Pharma Change Control

Strategies for Successful Company-Wide Implementation

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## Table of Contents

About the Authors

Principles of Change Control..................................................................................................................3

Introduction and Operation of Change Control Programs........................................................................6
  - Parallel Programs.................................................................................................................................7
  - Company-Wide Programs ...................................................................................................................7
  - Grading the Changes ............................................................................................................................8
  - Trials................................................................................................................................................10
  - Deviations.........................................................................................................................................10
  - Change Control Committee...............................................................................................................10

Documentation........................................................................................................................................12
  - Change Requests.............................................................................................................................12

Appendices............................................................................................................................................21
  - A. CMS’ Change Control Management Plan Version 1.0
  - B. Change Management Plan Version 1.0
  - C. EMA Questions and Answers on Post Approval Change Management Protocols
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Principles of Change Control

As a rule, before a company can manufacture a drug, it must first gain approval from the appropriate federal agency to make sure it meets quality, efficacy and safety requirements.

But in order to follow Good Manufacturing Practices (GMP), manufacturers must comply with numerous requirements. Firms must document instructions for manufacture and quality control procedures. They must specify materials needed and define the basic conditions required for a reproducible quality, such as suitable rooms, qualified facilities, trained personnel and type of documentation (See Figure 1).

Before a company can implement these requirements, it needs a regulatory body to review their suitability for the intended purpose. In the theoretical approval model, regulatory authorities carry out the review as part of an authorization procedure. If approved, applicants receive a notice that the product is suitable and authorized for use. Pharmaceutical manufacturing companies must prove the suitability of apparatus/facilities and procedures with qualification/validation. In these cases, someone responsible must sign the qualification/validation report confirming suitability and authorization for use.

The principle that companies must adhere to suitable requirements is not only valid the first time a drug is manufactured or the first time a facility follows a procedure. They must follow and adhere to these requirements throughout the whole history of a drug or procedure.

Just as firms must document the entire batch history, they must also document requirements, such as written specifications for materials or directions for procedures. Firms must also document each change control for the requirements.

As a result of scientific/technical development, changes to the legal basic conditions, or business restraints, manufacturers typically have to redefine, modify, enhance, or cancel requirements again and again in practice. In turn, this change to previously approved requirements requires a review and authorization procedure to keep the system in its original state of proven suitability. This is the task of the change control.
Change control programs are considered essential elements of pharmaceutical quality assurance systems. The glossary to Annex 15 of the EU GMP Guidelines defines “change control” as:

“A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.”

Chapter 5.23 of the EU GMP Guidelines says this about the handling of changes:

“Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.”

There are also two brief notes in the Code of Federal Regulations (CFR) on the topic of “change control” (21 CFR, 211.100 and 21 CFR, 211.160):

§ 211.100 Written procedures; deviations.

(a) “There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.”

§ 211.160 General requirements.

(a) “The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.”

In the US the quality control unit is responsible for the verification and authorization of changes. The responsibility is not assigned in the relevant EU regulations. However, as change control is considered an essential element of the pharmaceutical quality assurance system, it makes sense to transfer the responsibility for the function of the change control program to the person responsible for quality assurance (QA representative, QA head).

Change control is not department-specific, rather the task of the whole company. This is due to the wide area of application of change control, as described in both Annex 15 and in The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) document PI 006-2.

“Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect
product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications. “(Annex 15, no. 43)

“Change control is an important element in any Quality Assurance system. Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or support system operation.” (PIC/S document PI 006, section 6.7.1)

In this way, the change control monitors all types of changes which can influence the process reliability or product quality, evaluates them in reference to the relevant established requirements, and determines the measures necessary for implementing the change or decides that a change should not be implemented. The change control therefore ensures that a system remains in its suitable state.
Introduction and Operation of Change Control Programs

“Commitment of the company to control change to premises, supporting utilities, materials, equipment and processes used in the manufacture of medicinal products is essential to ensure a continued validation status of the systems concerned. This commitment should be stated in the relevant company documentation. For example, the Quality Manual, Quality Policy Documents or the Validation Master Plan. As part of its Quality Management System the company should have a defined and formalised Change Control Procedure.” (PIC/S document PI 006, section 2.6)

In order to successfully introduce a change control program, you must have the support of the company’s top managers. The program also needs a corresponding statement for quality management (see Figure 2).

Many types of changes affect several regulation areas simultaneously (e.g. GMP requirements, authorization requirements, and employment protection requirements). Quality-relevant changes can affect several areas of a company (e.g. research/development, regulatory affairs, manufacture, quality control, engineering, and marketing); therefore, the control must be a task for the whole company (see Figure 3).