, upgrades to network routing tables, or changes to the electrical power systems supporting such infrastructure.

IT Change control process is the sequence of six steps: record/classify, assess, plan, build/test, implement, close/gain acceptance.

Record

A user initiates a change by making a formal request.

Classify

The change control team then records and categorizes that request. This categorization would include estimates of importance, impact, and complexity.

Assess

Change control team makes an assessment typically by answering a set of questions concerning risk, both to the business and to the process, and follow this by making a judgment on who should carry out the change.

Plan

Management will assign the change to a specific delivery team. The team will plan the change in detail and construct a regression plan in case the change needs to be backed out.

Build/Test

If all stakeholders agree with the plan, the delivery team will build the solution, which will then be tested. They will then seek approval and request a time and date to carry out the implementation phase.

Implement - Solution is implemented.

Close/gain acceptance

Post-implementation review and if users agree that the change was implemented correctly, the change can be closed.

GxP/GMP and Information Technology

For a product to be produced in a GMP compliant manner, some specific information technology practices must be followed. Computer systems involved in the development, manufacture, and sale of regulated product must meet certain requirements:

- secure logging: each system activity must be registered, in particular what users of the system do in the system;
- no change allowed - the logged information has to be secured so that it cannot be changed once logged, not even by an administrative user of the system;
- auditing: a system must be able to provide conclusive evidence in litigation cases, to reconstruct the decisions and potential mistakes that were made in developing or manufacturing a regulated product;
- regular back-up and off-site storage of backed up data;
- keeping archives: relevant audit information must be kept for a set period. In certain countries, archives must be kept for several decades. Archived information is still subject to the same requirements, but its only purpose is to provide trusted evidence in litigation cases;
- accountability: every piece of audited information must have a known author who has signed into the system using an electronic signature. No actions can be performed by anonymous individuals;
- non-repudiation: audit information must be logged in a way that no user could say that the information is invalid, e.g. saying that someone could have tampered with the information. One way of assuring this is the use of digital signatures.

IT Systems Validation

GMP guidelines require that IT systems must be validated by adequate and documented testing.

GMP Requirements – "The software development process should be sufficiently well planned, controlled, and documented to detect and correct unexpected results from software changes."

Validation is defined as the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results.

To validate software, it must be:

- structured, documented, and evaluated as it is developed;
- checked to make sure that it meets specifications;
- adequately tested with the assigned hardware systems;
- operated under varied conditions by the intended operators or persons of like training to assure that it will perform consistently and correctly.

It is important to note that since a document management system is required to control documents, this document management system must meet these validation requirements.

Conclusion

Quality does not come accidentally, it comes by practice. Forget the syndrome: "We will fix documentation later." Later will never happen and when the audit comes it will be too late. The best practice is to take care of documentation regularly.

References

GxP/GMP Regulations

1. https://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/default.htm
2. http://www.gmp7.com/