Pharma Change Control

Strategies for Successful Company-Wide Implementation

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Pharma Change Control:

Strategies for Successful Company-Wide Implementation

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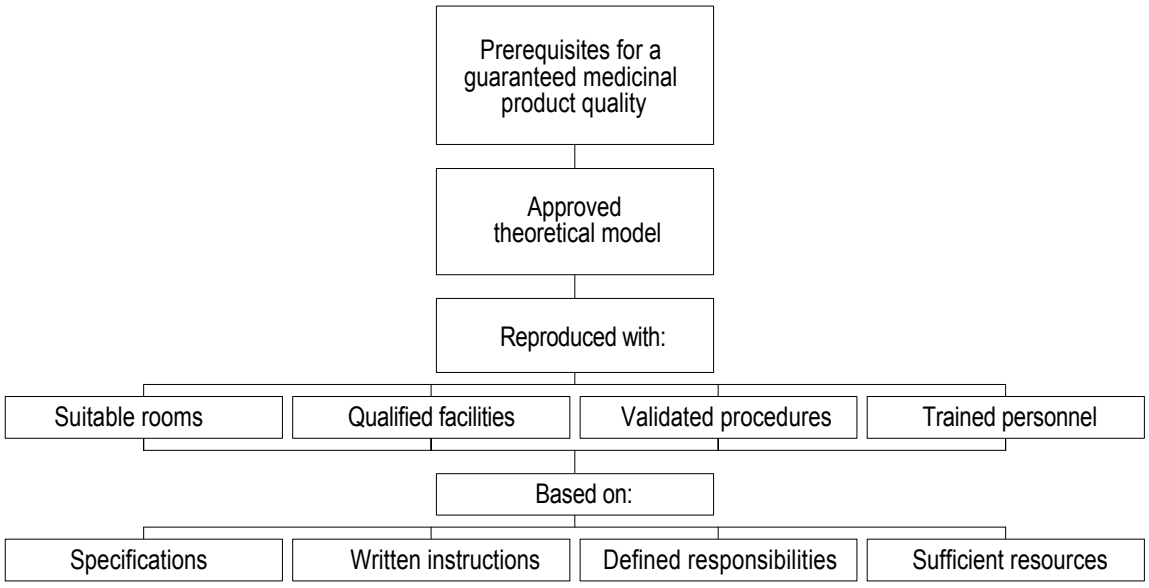
Principles of Change Control

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).

Figure 1: Change Control Area of Consideration



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)

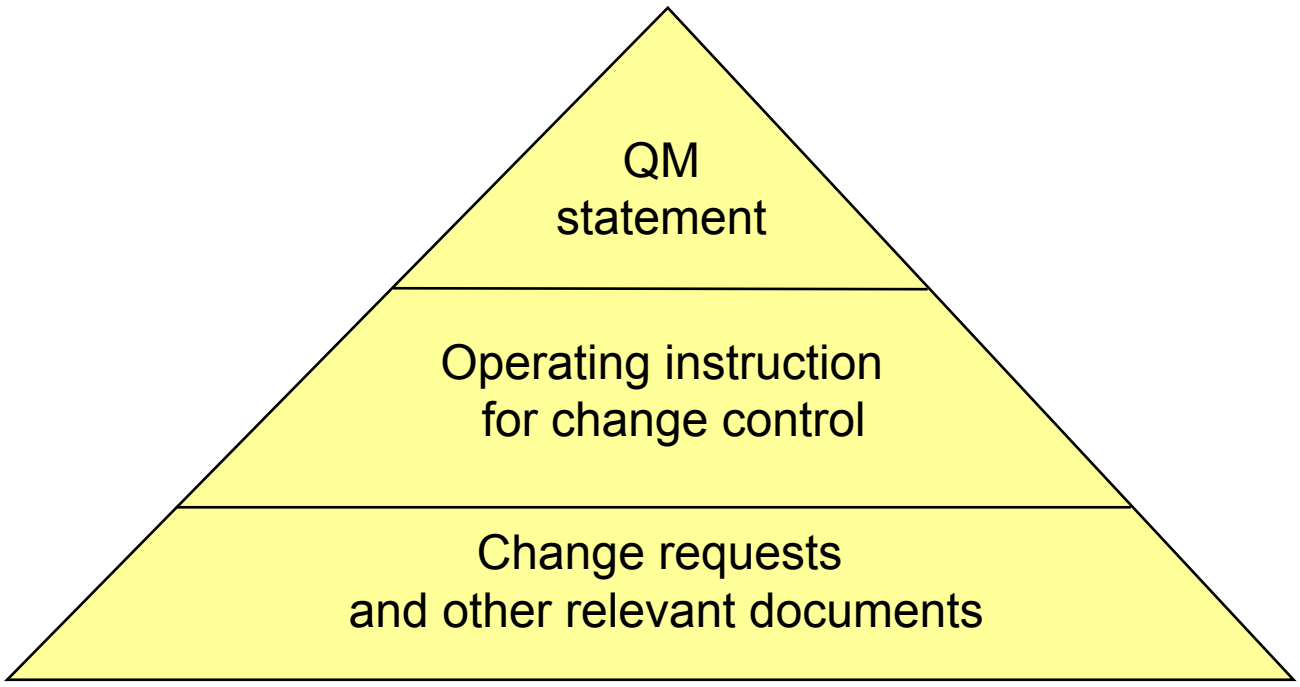
In this way, the change control monitors all types of changes which can influence the process reliability or product quality, evaluates them in reference to the relevant established requirements, and determines the measures necessary for implementing the change or decides that a change should not be 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)

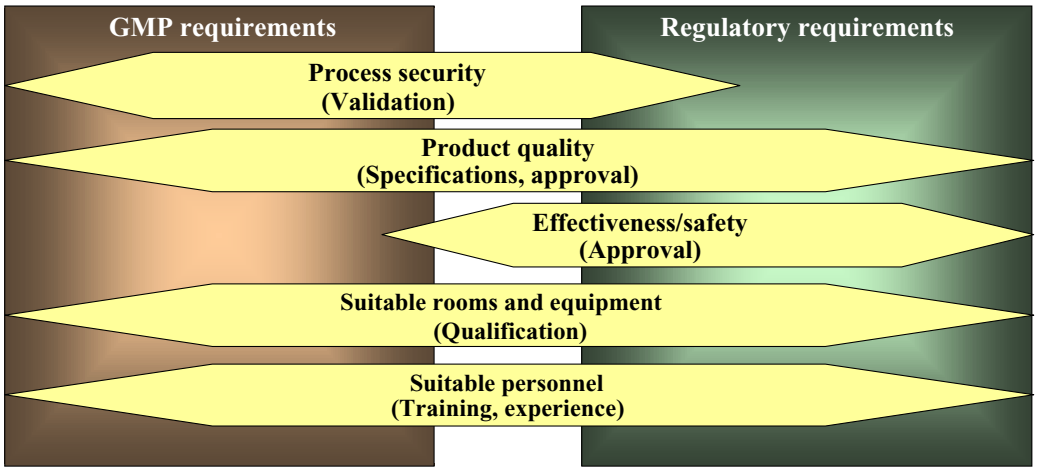
In order to successfully introduce a change control program, you must have the support of the company's top managers. The program also needs a corresponding statement for quality management (see Figure 2).

Figure 2: Structure of Change Control



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).

Figure 3: Areas of Change



Parallel Programs

As a rule, don't operate different parallel and independently working interdepartment change control programs. In the past, companies didn't recognize the need for change control as a quality assurance task for their entire staff. Instead separate departments handled their own change control. Some companies are still making this mistake and work with parallel change control programs: a change control program for the (electronic data processing) (EDP) area, a change control program for the regulatory affairs department, and a change control program for the engineering department.

The problem with this method is that different departments don't always collaborate on change control. For example, control software was changed in the manufacturing area, without the head of production being aware of this because he or she was not a member of the change control committee for the EDP department that implemented this change autonomously.

Independent change control programs cause an unwanted attitude in the department, expressed as delimitations of responsibility, ineffective inter-department communication, and unfavorable procedure- and target-oriented attitudes. In addition, decision procedures and documentation formats/contents are not always consistent and not well suited.

Company-Wide Programs

The central processing of change procedures, coordinated by the quality assurance department, has several advantages compared to the handling of change control within various departments:

- There is a common understanding of what a change represents;
- The classification schemes used by the staff involved to grade changes are consistent;
- The risks connected with the change can be evaluated in a multi-disciplinary manner; and
- There is a uniform documentation and authorization procedure.

The main requirement for the introduction of a change control program is high-quality awareness and an understanding for the functionality of quality assurance systems among the staff. Change control can therefore not be assigned "from above," and instead managers must communicate the significance and benefits of the program as part of an intensive training. Changes that require control must be first recognized as such "on site" so that the company can initiate necessary procedures. Only when staff are motivated to continuously improve the quality of the product they manufacture will they accept the change control as a suitable tool and not reject it as bureaucratic formality.

The type and scope of a change control program must comply with the individual company requirements:

- In classical GMP-relevant areas, the change control serves to maintain the validated and specified status. Validated processes and qualified facilities can be influenced in their state by changes so that the drugs manufactured no longer certainly comply with specifications. The same applies for changes to material specifications. A complete revalidation/requalification can then be necessary. In these cases, companies need a formalized procedure to evaluate the risks associated with the change, determine the measures necessary to maintain the validation status, and authorize the change after successful revalidation.
- Holders of marketing authorizations must guarantee that for changes requiring reporting or agreement, the necessary regulatory prerequisites are first met. Contract manufacturers that do not have their own authorizations and resulting obligations for reporting must guarantee that the contract giver is informed of the company-internal changes that could have an influence on their application documentation. This requires that the contract giver is included in the change control program of the contract manufacturer. Conversely, it is frequently the holder of the authorization that causes the corresponding subsequent changes with the contract manufacturer because he or she changed authorization. Change control is in this case not only a task that applies within the company, rather a task that applies across companies. This is valid in particular for multi-national companies: changes can affect the approval status in different countries or affect the utilities at different manufacturing sites.
- In areas where drugs are developed, processes are optimized, or clinical research takes place, it's not always necessary to comply with the strict reporting obligations linked with the approval. However, persons working in this area expect their work to be comprehensible. Changes in these areas should also be evaluated and documented in accordance with a described procedure. During the approval procedure at the latest or during inspections before the approval (pre-approval-inspection), the development of a drug or process must be consistently proved.

Grading the Changes

According to the area of consideration (e.g. approval conformity or validation status), it may be necessary to use different change procedures as a base. This is the way many companies deal with changes to printed packaging material (information for use, folding cartons, and labels) in accordance with a special change control procedure, because these changes occur relatively frequently in practice and the process sequences can be standardized easily. In these cases, the sequences and the criteria used are not independent, but are carefully matched to suit and coordinate with each other.

The examples (lists, flow charts) for grading the changes, as used in many companies, can and should not replace the individual evaluation of a change, in particular the linked consideration of risk.

The example in Figure 4 only shows one way to grade changes. Some companies use different and extensive grading categories. Others have extensive lists of possible changes and their grades. The display of change procedures contains large flow charts, which are often complicated and hard to understand. These companies have previously tried to show all potential types of changes and define the required sequences in diagrams. Such a procedure is not incorrect because it shows the scope of consideration of the change control and example help in the introduction phase for evaluation and development of changes. This can however deceive one into thinking everything is regulated. After the introduction phase, most companies find that changes do not always fit into a prefabricated chart and instead it's important to rely on experience and know-how for particular cases.

Figure 4: Grading of Changes

	Changes requiring control		Not requiring control
	Major (major change)	Minor (minor change)	
Significance of change	Influences product quality or process reliability.	Influences a unit requiring control.	No relevance to GMP or authorization
Possible measures (selection)	• Official license • New approval • Revalidation	• Amendment • Review • Documentation	• No relevance to GMP or authorization
Examples	• Change of manufacturer: other synthesis route of a starting material (other impurities) • Removal of processes to another site • Change in the product composition • Change to the process parameters	• Replacement of apparatus part of the same design • Change of cleansing agent for floors • Change of laundry for work clothing (non-sterile or antibiotics area) • Introduction of co-sales right	• Change to working times • Renovations in administration area • Installation of air conditioner in staff room • Introduction of electronically-readable plant ID cards

Other classifications not included in Figure 4 are possible. It is not decisive which and how many change classes a company has determined, but how it is guaranteed that changes requiring control are recognized as such and implemented according to a defined procedure.

See the PIC/S document PI 006 for notes on grading changes. In chapter 6.7.4., there is a list of changes that may make a revalidation necessary, including:

- Physical characteristics of the raw material

- Origin of the starting material (change of supplier)
- Packaging material (e.g. replacement of plastic with glass)
- Process changes (e.g. mixing times, drying temperatures)
- Equipment (e.g. introduction of an automatic detection system)
- Production area and supply systems (e.g. new water plant)
- Moving manufacturing into a new building

Trials

The so called “trials” cause a problem area in change control. Trials are preliminary, temporary changes which can be permanently established or revoked after a trial period. With trials, there is a risk that these intended temporary changes gradually become permanent changes, without a formal change control procedure being carried out. Regardless of how long a trial is retained and whether it is withdrawn after a trial phase or introduced permanently, trials should be dealt with according to the same procedure as all other changes. Before the trial phase starts, the company should implement an analogous change control procedure.

Deviations

Deviations should not be treated as changes, not even when deviations become changes after the company clarifies the failure. A deviation is an unplanned and undesirable variation from a requirement. It does not correspond with the aim and procedure of change control and should be dealt with according to a special procedure about handling deviations.

Change Control Committee

An important function as part of the change control program is fulfilled by the change control committee (also known as: change control team, change control panel). This permanent committee generally consists of the head of quality assurance, who frequently also chairs and the heads of manufacturing, quality control, sales, regulatory affairs and the information representative. If necessary, further departments (e.g. research/development, EDP, and engineering) also become involved. The task of the committee is to evaluate changes, determine the measures required, coordinate measures for the departments affected by the change, and provide final authorization.

A major problem, especially during the introduction phase of the change control system, is the issue of which changes the change control committee should deal with first. It is obvious that this committee cannot deal with all changes in a company due to capacity reasons. As a matter of fact, the committee should process only changes requiring control. These are changes relevant for the regulatory status and involve reporting or authorization procedures. They are also changes that could have an influence on the attributes of a GMP-relevant system, facility, apparatus, material/product, or a procedure/process. This influence may be critical as it regards the product quality/process reliability and may require a revalidation/requalification or the compilation/update of documentation. The change control committee is also involved in changes for which their implementation is often extensive and coordinating measures are necessary. The committee should also deal with all changes whose grade or implementation is unclear or questionable.

The question of how the committee members communicate with each other is significant. Not all change control procedures urgently require the convening of a meeting, at which many important function heads must often be present in person. For cases that will involve an easy decision, it is also worth considering traditional paper-based circulation procedures (serial or parallel), e-mail agreements, or common access to Intranet-based forms.

The committee can only deal with change applications if they are actually assigned. A high involvement is transferred to the other staff in the company. If no one evaluates a critical change and fails to introduce a formalized change control procedure, this can cause severe problems with quality.

When a company has introduced a change control program, the committee can review the effectiveness of the system using data, which is easy to determine. It includes:

- Number of completed change procedures/year
- Number of prematurely terminated procedures of procedure deviations
- Work expenditure/change type
- Duration of procedure: from application to completion
- Number of grading problems/total number of change procedures
- Number of OOS results/year
- Number of internal or external complaints/year
- Stability problems/batch reviews/recalls

It can measure the functionality of the system by taking into account the effort and speed of change procedures, for example, or by examining the deviations. The effectiveness of a change control program depends on the knowledge and experiences of the staff involved. The regular training about change control procedures is therefore extremely important. Committees should structure documentation procedures and communication sequences as simply as possible to enable rapid implementation.

Deviations are unplanned and generally unwanted changes. They are expressed in the form of internal and external complaints, stability problems, or batch recalls. If they occur, this can be an indication that the change control program has failed. It is possible that the change to a critical process parameter or material specification has been overlooked or a negative trend in the development of process data has not been noticed in time.

Documentation

> *"All changes should be formally requested, documented and accepted by representatives of Production, QC/QA, R&D, Engineering and Regulatory Affairs as appropriate. The likely impact (risk assessment) of the change on the product should be evaluated and the need for, and the extent of Re-validation discussed. The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorised." (PIC/S document PI 006, section 6.7.2)*

> *"All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined." (Annex 15, no. 44)*

Change control requires a written procedure (change control program) to regulate at least the following points:

- What types of changes does change control take into account; for which areas does this operating instruction apply?
- Who can suggest/initiate changes?
- How are changes requested (forms, methods of communication)?
- How are changes graded, who is responsible for the grading?
- How are the measures necessary for carrying out the change determined; who compiles the directions required?
- Who is responsible for the execution and monitoring of all necessary measures?
- How is the change control committee assembled; what are the duties of the committee?
- How is the change documented (format, content, storage)?
- Who is responsible for authorizing changes?
- What are the special regulations for urgent changes?

If the change affects a manufacturing or testing process, then the qualified person must take this into consideration when releasing the batch (cf. PIC/S document PI 006, chapter 6.7.3).

He or she should document all quality-relevant changes in full to ensure that they are comprehensible. The records can be archived in paper form or electronically. Keep in mind that when storing these records, you need to have raw data and other relevant documents accessible.

Change Requests

Changes requiring control are generally documented in the form of a change request, in which the applicant for the change proposes the type of grade/evaluation of the change, specifies the time frames and

measures for carrying out the change, and requests that and the change is authorized or declined by the change control committee. The documentation for the change procedure should prove that the change was evaluated (risk analysis) and the subsequently defined measures were implemented as predetermined. When implementing the change, you will need to coordinate several measures regarding timing and contents. A clear display of the individual measures for a project plan is useful for the coordination of complex changes.

The "change control" operating instruction describes the procedure of change control and contains an application form for documenting the change procedure. See the example below.

Sample Change Control Document

<table>
<tr><td colspan="2">[Company] Change control procedures</td><td>Page/pages x of y</td></tr>
<tr><td>Document number:
[Enter document no.]</td><td>Version:
[Enter version no.]</td><td>valid from: [Enter date]
valid to: [Enter date]</td></tr>
<tr><td colspan="3">File name/path:
[Enter file name/path]</td></tr>
<tr><td colspan="3">Area of application:
Changes to materials, products, facilities/apparatus, processes/procedures and systems in the areas of purchasing, manufacture, quality control, engineering, research/development, marketing authorization, sales, EDP, contract manufacturing and external testing places, excluding changes to printed packaging materials</td></tr>
<tr><td colspan="3">Key words:
Change, procedure</td></tr>
<tr><td colspan="2">Replaces version:
[Enter version no.]</td><td>from:
[Enter date]</td></tr>
<tr><td colspan="3">Changes made since last version:
[Enter main content of changes]</td></tr>
<tr><td colspan="3">Cross references:
[Valid documents: Enter document no.]</td></tr>
<tr><td colspan="3">References:
EU GMP Guideline, Annex 15, PIC/S document PI-006-2, Appendix I of the regulation (EC) no. 1084/2003</td></tr>
<tr><td colspan="3">Distribution list:
[Enter recipients of document]</td></tr>
<tr><td>Compiled by:
[Name/signature of person who compiled it]

on:
[Date of compilation]</td><td>Checked by:
[Name/signature of person carrying out check]

on:
[Date of check]</td><td>Approved by:
[Name/signature of person giving authorization]

on:
[Date
of approval]</td></tr>
</table>

[Company] Change control procedures		Page/pages x of y
Document number: [Enter document no.]	Version: [Enter version no.]	valid from: **[Enter date]** valid to: **[Enter date]**

1. Purpose of the instruction:

Internal requirements are specified in order to comply with the legal drug product provisions and the GMP Guideline, as well as to ensure that the quality of the medicinal product complies with the approval and is reproducible. These requirements cover the entire manufacturing process and the quality control for a medicinal product, including the materials and facilities/apparatus used. The purpose of this instruction is to ensure that the quality of the medicinal product, the safety of facilities/apparatus, the safety of procedures/process and conformity with the applicable application files for marketing authorization are maintained in the event of changes to these requirements.

2. Definitions/abbreviations:

Deviations: unplanned and undesirable deviation from a requirement

CCC: change control committee

Change: planned deviation (extension, replacement, removal, addition) as part of a requirement

Change control: system with which qualified representatives from corresponding departments evaluate current or planned changes in terms of their effects with regard to a specific status. The aim is to establish precautions that are necessary to prove and document compliance with the specific status.

Facility: total of all apparatus linked together with a common purpose.

Applicant: person who is initiating a change with a change request

Apparatus: object characterized by the technical processes carried out in it.

Minor change: change which fulfills the conditions of Appendix I of Regulation (EC) no. 1084/2003 or which affects the attributes of a system, facility, apparatus, material/product or procedure/process. Impairment of the product quality/process reliability is not likely. Minor changes may require notification to the regulatory or supervisory authorities.

Major change: change which cannot be classified as a minor change or which may affect the critical attributes of a system, facility, apparatus, material/product or procedure/process. Impairment of the product quality/process reliability is likely. Major changes may require authorization by the relevant regulatory or supervisory authorities and/or prior revalidation or requalification.

Process: set of interrelated methods and activities which convert an input into results.

System: total of all facilities linked together with a common purpose.

Procedure: established way of carrying out an activity.

Trial: preliminary, temporary changes which are permanently established or revoked after a trial period

[Company] Change control procedures		Page/pages x of y
Document number: [Enter document no.]	Version: [Enter version no.]	valid from: **[Enter date]** valid to: **[Enter date]**

3. Responsibilities:

3.1. Responsibilities for the established procedures

3.1.1. The legal medicinal product responsibility for proper planning, implementation and authorization of changes is borne by the head of production, the head of quality control, the sales manager and the information representatives for their relevant area. In particular, they must ensure that:
the qualification status of the rooms and facilities that are affected by a change is maintained or that a requalification is implemented
the validation status of the processes/procedures that are affected by a change is maintained or that a revalidation is implemented
changes to manufacturing, analysis and labeling of a medicinal product are based on a valid approval/registration
the documentation required for the change is compiled or updated

3.1.2. The organizational processing and documentation of change control procedures is conferred to the change control committee (CCC). The CCC comprises those in the roles mentioned above and the head of regulatory affairs and the QA representative. Other heads of department or experts may be called in at the wish of one of the members. The committee has the following tasks:
Risk evaluation of the change request
Authorization or rejection of the application
Establishing and scheduling necessary measures

3.1.3. The chairman of the CCC is the QA representative. He has the following tasks:
Calling the CCC meetings and taking minutes
Coordination of circulation procedure
Maintenance of the database of change control procedures
Formal control of the change requests
Monitoring compliance with deadlines
Archiving the completed change requests

3.2. Responsibility for the revision of this instruction
The QA representative is responsible for checking this instruction regularly to make sure it is up to date and for revising it if necessary. He must release a new version at least every two years.

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Document number: [Enter document no.]	Version: [Enter version no.]	valid from: **[Enter date]** valid to: **[Enter date]**

4. Procedure

4.1. Basic principles

4.1.1. GMP or approval-relevant changes must only be implemented if they have been previously requested in writing and authorized.

4.1.2. Trials are also subject to this procedure.

4.1.3. Deviations are not subject to this procedure, but to operating instruction [enter doc. no. /version no.] "Handling deviations".

4.1.4. Changes can be requested by any staff member using the form in Appendix 1.

4.1.5. Changes of which the grade is debatable or unclear must also be requested using this procedure.

4.2. Implementation of change control procedures

4.2.1. Forms for change control procedure are issued by the QA department. If a new form is issued, a change number is automatically allocated to the change procedure by the change database and is entered on the form.

4.2.2. The applicant should specify the object of the change and the significant reasons and circumstances of the change in no. 1 on the change request. He should then sign and date it.

4.2.3. The heads of area affected by the change should have the opportunity to give their opinion on the intended change, to identify any risks and to suggest necessary measures and schedules. In any case, they should be acquainted with the planned change. This is documented in no. 2 on the change request.

4.2.4. The QA representative transfers the data required to identify the procedure into the change control database.

4.2.5. The members of the CCC jointly carry out a risk analysis of the change request under no. 3.1, classify the change under no. 3.2 and give their decision to authorize or reject the change application under no. 3.3. Authorization may be associated with a time scale. The applicant and his head of area are informed of the decision via a copy of the completed change request.

4.2.6. A decision by the change control committee in accordance with 4.2.5 may only be made if all the information and documents relevant to the decision are submitted. If necessary, the request may be returned to the applicant for completion.

4.2.7. If the change is authorized, the CCC can establish a measures plan in no. 3.4 of the change request (tasks, responsibilities, schedule). This must be completed and authorized for the change procedure to be completed.

4.2.8. Those responsible in accordance with the measures plan shall each receive a copy of section 3.4 and shall inform the QA representative when the established measures have been completed.

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Document number: [Enter document no.]	Version: [Enter version no.]	valid from: **[Enter date]** valid to: **[Enter date]**

4.2.9. The QA representative shall collect all the completed measures plans, check them for successful completion of each task and include them with the original change request. The completed change request is archived and the result and date of the completion is entered in the change database.

4.2.10. In simple cases, in which the applicant can implement the change himself without requiring any scheduling, an electronic copy of the request may be distributed to the CCC via the internal e-mail system instead of at a meeting (circulation procedure). Each CCC member then gives his written vote regarding the change request via e-mail with electronic signature. The change request and electronic voting from the CCC member are to be archived in accordance with chapter 4.3. If there is no unanimous decision, the QA representative calls a meeting about the request.

4.3. Documentation

4.3.1. The procedure in accordance with chapter 4.2 must be documented on the "change request" form in Appendix 1.

4.3.2. If necessary, documents relevant to the decision should be added to the change request.

4.3.3. The change request and documents relevant to the decision must be kept indefinitely in the "quality assurance" area of the department.

4.3.4. If necessary for capacity reasons, the paper copy of the change request and its associated documents may be replaced with an electronic archive file.

4.4. Deviation from the procedure

4.4.1. It is permissible to deviate from the regulations in chapter 4.2 only if:

an immediate change is urgently required for operational or staff safety or

an immediate change has considerable significance for the unit, the need for it was not foreseeable and it was not possible to comply with the formal procedure in chapter 4.2 in the time available.

4.4.2. In the cases in chapter 4.4.1, the consent of the responsible head of area or his representative should be sought before the change is implemented.

4.4.3. Once the change has been implemented, the procedure in chapter 4.2 must be followed at the earliest opportunity.

5. Appendices

Appendix 1: change request form

<table>
<tr><td>[Company]</td><td colspan="2">Change control procedure
Appendix 1</td><td>Page/pages x of y</td></tr>
<tr><td>Document number:
[Enter document no.]</td><td>Version:
[Enter version no.]</td><td colspan="2">valid from: [Enter date]
valid to: [Enter date]</td></tr>
<tr><td>Company</td><td colspan="2">Change request
[Cross reference to the operating instruction on which it is based]</td><td>Page/pages
[enter page no.]</td></tr>
<tr><td colspan="2">Change no.:
(to be entered by QA)</td><td colspan="2">Change designation:
(to be entered by QA)</td></tr>
<tr><td colspan="4">1. Applicant</td></tr>
<tr><td colspan="2">Name …</td><td colspan="2">Department …</td></tr>
<tr><td colspan="4">1.1. Object of the change (mark with a cross)</td></tr>
<tr><td colspan="2">• Rooms
• Manufacturing facilities
• Quality control facilities
• Media supply
• Computer-assisted system
• Organization
• Contract acceptor/giver
• Supplier
• Marketing authorization
• Documentation</td><td colspan="2">• Manufacturing procedure
• Test procedure
• Cleaning procedure
• Other procedure
• Starting materials
• Packaging material
• Semi-manufactured/bulk product
• Finished medicinal product
• Other material
• …</td></tr>
<tr><td colspan="4">1.2. Description of change:</td></tr>
<tr><td colspan="2">• Cause, reason for the change
• Products, procedures, facilities affected
• Necessary time frames
• Suggestion for implementing the change
• Estimated costs</td><td colspan="2">• Alternatives
• Cross reference to appendices where necessary.
Date and signature of the applicant: .....</td></tr>
<tr><td colspan="4">2. Area head
Response/risk assessment of the affected areas
Area:

Date and signature of the person responsible:</td></tr>
<tr><td colspan="4">Area:

Date and signature of the person responsible:</td></tr>
<tr><td colspan="4">Area:

Date and signature of the person responsible:</td></tr>
</table>

[Company]	**Change control procedure** **Appendix 1**	Page/pages x of y
Document number: [Enter document no.]	**Version:** [Enter version no.]	**valid from:** [Enter date] **valid to:** [Enter date]

3. Change control committee:

3.1. Additional risk assessments:

3.2. Grade of change

- o Major change
- o Minor change
- o No major or minor change

3.3. Decision:

- o The change is authorized. Time limit for the implementation:
- o The measures list in no. 3.4 must be observed.
- o The change is not authorized. Rationale:

Date and signatures of the CCC members

Head of Production:

Head of Quality Control:

Sales manager:

Information representative:

Head of regulatory affairs:

QA representative:

Other members:

<table>
<tr><td>[Company]</td><td colspan="3">Change control procedure
Appendix 1</td><td>Page/pages x of y</td></tr>
<tr><td>Document number:
[Enter document no.]</td><td colspan="2">Version:
[Enter version no.]</td><td colspan="2">valid from: [Enter date]
valid to: [Enter date]</td></tr>
<tr><td colspan="2">3.4. Measures list

Directions for implementing and documenting the measure

Cross references to affected documents that require revision

Extensive directions or project planning may be recorded in separate documents</td><td>Responsible …</td><td>Time limit …
Completed on …</td><td>Signature …</td></tr>
<tr><td colspan="5">4. QA head

Completion of procedure
• The procedure has been completed correctly.
• The procedure has not been completed correctly. It should be abandoned and not continued. Rationale:
• The procedure has not been completed correctly. Deviations occurred and measures required for procedure completion:

Date and signature of the QA head.....</td></tr>
</table>

Appendices

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

Appendix A: CMS' Change Control Management Plan Version 1.0

Change Control Management Plan
Version 1.0

Revision History

DATE	REV	AUTHOR	DESCRIPTION
MM/DD/YY	1		

Table of Contents

List of Tables

List of Figures

1. Purpose

This document describes the process to request and manage changes to work products created or maintained by the ICD-10 project team members. These changes may apply to any area impacted by ICD-10, including policies, processes, and systems. This process will allow for the following:

- Facilitate communication regarding requested changes among the stakeholders of the project team;
- Provide a common process for resolving requested changes and reported problems; and
- Reduce the uncertainty around the existence, state, and outcome of a change that has been requested in a work product.

2. Scope

Any stakeholder of the ICD-10 project can submit the following types of change requests for consideration:

- Requests for scope, schedule, or resource changes that may affect program administration;
- Requests for requirements changes (additions, deletions, modifications, deferrals) in software currently under development;
- Reports of problems in current production or test environments;
- Requests for enhancements in current production systems; and
- Requests for new development projects.

This change control process applies to baselined deliverables/work products created or managed by the members of the ICD-10 project team, including:

- Software that has been released to production or is in beta test;
- Requirements specifications for MMIS or other systems impacted by ICD-10;
- Group procedures and processes; and
- User and technical documentation.

The following work product classes are exempted from this change control process:

- Work products that are still under development, except for requirements changes requested in new projects;
- Interim or temporary work products created during the course of a project; and
- Any work products intended for individual use only.

3. Definitions

Change Request (CR):	An item submitted by a stakeholder for consideration through the change control process.
Stakeholder:	Someone who is affected by or who can influence the project.

4. Roles and Responsibilities

All ICD-10 project team members play a role in change management and should understand the impacts and opportunities of ICD-10 on their business areas (see Table 1). In addition, the project manager, or designee, should include consideration of Change Control Board (CCB) inputs and outputs on the ICD-10 project scope, cost, and schedule.

Table 1: Roles and Responsibilities

Role	Activity
ICD-10 Steering Committee	The group that charters the CCB and approves or rejects ICD-10 project changes where either CCB consensus is not reached or program administration may be affected (e.g., scope, schedule, or costs).
CCB	The group that approves or rejects proposed changes for the project.
CCB Chair	Chairperson of the CCB; has decision-making authority as granted by charter (e.g., may have final decision-making authority if the CCB does not reach agreement); directs someone to be the Evaluator for each CR; and directs someone to be the Modifier for each approved CR.
Evaluator	The person whom the CCB Chair asks to analyze the impact of a proposed change.
Modifier	The person who is assigned responsibility for making changes in a work product in response to an approved CR; updates the status of the request over time.
Originator	The person who submits a new change request.
Project Manager	The person who is responsible for overall planning and tracking of the development project activities.
Verifier	The person who determines whether a change was made correctly.

5. Process

Outlined in Table 2 and Figure 1, the change management process begins when a stakeholder, at any ICD-10 program level, submits a change request for consideration by the CCB.

Table 2: Process Summary

Inputs	Process	Outputs
• **Charters (e.g., Program, Project, and CCB)** • **Baselined work products** • **Project Plan** • **Risk Assessment Checklist** • **Business/User Requirements** • **Schedule/WBS** • **Valid CR submitted on standard form**	Regularly scheduled CCB meetings to **Evaluate** CRs; **Modify** policies, processes, and systems; and **Verify** any approved changes were made correctly. [See Figure 1 and Table 3]	• Change Management Log reflecting status of issue is either 'Rejected' or 'Closed' • Modified work products • Updated requirements, including traceability information • Status Reports

Note: The Change Management Log is managed at the Workgroup or Project Level.

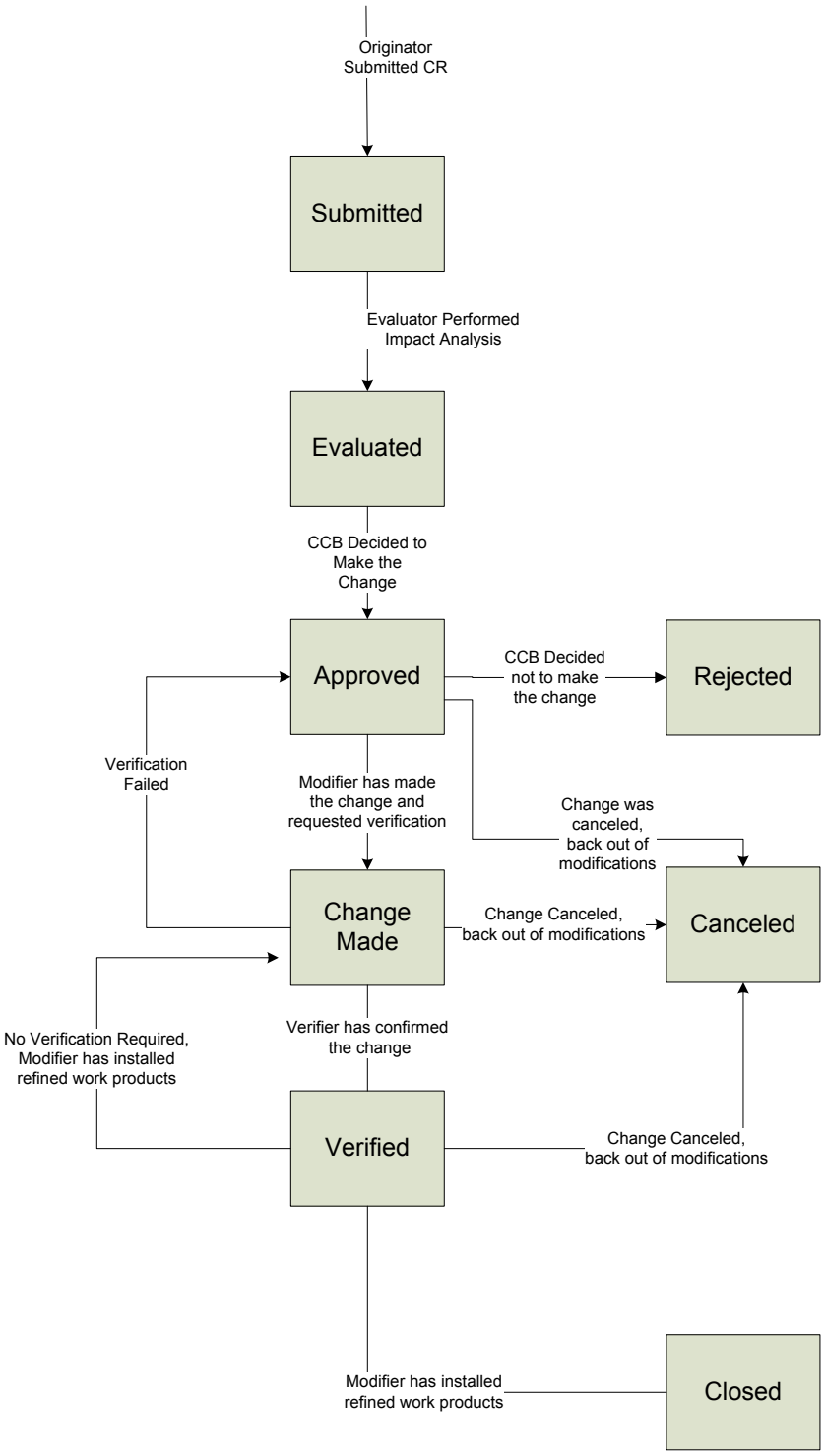


Figure 1: Change Management Process Flowchart

Table 3: Change Management Process Steps

Role	Action
Originator	1. Documents CR using standard change request form 2. Stakeholder consults with project team lead (Workgroup/Project Level) about CR 3. Stakeholder and/or project team lead submit CR to CCB
CCB	4. Sets initial CR status to 'Submitted' 5. Assigns CR to Evaluator
Evaluator	6. Assesses the CR as to feasibility, whether it really pertains to the indicated project, whether a reported problem can be reproduced, an estimate of the labor hours needed to implement the change, and other criteria as decided upon by CCB charter. 7. Change CR status to 'Evaluated'
CCB	8. The CCB decides whether the requested change should be made (or the reported problem fixed) at this time, at some point in the future, or not at all. Input should be solicited from others potentially affected by the change before making the decision. 9. If the change was accepted, the CCB Chair assigns a Modifier, sets the status to 'Approved,' enters any explanation in the Response attribute, and schedules the work. The Project Manager negotiates any necessary changes in project commitments with affected stakeholders. Communication is sent to the assigned Modifier and the Originator. 10. If the change was rejected, the CCB Chair sets the status to 'Rejected' and enters an explanation of why in the Response attribute. Communication is sent to the Originator and CCB. 11. The CCB Chair and the Originator determine whether formal verification of the change will be required, following the procedure in the **Verification** section. If so, they select the verification method to be used and the CCB Chair assigns a Verifier.
Modifier	12. Makes the necessary changes in the affected work products and notifies any other affected parties if corresponding changes need to be made, such as user documentation, help screens, and tests.
Workgroup Lead **Project Manager**	13. Updates the project plans, task lists, and schedules to reflect the impact of the change on project work remaining to be done. The Project Manager revises any task dependencies as necessary.

Role	Action
Modifier	14. If it becomes apparent during the work that the requested change is not feasible after all, the Modifier notifies the CCB Chair, who may then set the status to 'Canceled.' The Modifier backs out of any modifications made, restoring the work products to their previous baseline. Communication is sent to the Originator, CCB Chair, Modifier, and Project Manager. 15. When the change is completed, the Modifier sets the status to 'Change Made,' updates the issue in the database with appropriate notes in the Response attribute, and enters the hours of effort that were required to make the change in the Actual Hours attribute. Communication is sent to the Originator and CCB Chair. 16. Notifies the Originator and Verifier (if one was assigned) that the change has been made and makes all modified work products available to the people responsible for verification.
Verifier	17. Performs the agreed-upon verification steps. 18. If verification is successful, the Verifier sets the status to 'Verified.' Communication is sent to the Originator and Modifier. 19. If verification is not successful, the Verifier sets the status back to 'Approved' and describes the problem in the Response attribute. Communication is sent to the Originator and Modifier. The procedure continues back at step 12.
Modifier	20. For a problem report CR or an enhancement request CR, the Modifier installs the modified work product as appropriate and updates the product baseline. For requirements changes, the Modifier updates version numbers on all modified work products per the project's version control procedure, checks them back into the version control system, updates requirements traceability information, and requirements status attributes as necessary, and updates the requirements baseline. 21. Sets the status to 'Closed.' Communication is sent to the Originator and CCB Chair.

Appendix A: Attributes Stored for Each Issue

Field	How Set	Contents
Actual Hours	Modifier	Actual labor hours of effort needed to implement the change.
Description	Originator	Free-form text description of the change being requested. This cannot be changed after it is entered. If reporting a problem, enter the exact error message text observed here.
Date Submitted	System	Date this CR was submitted to the CCB.
Date Updated	System	Date this CR was most recently updated.
Estimated Hours	Modifier	Estimated labor hours of effort needed to implement the change.
Implementation Priority	CCB Chair	Relative importance of making the change: Low (default), Medium, High.
CR ID	System	Sequence number assigned to the CR.
CR Type	Originator	Type of change request: Scope, Schedule, Resources, Problem, Enhancement, Requirement Change, New Project.
Modifier	CCB Chair	Person who is assigned responsibility for implementing change.
Originator	Originator	Originator's name.
Originator E-Mail	Originator	Originator's e-mail address.
Originator Phone	Originator	Originator's phone number.
Originator Priority	Originator	Originator's relative importance of change: Low, Medium, High.
Planned Release	CCB Chair	Product release number for which this approved change is scheduled, determined by CCB.
Product	Originator	Name of the product or project in which a change is being requested or a problem reported.

Field	How Set	Contents
Problem Severity	Originator	For a problem report, set severity of the change (see below). **Minor** - Cosmetic problem, usability improvement, unclear error messages; customer can live with the problem (default) **Major** - Problem adversely affects product functioning, but a workaround is available; customer will be annoyed; serious usability impairment; problem blocks some testing **Critical** - Product does not function at all or crashes; wrong results are generated; further testing of application is not possible **Emergency/Escalated** - Anything that requires a change to be made immediately, bypassing the change control process temporarily for executive sponsor review
Response	CCB Chair, Modifier	Free-form text log of responses made to the change request.
Status	Originator, Modifier	Update current status of the change request as it moves through the states described in the **Change Request Status** section.
Title	Originator	One-line description of the CR.
Verifier	CCB Chair	Name of individual who is responsible for verifying that changes were made correctly.

Appendix B: Change Control Board Charter Template

Purpose

<Describe the objectives of the CCB. This section may read: "The Change Control Board (CCB) represents the interests of program and project management by ensuring that a structured process is used to consider proposed changes and incorporate them into a specified release of a product. The CCB shall request that impact analysis of proposed changes be performed, review change requests, make decisions, and communicate decisions made to affected groups and individuals." Define the relationship of this CCB to any other CCBs in the organization or other decision-making bodies, such as a project steering committee.>

Scope of Authority

<Indicate the scope of decisions that the CCB makes. This scope could be over a specific organizational range; a project, group of projects (program), or subproject; a maximum budget or schedule impact. This scope boundary separates decisions that this CCB can make from those that it must escalate to a higher-level CCB or manager for resolution.>

Membership

<List the members of this CCB. The CCB typically includes representatives from program management, project management, software engineering, hardware engineering, testing, documentation, customer support, and marketing. One individual is designated as the CCB Chair. Keep the CCB as small as possible, to facilitate its ability to make rapid decisions, but make sure that the critical perspectives are represented. Indicate who should be responsible for escalated changes (e.g., scope, schedule, and resources).>

Operating Procedures

<State the frequency of regularly scheduled CCB meetings and the conditions that will trigger a special meeting. Describe how meetings will be conducted, the number of CCB members who constitute a quorum to make decisions at a meeting, and the roles that must be represented for the meeting to proceed. Identify whether guest participants may attend, such as the individuals who proposed the change requests being considered at a specific meeting.>

Decision-Making Process

<Describe how the CCB will make its decisions. Indicate whether voting, consensus, unanimity, delegation to a specific individual, or some other decision rule is used to make decisions. State whether the CCB Chair or another manager is permitted to overrule the CCB's collective decision.>

Communicating Status

<Describe how each decision that the CCB makes will be communicated to the individual who requested the change, senior management, project management, affected team members who

must implement the change, higher- or lower-level CCBs, and any other stakeholders. Indicate where the decisions and any supporting information, rationale, or data will be stored.>

Appendix B: Change Management Plan Version 1.0

<PROJECT NAME>

CHANGE MANAGEMENT PLAN

Version Number: 1.0

Version Date: <mm/dd/yyyy>

Notes to the Author

[This document is a template of a Change Management Plan document for a project. The template includes instructions to the author, boilerplate text, and fields that should be replaced with the values specific to the project.

- *Blue italicized text enclosed in square brackets ([text]) provides instructions to the document author, or describes the intent, assumptions and context for content included in this document.*
- *Blue italicized text enclosed in angle brackets (<text>) indicates a field that should be replaced with information specific to a particular project.*
- *Text and tables in black are provided as boilerplate examples of wording and formats that may be used or modified as appropriate to a specific project. These are offered only as suggestions to assist in developing project documents; they are not mandatory formats.*

When using this template, the following steps are recommended:

1. *Replace all text enclosed in angle brackets (e.g., <Project Name>) with the correct field document values. These angle brackets appear in both the body of the document and in headers and footers. To customize fields in Microsoft Word (which display a gray background when selected) select File->Properties->Summary and fill in the appropriate fields within the Summary and Custom tabs.*

   After clicking OK to close the dialog box, update all fields throughout the document selecting Edit>Select All (or Ctrl-A) and pressing F9. Or you can update each field individually by clicking on it and pressing F9.

   These actions must be done separately for any fields contained with the document's Header and Footer.
2. *Modify boilerplate text as appropriate for the specific project.*
3. *To add any new sections to the document, ensure that the appropriate header and body text styles are maintained. Styles used for the Section Headings are Heading 1, Heading 2 and Heading 3. Style used for boilerplate text is Body Text.*
4. *To update the Table of Contents, right-click on it and select "Update field" and choose the option - "Update entire table".*
5. *Before submission of the first draft of this document, delete this instruction section "Notes to the Author" and all instructions to the author throughout the entire document.*

VERSION HISTORY

[Provide information on how the development and distribution of the Change Management Plan will be controlled and tracked. Use the table below to provide the version number, the author implementing the version, the date of the version, the name of the person approving the version, the date that particular version was approved, and a brief description of the reason for creating the revised version.]

Version Number	Implemented By	Revision Date	Approved By	Approval Date	Description of Change
1.0	*<Author name>*	*<mm/dd/yy>*	*<name>*	*<mm/dd/yy>*	*<description of change>*

TABLE OF CONTENTS

1 INTRODUCTION

1.1 PURPOSE OF THE CHANGE MANAGEMENT PLAN

[Provide the purpose of the Change Management Plan. This document should be tailored to fit the particular project needs.]

The Change Management Plan documents and tacks the necessary information required to effectively manage project change from project inception to delivery.

The Change Management Plan is created during the Planning Phase of the project. Its intended audience is the project manager, project team, project sponsor and any senior leaders whose support is needed to carry out the plan.

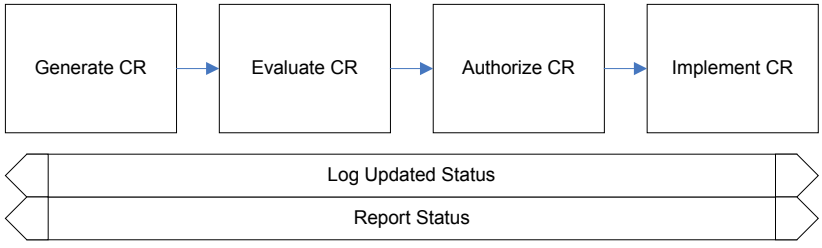
2 CHANGE MANAGEMENT PROCESS

The Change Management process establishes an orderly and effective procedure for tracking the submission, coordination, review, evaluation, categorization, and approval for release of all changes to the project's baselines.

2.1 CHANGE REQUEST PROCESS FLOW REQUIREMENTS

[Outline the project team's agreed upon change request (CR) process flow. The following outlines a generic change request process flow.]

Step	Description
Generate CR	A submitter completes a CR Form and sends the completed form to the Change Manager
Log CR Status	The Change Manager enters the CR into the CR Log. The CR's status is updated throughout the CR process as needed.
Evaluate CR	Project personnel review the CR and provide an estimated level of effort to process, and develop a proposed solution for the suggested change
Authorize	Approval to move forward with incorporating the suggested change into the project/product
Implement	If approved, make the necessary adjustments to carry out the requested change and communicate CR status to the submitter and other stakeholders



2.2 CHANGE REQUEST FORM AND CHANGE MANAGEMENT LOG

[List and define the data elements the project team needs to include on the Change Request Form and in the Change Management Log. At a minimum, the following data should be included on the project's Change Request Form and Change Management Log.]

Element	Description
Date	The date the CR was created
CR#	Assigned by the Change Manager
Title	A brief description of the change request
Description	Description of the desired change, the impact, or benefits of a change should also be described
Submitter	Name of the person completing the CR Form and who can answer questions regarding the suggested change
Phone	Phone number of the submitter
E-Mail	Email of the submitter
Product	The product that the suggested change is for
Version	The product version that the suggested change is for
Priority	A code that provides a recommended categorization of the urgency of the requested change (High, Medium, Low)

2.3 EVALUATING AND AUTHORIZING CHANGE REQUESTS

[In order to evaluate and prioritize a change request, the "priority" and "type" of the change are taken into consideration. Use the first and second tables below to list and define the "priority" and "type" data elements that are applicable for the project. The third table provides examples of commonly used project status types. The list of elements is at the discretion of the project manager.]

Change requests are evaluated using the following priority criteria:

Priority	Description
High	*<Insert the definition the project assigns to a high priority CR>*
Medium	*<Insert the definition the project assigns to a medium priority CR>*
Low	*<Insert the definition the project assigns to a low priority CR>*
<priority>	*<Insert the definition the project assigns to this level of priority CR>*

Change requests are evaluated and assigned one or more of the following change types:

Type	Description
Scope	Change affecting scope
Time	Change affecting time
Duration	Change affecting duration
Cost	Change affecting cost
Resources	Change affecting resources
Deliverables	Change affecting deliverables
Product	Change affecting product
Processes	Change affecting process
Quality	Change affecting quality
<change type>	*<define this change type>*

Change requests are evaluated and assigned one of the following status types:

Status	Description
Open	Entered/Open but not yet approved or assigned
Work in Progress	CR approved, assigned, and work is progressing
In Review	CR work is completed and in final review prior to testing
Testing	CR work has been reviewed and is being tested
Closed	CR work is complete, has passed all tests, and updates have been released.
<status type>	*<define this status type CR>*

2.3.1 Change Control Board

[A Change Control Board (CCB) is a formally constituted group of stakeholders responsible for approving or rejecting changes to the project baselines. This group may meet on a predefined schedule or on an as needed basis. The table below provides a brief description of personnel acting as the Change Control Board (CCB) and their role/level of authority within that group.]

Role	Name	Contact	Description
[Insert Role]	*[Insert Name]*	*[Insert Contact #]*	*[Insert Role Description]*

3 RESPONSIBILITIES

[Provide a brief description of persons responsible for each step of the change management process for the project.]

Role	Name	Contact	Description
Project Manager			
Change Manager			
[Insert Role]	*[Insert Name]*	*[Insert Contact #]*	*[Insert Role Description]*

Appendix A: Change Management Plan Approval

The undersigned acknowledge that they have reviewed the ***<Project Name>*** **Change Management Plan** and agree with the information presented within this document. Changes to this **Change Management Plan** will be coordinated with, and approved by, the undersigned, or their designated representatives.

[List the individuals whose signatures are desired. Examples of such individuals are Business Owner, Project Manager (if identified), and any appropriate stakeholders. Add additional lines for signature as necessary.]

Signature: _____ Date: _____

Print Name: _____

Title: _____

Role: _____

Signature: _____ Date: _____

Print Name: _____

Title: _____

Role: _____

Signature: _____ Date: _____

Print Name: _____

Title: _____

Role: _____

APPENDIX B: REFERENCES

[Insert the name, version number, description, and physical location of any documents referenced in this document. Add rows to the table as necessary.]

The following table summarizes the documents referenced in this document.

Document Name	Description	Location
<Document Name and Version Number>	*<Document description>*	*<URL or Network path where document is located>*

APPENDIX C: KEY TERMS

The following table provides definitions and explanations for terms and acronyms relevant to the content presented within this document.

Term	Definition
[Insert Term]	*<Provide definition of term and acronyms used in this document.>*

CDER's Enterprise Performance Lifecycle (EPLC) Initiative.

Appendix C: EMA Questions and Answers on Post Approval Change Management Protocols

30 March 2012
EMA/CHMP/CVMP/QWP/586330/2010
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on post approval change management protocols

Draft agreed by CHMP / CVMP Quality Working Party	9 September 2010
Adopted by CHMP for release for consultation	23 September 2010
Adopted by CVMP for release for consultation	14 October 2010
End of consultation (deadline for comments)	28 February 2011
Agreed by CHMP / CVMP Quality Working Party	2 February 2012
Adopted by CVMP	8 March 2012
Adopted by CHMP	15 March 2012
Date for coming into effect	1 October 2012

Keywords	Post approval change management protocol; Variation; Control strategy

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Use of Post Approval Change Management Protocols

1. Introduction:

The concept of post approval change management protocols has been introduced in the EU through the Commission's Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01) that supports the Variations Regulation (Commission Regulation (EC) No 1234/2008).

This Questions and Answers document sets some general principles about the content and future use of these protocols and will be updated in the light of more experience, particularly for biological products.

2. Scope:

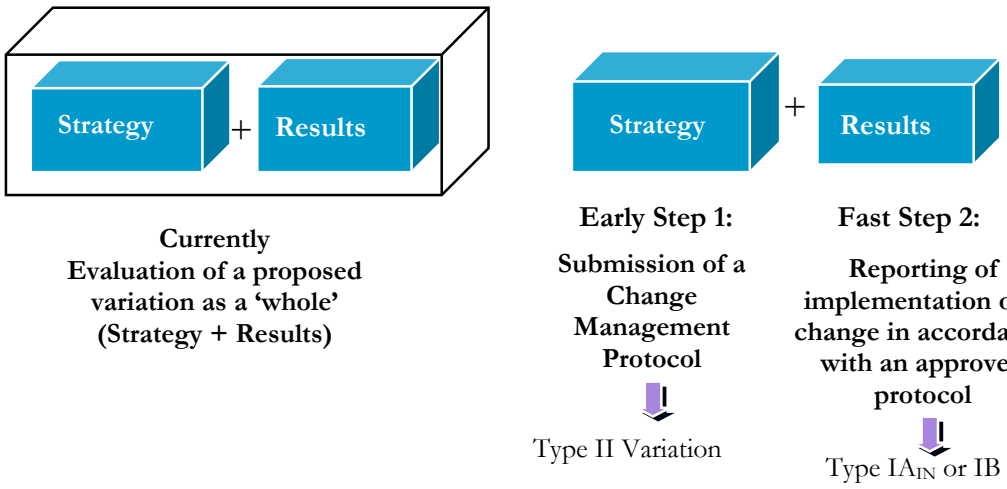
This Questions and Answers document is intended to apply to all medicinal products for human and veterinary use including biotechnological or biological products. It applies to all types of products, irrespective of whether a traditional or enhanced Quality by Design (QbD) approach has been used for product development. The use of Post Approval Change Management Protocols is optional.

3. What is a Post Approval Change Management Protocol?

A post-approval change management protocol describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. It is a step-wise approach in the assessment of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy (Figure 1). Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

Typically the variation category designated for reporting changes under an approved post approval change management protocol is at least one category lower than would normally be the case.

Figure 1: Post Approval Change Management Protocols



4. What should be in the content of a post approval change management protocol?

In general, in order to support the proposed change, the company should submit all relevant information that can demonstrate that it has acquired adequate knowledge to prepare and manage the impact of the change.

The content of the protocol could include the following, depending on the nature of the change:

- Justification that there is a recognised future need for the specific change within a reasonable timeframe and that adequate knowledge has been acquired to define criteria to appropriately evaluate and manage the change for the specific product concerned;
- A detailed description of the proposed change. The differences with what is already approved should be clearly highlighted (preferably in a tabular format). Depending upon the nature of the change, it should be demonstrated, preferably with data from development or pilot scale studies, that the proposed approach is feasible. If only lab-scale data are provided the potential scale up effect should be discussed;
- Risk assessment of the impact of the change on product quality. This should include identification of the potential risks and detailed strategy of how these risks will be mitigated or managed;
- Discussion on the appropriateness of the approved control strategy to identify and manage these risks and, if required, description of the additional controls that might be needed to be put in place. This should take into consideration the extent of the change and therefore the potential impact on the quality of the active substance and/or finished product, as appropriate;
- Description of the studies to be performed, and the test methods and acceptance criteria that will be used to fully assess the effect of the proposed change on product quality[1].The applicant should justify the appropriateness of the methods proposed to assess the impact of the proposed change. Data from development or pilot scale studies can provide assurance about the relevance and adequacy of the proposed tests;
- For biologics, the approach to be used to demonstrate the comparability of the pre- and post-change product;
- A plan for stability studies should be included, if appropriate;
- Commitment to update the approved protocol, if this becomes invalid, due to significant changes to the proposed test methods/acceptance criteria or a significant body of new knowledge or new regulatory requirements;
- In case that the protocol describes several changes, a justification showing that how the changes are related, and that a simultaneous review under a single protocol is meaningful;
- For chemical medicinal products, a proposal of how the implementation of the change will be reported to the relevant competent authorities using the existing variation procedures, e.g., as a Type IA / IAIN variation (implemented prior to notification) or Type IB variation (requires approval before implementation);

[1] Whenever a particular change is investigated it should be evaluated against the specified acceptance criteria in terms of the relevant registered specification(s) and analytical methods at that point in time. It is recognised that these tests and limits may have changed since the original protocol was presented and accepted.
However, the protocol will still remain valid provided the changes to the tests and limits are minor in nature and therefore do not fundamentally impact the basis for the original protocol and have already been formally registered and, where relevant, assessed and approved.

- If a Type IA/ IAIN variation has been chosen, then the conditions that need to be fulfilled by the marketing authorisation holder (MAH) prior to the implementation of the change, as well as a description of the amount and level of detail of the data to be provided, need to be clearly stated;
- If a Type IB variation has been selected, then a description of the amount and level of detail of the data to be provided should be included;

- For biological medicinal products, in accordance with the Variations Classification Guideline, the reporting will always be made as a Type IB variation.

If this is not the case, or if there are other fundamental changes to the protocol, they will need to be separately updated as part of a Type IB variation before the change can be notified. However, in the event that there are minor changes to an approved protocol that has already been agreed to be notified as a Type IA (annual or immediate), where necessary, it will be possible to include the minor changes to the protocol at the same time as the submission to implement the change.

These will need to be notified as Type IB variations and the change cannot be implemented prior to approval.

5. What is the mechanism for the submission and evaluation of a Post approval Change Management Protocol?

A post approval change management protocol may be included in an original marketing authorisation application or (line) extension application, or may be submitted subsequently as a stand alone variation. The Variations Classifications Guideline includes specific scopes for the introduction (Change no. B.1e.2) or deletion (Change no. B.1e.3) of a protocol for the active substance and the finished product (introduction B.2.g.2) (deletion B.2.g.3).

When submitted as part of the original marketing authorisation or a (line) extension application, the evaluation of a post approval change management protocol will follow the rules of procedure applicable to the actual marketing authorisation or extension application.

When submitted post approval, the evaluation of a post approval change management protocol will follow the rules of procedure applicable for all Quality Type II variations with a 60 days timetable.

A change to an already approved protocol will be processed as a Type IB variation, unless it fundamentally changes the content of the protocol. In the later case, the submission of a new protocol would be required. This is very relevant for biological/biotech products where comparability principles apply.

6. How will the change be implemented after all the studies described in the approved protocol have been performed?

A prerequisite for the implementation of a change described in an approved protocol is that all studies described in the protocol have been performed, and the results of the studies comply with the predefined criteria set out in the protocol.

In all cases, a justification that the approved protocol is still valid should be provided, together with the procedure number of the application that led to the approval of the protocol.

In the event that any of the relevant specifications (limits or analytical methods) that are to be used for the evaluation have changed in a minor way since the original protocol was accepted, provided the

changes have in the interim been formally registered, there is no requirement to submit an updated protocol before the change is notified.

However, any changes to the specifications should be clearly highlighted as part of the reporting variation. If this is not the case, or if there are other changes that fundamentally impact the basis of the original protocol, the protocol itself should be formally updated before the change is notified (Type IB variation) or a new protocol should be submitted (Type II variation) Minor deviations to the protocol may be reported and justified in the variation (Type IB) submitted in support of the implementation of the change. However, the change(s) cannot be implemented prior to approval.

The implementation of a change in accordance with an already approved protocol can be made via a Type IAIN or Type IB variation (Change no. B.V.c.1 of the Variations Classification Guideline) depending on whether it requires the evaluation of supportive data.

If a Type IAIN variation has been agreed during the evaluation of the protocol, then the applicant may implement the change without any further regulatory evaluation prior to its approval. A notification of the implementation should immediately be sent to the relevant competent authority.

If a Type IB variation has been agreed during the evaluation of the protocol, or is mandatory, as is the case for biological medicinal products, then the applicant may only implement the change upon receipt of a positive notification from the relevant Competent Authority. In both cases the respective timelines and procedural requirements for Type IA and IB variations apply.

If the same protocol has been submitted for several products changes, the implementation of the change can be made using the existing Grouping and Worksharing procedures.

7. Can applicants submit post approval change management protocols for any type of change?

The types of changes that would benefit from, and consequently could be included in such a protocol, depend on the complexity of the product and its manufacturing process, as well as the understanding that the company has gained about them. It is not possible to set a priori a list of acceptable changes since it depends on the type of the products, and the type of information presented in the dossier. However, protocols should be specific to a product and should therefore not name multiple products, although the proposed change(s) and management strategies may be applicable to other products and processes.

In order for a change to be submitted and accepted as part of a protocol, the company should demonstrate suitable scientific knowledge and understanding of the active/product and the process, coupled with the use of an appropriate quality risk management and an efficient pharmaceutical quality system.

Consequently, it is strongly recommended that companies submit post approval change management protocols only for those changes that they are highly likely to implement and whose feasibility has already been investigated and is supported by relevant data.

For a biological medicinal product where non-clinical/clinical data are needed as part of the comparability exercise, a post approval management protocol will not be feasible.

Changes that should not be submitted in a post approval change management protocol include any change that would result in a (line) extension to the original marketing authorisation.

8. Can a post approval change management protocol cover multiple changes?

It is possible to cover more than one change in a single protocol provided that they are directly related and a simultaneous review under a single protocol is meaningful. A justification should be provided in the protocol.

Depending upon the specific nature of the change(s), it is also possible for the content of a protocol to be applied on more than one occasion, e.g., new manufacturer of active substance starting material. However, this will depend upon successful implementation each time, in line with the protocol. In addition, the possibility will need to be transparent and therefore, if applicable, clearly stated in the protocol itself.

9. Where should the requested documents (description of change/change management protocol) be placed in the application?

The protocol should be included in the marketing authorisation application as part of the Regional Section 3.2.R of Module 3 (or in Part 2.G for veterinary applications). The relevant section(s) of Module 3 (or Part II for veterinary), affected by the proposed change, should cross refer to the protocol.

At the time of submission of the protocol (Type II) only 3.2.R/2.3.R (or Part 2.G for veterinary) is affected. Update of the relevant section(s) of Module 3 (other than 3.2.R) (or Part II for veterinary) is done with the Type I variation to implement the protocol.

A listing of the approved protocols should also be provided and maintained in Module 3.2.R (or Part 2.G for veterinary). This should include a listing of all the protocols with a description of the change, the proposed reporting category and a reference to the relevant section in Module 3 (or Part 2 for veterinary).

10. Are post approval change management protocols applicable to all types of applications?

Change Management protocols are applicable to all types of applications, irrespective of the development approach that has been followed, i.e., traditional or enhanced. However, it is expected that if the applicant has applied Quality by Design principles during product development, then an increased product and process understanding is achieved, thus making it easier to predict the impact of a change on the active substance or finished product quality.