Change Control – Dealing with Changes in Investigational Medicinal Products

by Kerstin Kruithoff-Ley

Changes accompany us throughout our lives. We have to be able to deal with them successfully and use them to our advantage. The manufacture of investigational medicinal products (IMPs) is almost always more complex than manufacturing marketed products. It is rarely a routine matter. Therefore, versatile processes are imperative if manufacturing and testing are to be adapted to a particular, growing level of knowledge. This being the case, does R&D need any formalised change control at all?

What is change? And what is the difference between change and deviation?

Change is a planned, desired modification such as the expansion, exchange, removal, addition or optimisation of requests, regulations, specifications, devices, input materials, methods, processes and parameters. The modification made is prospective (future oriented) and lasting (long-term to permanent).

In contrast to this, deviation is undesired, occurs retrospectively and is unplanned.

Authorities' expectations and GMP principles

The EU GMP Guide in its entirety also applies in principle to the manufacture of IMPs. In addition, Annex 13 lists special GMP requirements that apply to IMPs. However, no provisions for facilitating change control are made.

Moreover, the development of a medicinal product must be seamlessly documented and traceable. This is also true in view of the qualitative differences between IMPs that were used in various different clinical trials. Any change made here is linked to the assessment of the clinical efficacy and safety of the later on marketed product.

It is true that IMPs themselves are not subject to authorisation requirements. However, both the sponsor of a study and the Qualified Person must ensure that the manufacture and testing of IMPs conform to the approval documents for a particular clinical trial. In this context the Qualified Person may only release a batch if the batch documentation was reviewed beforehand. And this documentation must contain all deviations and all planned changes and include the reviews and investigations made as a result.

The health of the patient has the highest priority. The patient shall not be exposed to any risk due to inadequate safety, quality or efficacy of the IMP. That is why changes, particularly when concerning IMPs, must be examined and evaluated with special care.

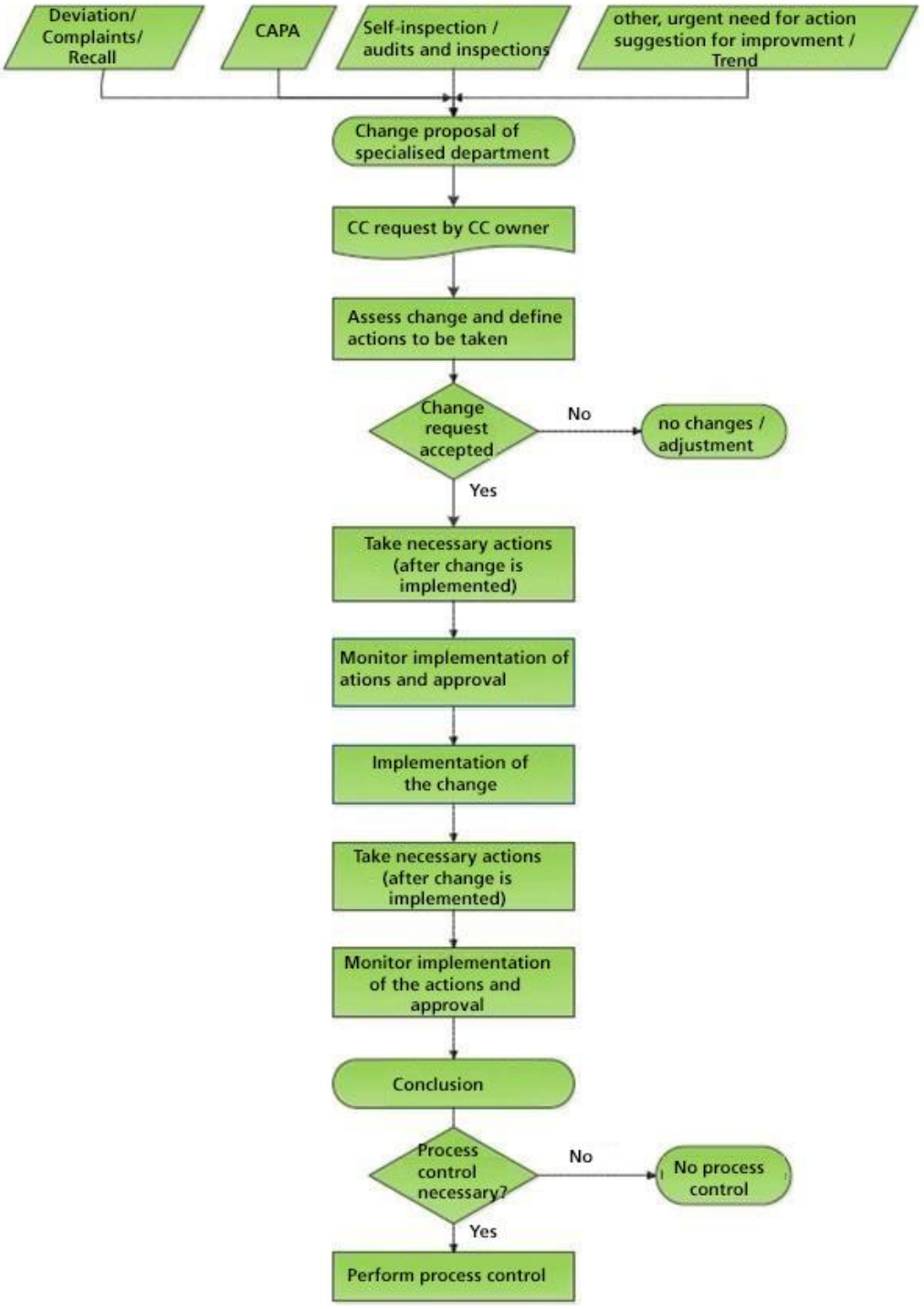
Causes and Motives for Changes

Manufacturing and testing IMPs can be affected by a variety of changes, which may relate to the starting material, product components, process, equipment, premises, product selection, suppliers and service providers, production method, test method, specifications, batch size, storage and transport. (And even this long list is not complete.) The possible causes of the changes are equally varied. They can be motivated internally (e.g., through experience from development, process optimisation, business aspects such as cost reduction, or strategic considerations such as a change in suppliers) or externally (e.g., a change in the supplier's active ingredient specification).

Procedure

Figure 1 shows an overview of the workflow of a change control procedure.

Figure 1: Change control workflow



Change request and assessment

The first thing to do when planning a change is to document it in writing in the form of a change request. Any knowledgeable employee of the material can initiate a change procedure of this kind. Paper-based request forms are available or a database validated in accordance with GMP can be used. To reduce the reluctance of filling out a change request form, the documentation template should have a clear layout and be self-explanatory.

The change request should include the following content:

- Description of the change (generally understandable and complete)
- Reasons (what triggered the change, what alternatives there are, what are the consequences if the change is not implemented?)
- Cost-benefit analysis including an assessment of relevance to quality
- Planned implementation date
- Requester's remarks / proposals for implementation (such as measures to be taken before and after implementation of the change)
- Attachments in support of assessment of the request

The change requests are then further processed by a central functional unit within Quality Assurance. Since change control under the EU GMP Guide represents a key element of the Pharmaceutical Quality System, it only follows that responsibility for process control should be transferred to Quality Assurance.

Changes must always be critically scrutinized with regard to their impact. The important things here are, first of all, whether these changes are relevant to quality and, secondly, whether they are subject to requirements for authorisation by federal authorities or if the authorities at least have to be informed. The cost and effort expended for the change control procedure should be commensurate with the degree of risk of the change. Classifying the change (e.g., low, major, critical) enables precise control of the particular processing expenditure. The assessment is made in accordance with the principles of quality risk management.

Planned changes are then assessed by a special change control committee with management-level members from various functional units who meet periodically, or who alternatively use a circulation procedure to assess the change request. In addition to managerial staff such as the head of Quality Control, head of Production and Quality Assurance, others may also be included from Regulatory Affairs, Sales and Distribution, IT and other specialised departments, depending on the change being planned. Companies frequently involve the Qualified Person in the assessment of a change request. In any event the Qualified Person must take the change into consideration when making a decision on releasing the batch(es). He or she must also ensure that the assessments of the change that affects the batch have been concluded. At the same time it must be ensured that the change is properly reflected in the product specification file and that it is available for release.

Change Follow-Up

As part of process control it is necessary to look into whether the defined objective has been accomplished by the change and to confirm that no negative impact compromises the quality of the medicinal product as a result of the change. Possible measures to take for this are controlling the batch documentation (particularly evaluations of in-process and quality control results), stability tests, evaluating trend analyses or the management review.

In this way it can be verified that the change was successfully implemented and the process is under control. Otherwise, the risk of the change must be newly assessed and additional measures must be taken. If necessary, the change can be expanded or, conversely, even withdrawn.

Summary

Investigational medicinal products (IMPs) are also subject to formalised change control.

Change is defined as a planned and desired modification of a lasting nature that is made prospectively. The patient's health has the highest priority. IMPs must be suitable for their intended use even after a change has been implemented. The manufacture and testing must be carried out – even after a change – in conformity with the approval of the clinical trial and with the product specification file. For the batch release, the Qualified Person must take planned changes into consideration.

In the case of change plans that are triggered internally or externally, management-level staff members are responsible for assessing the proposals with regard to quality, criticality and regulatory relevance, including a possible requirement for approval by responsible authorities. The change proposal is fully and traceably documented.

For the final process control it is necessary to look into whether the objective of the change has been achieved and to verify that no negative impact that compromises the quality of the medicinal product can be found.

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