

A Simple and Robust Change Control System OR How to Maintain a Focused View of Changes in Healthcare Manufacturing

BY GAMAL AMER, P.H.D.

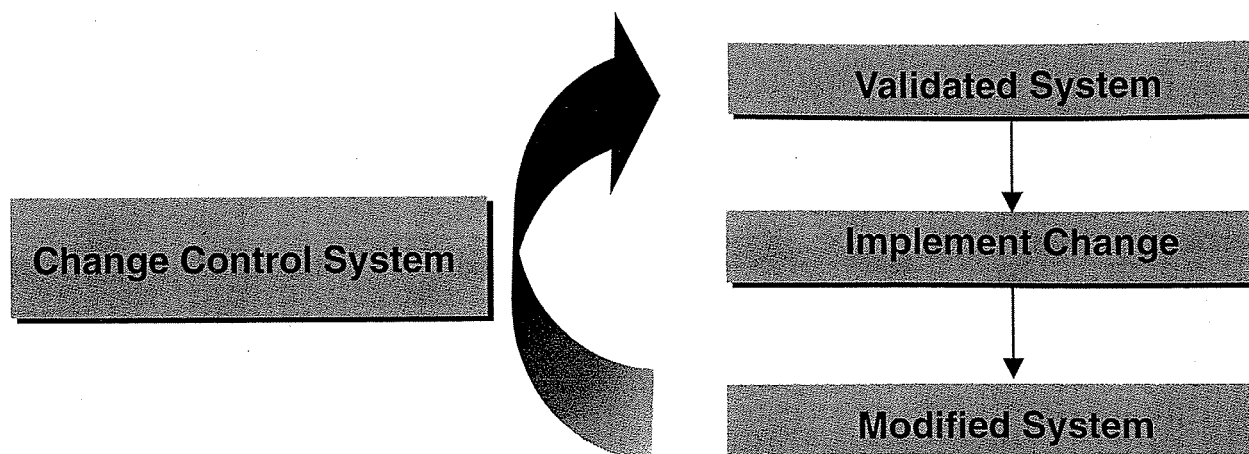


CGMP, or Current Good Manufacturing Practice, is a regulatory requirement defined by the Code of Federal Regulations (CFR) 21, sections 210 and 211 for drug manufacturing. One of the main requirements of Good Manufacturing Practice (GMP) is validation of the manufacturing operation and ensuring that the manufacturing system remains in a compliant and validated state throughout its lifecycle. As we all know, validation is defined as “establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce product meeting its predetermined specifications and quality attributes.”

Validation, which is confirmatory in nature, is a snapshot in time. That is, once a system is validated, one could only say, with a high degree of confidence, that the system is capable of producing a product with the required quality attributes on the day or at the time the validation was complete. This is due to the fact that as time goes by, there is no guarantee that the system will remain in the same validated state unless the system meets certain criteria to support the fact that it is still in a validated state. These criteria include the following:

1. The system was originally validated properly.
2. The system uses essentially the same equipment now as it did when it was originally validated.
3. The same procedures are followed when using the equipment.
4. The equipment is maintained and continues to be maintained in its original state of repair.
5. All instruments and controls associated with the operation are maintained in a calibrated state.
6. All inputs to the system, such as raw materials and utilities, are essentially the same as when the system was validated.
7. No significant alteration or changes to the system were undertaken.

While most of the above stipulations can be maintained and observed, it is obvious that without changes, process improvement, and the ability to benefit from scientific and technological advances, would be impossible. Thus, process and manufacturing systems in the healthcare industry are known to continually require change to many of their components and inputs due to new technological developments and im-

Figure 1**The Validation Lifecycle**

provements in manufacturing equipment, new scientific findings and subsequent process development or improvement, changes in quality of raw materials or other supplies used in the process, and equipment maintenance related changes.

The industry standard as well as the regulatory requirement is to manage the changes to the manufacturing system by using a change control management mechanism. Such a mechanism is referred to as a Change Control System, which is imposed using a specific procedure. The objective of this article is to assist the reader in identifying the requirements for such a system and illustrating the components of a change control procedure.

The Validation Compliance Lifecycle

Once a system is validated, it is presumably capable of consistently producing a product with a given set of quality attributes. Such quality attributes must be maintained to guarantee product safety and efficacy. Once a change is imposed on the process, the system must be updated or verified to produce the proper product, despite the change. This is accomplished using a change control management system.

Should the system undergo significant changes, certain requirements for updating the system would be completed through following a formal procedure known as the change control procedure. Once the change is implemented and the

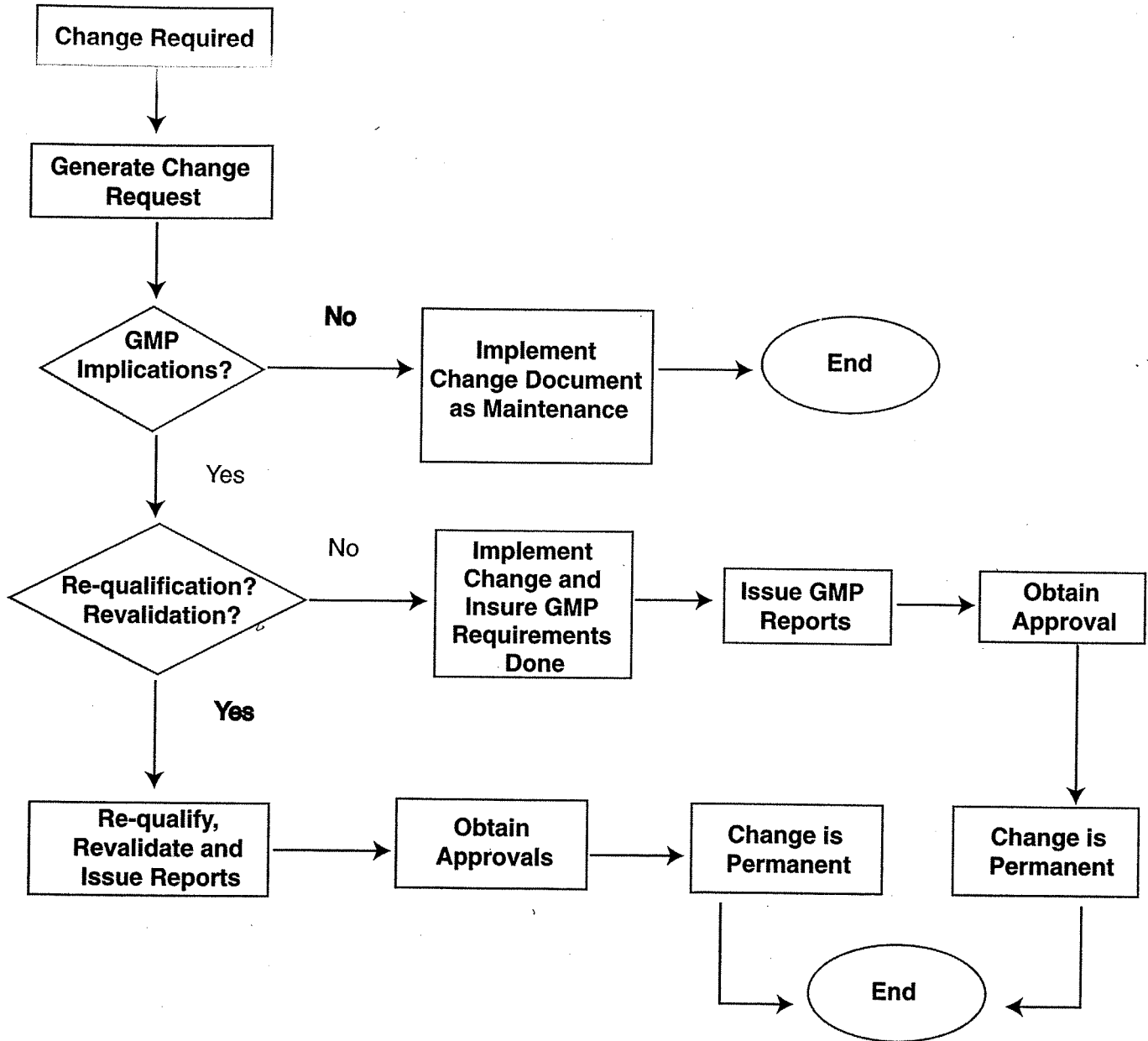
system is updated according to the requirements identified as part of the change control procedure, the system is returned to its original validated state and the change becomes permanent. Any additional changes to the system should be treated in the same manner, even if the change is to return the system to its original condition. This is what is referred to as the validation lifecycle (See Figure 1).

Change and Change Control

Any manufacturing system within the healthcare industry may undergo change at any time during its lifecycle. These changes could be made to processing equipment, utility equipment, facility setup or configuration, raw materials or their suppliers, services or their suppliers, operating procedures, maintenance procedures, calibration procedures, personnel training, etc. This is by no means an all-exhaustive list, but the reader should recognize that changes could be anywhere and to any component of the manufacturing operation and its supporting systems or operations. Therefore, any and all changes that are made to the manufacturing operation should, without exception, be treated with suspicion and dealt with through the change control system.

Figure 1

The Validation Lifecycle



Types of Changes

Changes to manufacturing systems can be divided into two categories based on the timing of the change:

1. Planned changes occur when the proposed change has been developed over time, and all of its possible implications have been carefully studied. In addition, the reactions needed to ensure that the system continues to comply with GMP requirements and to remain in a validated state have been fully identified. Finally, the program to implement these actions would also be defined and fully developed prior to implementing the change.
2. Emergency changes are those that had to be implemented on an emergency basis. Such changes are usually associated with emergency maintenance issues, such as replacing a non-functioning pump with another in order to keep the operation running.

In addition, changes can further be divided into two categories based on their complexity and their expected impact on the product:

1. Major, or critical, changes are typically expected to impact the quality (not only as defined by the purity, but also the impurity profile), safety, and efficacy of the product. These usually require extensive engineering work and a considerable expenditure of funds to implement. Normally, such changes introduce a high level of uncertainty as to their possible effect on the process that they would require some level of validation of the modified system to ascertain that the system is still GMP compliant. These changes are usually associated with the utilities, the facility, or the process itself.
2. Minor, or non-critical, changes are not expected to impact the product in any way and would not normally require a subsequent validation effort. Such changes are typically handled as part of the preventive maintenance program. They are normally easy to implement and will not affect the validated state of the system. This type of change may affect the compliance state of the system, in the sense that they may require modifications to documentation, procedures, or drawings amongst others.

The Change Control Procedure

Change control is a formal system, which is designed not to prevent change, but rather to document and control it. Its main purpose is to ensure that a system, process, or operation is always in a GMP compliant and validated state, regardless of changes made to it. The results ensure that the quality, safety, and efficacy of the product are uncompromised. It should be implemented using an established procedure.

An organization should have only one change control procedure to handle all types of changes that may take place within its boundaries. A robust change control procedure should be capable of managing changes to procedures, suppliers, process equipment, control systems, facility, utility systems, etc. Such a scope should be clearly stated in the beginning of the procedure.

On the other hand, prudence may require a different procedure for different facilities or sites within one company to reflect the varied standards and approaches under which these sites labor. In such cases, an overall corporate procedure for a multi-site company may be very difficult to implement and prove unwieldy.

Whichever format is judged best for your situation, all change control procedures should include the following elements:

1. Define the change and provide supporting documentation and drawings. The initiator of the change request should also identify all suspected implications that a change may cause. These implications should not be limited to GMP and validation requirements, but should also address regulatory issues, safety issues, environmental issues, etc.
2. A group of knowledgeable personnel within the organization should first challenge the need for the change and ascertain that it is truly beneficial. Once the need for the change is established and confirmed, then a review of the possible implications of the change should ensue. The challenge and review should be the responsibility of the following functional groups within the organization:
 - User Group
 - Engineering
 - Validation
 - Technical Services or Technical Operations
 - Quality Assurance
 - Regulatory Affairs
 - Safety
 - Environmental

3. Once the review of the change and its implication is completed, a list of requirements is established. These are additional actions that should be implemented once the change is completed to ensure that the system remains in, or returns to, the compliant and validated state it originally had. Such actions may range from modifying a procedure or updating the preventive maintenance schedule for a piece of equipment to validating the entire process to ensuring that the product quality, safety, and efficacy have not been compromised.
4. A final review of all the data as well as any conclusions is conducted in a meeting with all the stakeholders (i.e., Change Control Committee) to ensure that an open and honest discussion takes place and that all concerns are addressed to the satisfaction of everyone. The Committee either approves or disapproves the change at the end of the review meeting. All of the actions, discussions, and rationale for all decisions should be well documented.
5. Once the change is implemented, and all of the requirements that were identified through the change control procedure have been completed, then the appropriate GMP reports should be issued. These reports summarize all aspects of the changes and claims that the system is back in compliance with GMP requirements and in a validated state. The GMP reports should be filed with the original change control request documentation. At that point, the change becomes part of the established operation and the change request is closed.

Change Request and Control Form

All the steps discussed above should be documented and summarized in a "Change Request and Control Form," which is a short report containing a maximum of two pages, to which all the supporting documentation and drawings can be attached.

The form should have a section with the originator's information including the date, a short title, and the reason for requesting the change. This section should also list all suspected or known GMP, regulatory, environmental, and safety issues which may result from the requested change.

The next section lists personnel with the knowledge base capable of reviewing the request and indicating whether or not the change is justified. Additionally, the section should have space to indicate what they consider to be the implica-

tions of the change. This section should have space for each responsible person to enter comments, sign, and date the form. Of course, all supporting documentation should be attached to the form and referenced in the body of the information.

The third section summarizes what transpired in the Change Control Committee meeting. It should indicate the date and time of the meeting, the attendees, and the final conclusions of the group. This section should also summarize what requirements are to be satisfied once the change is implemented. These may include validation, document or drawing modification, procedure modification, etc.

The final section provides an area for the Quality Assurance (QA) representative's signature and date indicating that it has been reviewed by QA.

How to Address Various Changes

It is important, in the case of emergency changes that may have occurred prior to its review and approval, to initiate the appropriate documentation and reviews immediately upon implementing the change. Reviews and definition of necessary compliance related actions should be performed as soon as possible, preferably within 48 hours. Additionally, the product produced with the change should be quarantined until it is determined that the change did not compromise its quality, safety, and efficacy. Finally, all GMP requirements identified should be implemented immediately and the change request form should be finalized and closed as fast as practicable.

Other types of changes are addressed depending on their complexity and potential impact on the product. It should be noted that not all changes would require validation or revalidation of the system undergoing change. Some changes may only require a notation in the maintenance logs while others may require updating a drawing or an SOP.

Figure 2 is a logic diagram depicting a proposed approach to addressing various situations that may be encountered while contemplating a change and implementing the change control procedure. In all cases, a change control form should be initiated and the change control procedure followed whenever changes to a manufacturing system are contemplated. This systematic and formal approach guarantees that changes that may have major implications are addressed properly and that the quality, safety, and efficacy of the product are never compromised. □