Guideline for the Establishment of a Control Procedure for Technical Equipment, including related Utilities, Computerised Systems and Facilities used in the Manufacture of APIs and Intermediates (revised Nov.2018)

1. Introduction

The accepted international Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, ICH Q7, requires under §13.10 that "a formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API". The guidance given in this APIC guideline covers only the part concerning technical equipment and related, utilities, computerised systems and facilities.

A formal change control system should be established to evaluate all changes that may affect production and control of the registered intermediate or API. There should be a written procedure in place to evaluate the impact of proposed changes on other possibly affected systems and to approve them.

The justification for the level of criticality (e.g. the decision if a technical change has minor or major impact on the product) should be documented. For example, in form of a risk assessment and it should contain the review, and approval by the appropriate organisational units, and review and approval by the quality unit(s).

As a part of the evaluation process, the need to obtain approval from or to notify the change to authorities and/or customers, must be evaluated. The need to requalify the equipment and eventually to potentially revalidate the process must be assessed and documented.

In case there is an impact on the qualification documentation (e.g. IQ, OQ, PQ), the affected documents should be listed, reviewed and updated and the timelines for their approval defined.

All the documents should be archived as necessary in compliance with the company's policy on document retention, to demonstrate the history of the changes that took place on the equipment.

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3. Objective of the guideline

3.1 Purpose

This document is intended to provide guidance for technical change control of equipment and related utilities, computerized systems [e.g. Process (PLC) and Distributed Control Systems (DCS)] and facilities for the manufacturing of active pharmaceutical ingredients (APIs) and Intermediates. In the following text, this is referred to as
“technical equipment”.
This guideline is based on the requirements of the ICH Q7 and industry best practices. Other relevant publications (see Appendix) were considered.

This document provides an example of commonly applied solutions and practical assistance on how technical change control can be handled and/ or interpreted. It is not intended to provide an exhaustive list of “how to do” technical change control, which a company should develop subsequently. Adoption of this guidance will provide companies with the confidence to have accomplished, with the minimal requirements, a change control system for technical equipment.

3.2 Scope

This guidance applies to technical equipment, used in the manufacture of APIs and intermediates for use in human drug (medicinal) products. It does not include Analytical Equipment.

4. Definitions

Change Control
A system to propose, review, justify, evaluate, document, implement, approve, and close changes to technical equipment used in the manufacture of APIs and intermediates to ensure a constant qualified status of the systems concerned.

Emergency change
An unplanned change of a piece of equipment as a result of an emergency, which needs to be repaired immediately in order to maintain personal or environmental safety or preserve the quality of the product.

"Like for like" Change
Replacement of a piece of equipment by another with identical characteristics and function (same material of construction, size, type, etc., but not necessarily from the same manufacturer). The fact if equipment is like for like needs to be thoroughly reviewed, justified and recorded with written approval of the Process Owner, QU and if applicable Regulatory Affairs. These changes can be considered minor impact changes.

Major impact changes
A change expected to have a potential impact on product quality. Changes with an uncertain impact level should be handled as major impact changes.

Minor impact changes
A change not expected to have an impact on product quality. Also called Standard change.

Process owner
The person who has the ultimate accountability for the system which is subject of the proposed change.

Quality Unit (QU)
An organisational unit independent of production that fulfils both Quality Assurance and Quality Control responsibilities.

Standard Changes:
See minor changes.

Technical Change
A technical change is a planned modification (expansion, replacement, removal, addition) with respect to qualified equipment (defined state of a piece of technical equipment).

Technical Equipment:
Manufacturing equipment, utilities, computerized systems [e.g. Process (PLC) and Distribution and Control Systems (DCS)] and facilities used in the manufacturing of APIs.

5. Impact of Changes on affected Systems

Important repairs and maintenance work, such as replacement of major parts of equipment, may affect the performance of the process and the quality of the product.

Rearrangements in manufacturing areas (for example rooms with defined environmental conditions) and/or support systems (utilities, e.g.: HVAC systems, systems for water, steam, CIP/SIP-systems) may result in changes in the process and therefore, revalidation/requalification may be necessary.

6. Responsibilities

6.1 Process owner

6.1.1 Responsible for technical changes and to follow the valid change control procedure.

6.1.2 Decides about the impact of the technical change on product quality (major/minor impact). The participation of the QU in this decision should be clearly established according to the company procedure in this matter.

6.1.3 It is recommended that the process owner should prepare a list of changes with minor impact on product quality (standard changes).

6.1.4 Every technical change with major impact should be assessed by the Process Owner.

6.2 Quality Unit (QU)

6.2.1 The involvement of the QU is required to decide if the change has, or potentially will have, impact on the product quality.

6.2.2 The QU is responsible for the implementation and maintenance of the change control system.

6.2.3 The QU must approve the minor or standard changes list. The QU needs to make sure the minor changes list is up-to-date, and re-approved whenever minor changes are added or removed from the list.

6.2.4 Every technical change with major impact should be assessed at least by the QU.

6.2.5 The QU is responsible for periodical evaluation of the system and its effectiveness

6.3 Regulatory Affairs (RA)

6.3.1 Every technical change with major impact should be assessed at least by RA. RA is required to assess the potential impact on regulatory filing. RA decides about the measures to be taken to document the change appropriately. In case an approved change has impact on regulatory filing it is the responsibility of the RA department to take appropriate action.

6.4 Technical Department (TD)

6.4.1 The TD is required to evaluate and approve the (technical) impact of a proposed change.

7. Criteria for criticality

Some typical questions that can help further to decide whether technical changes are major or minor, are given below:

If the component to be changed…

- can directly contact the product or product components, and is not considered a like for like change;
- can directly affect the product quality by normal operation or control (e.g., impurity profile, crystal form and size, residual solvent or stability of the API);
- indicates and records alarm functions critical to the process;
- is used to record, output or archive data for batch records or labels and other GMP documentation or labels;
- is used to demonstrate compliance with the registered process;
- can influence the quality and performance of support systems (e.g., water, steam, HVAC, etc.);
- is used to ensure access control to critical data or functions (user identification and authenticity);
- is used to perform analytical investigations that are relevant for batch release;
- is used for critical calculations (e.g., analytical data that are relevant for batch release);
- is used for batch release;
- is used to control batch status or shelf life;
- is used to control the production process (recipe/process description);
- is used to transfer critical data (interface) to another quality relevant system;
- is used to give information about the quality of the product (e.g. printers for process related data);
- is used to ensure or record critical conditions for warehouses;
- is used to control maintenance or calibration of critical equipment;
- is used to create, modify, record, document, review, approve GMP data;

…then, the change may have a potential impact on product quality and should therefore be carefully assessed and reviewed, considering traceability to design base risks, before implementation. These changes are considered major.

8. Procedure

8.1 The procedure should always begin with a request for a change. This request should be formalised in some way, for example as a form in paper or electronic form and be signed by the requestor.

8.2 The request triggers the question of the potential impact of the change on the product quality. It can be necessary to define several levels of impact on the

product quality, but it is recommended there should be at least two categories: major and minor impact. The treatment of these two options should be clearly different and defined as part of the local process.

8.3 There should be clear rules for the decision, whether the impact of the change on the product quality is major or minor: who decides and why the decision is taken (See under 6 and 7). All included in the decision (Process Owner, QU, RA, TD) need to sign for approval of the decision. If other aspects are affected by the change, other department need to be involved as well. For example, safety aspects, could require EHS department to be involved. Or Computerized System changes could need involvement of Subject Matter Experts.

8.4 For the management of changes, an early decision is required of who should be involved. The decision should be taken (and recorded on the change request) by the process owner, who normally has the best knowledge of the impact of changes on the product (or at least can estimate it with a high degree of certainty). The principle of double checking should be implemented at this point of the procedure. A signature by the Technical Department is first required. The QU should be involved as an approver to check the decision about product quality impact (unless the proposed change matches a pre-approved minor change in the list of minor or standard changes. RA should be involved to assess the potential impact on regulatory filing.

8.5 If the owner has decided that the change will have minor impact on the quality of the product, and all included in the decision (Process Owner, QU, RA, TD) agree with this decision, it can be implemented. The change should be adequately documented.

8.6 The implementation of changes with minor impact can be achieved in a more rapid and efficient manner using check lists of standard changes. The list of these changes should have been (pre)approved by the QU.

8.7 If the decision has been taken that the change can or will have a major impact on the quality of the product, the QU must be further involved. An adequate rationale (e.g. a risk assessment) and an appropriate action plan should accompany such a change request. This builds the basis for the approval by the QU.

8.8 After the QU approval, the change can be implemented. If other aspects are affected by the change, for example regulatory filing or safety aspects, additional release activities can be needed. Where such activities have been defined, these should be fulfilled before the reuse of the equipment. Release of the equipment itself, can be one of these activities.

8.9 The start of a change control system for technical equipment should be established immediately after the completion of qualification. This will ensure that the qualified status is maintained.

8.10 There shall be a process in place to manage changes that may occur during the qualification.

8.11 The change request for emergency changes can be formalised after the replacement. Emergency cases should be defined by each company in an appropriate way.

9. Appendix

9.1 List of relevant Guidelines

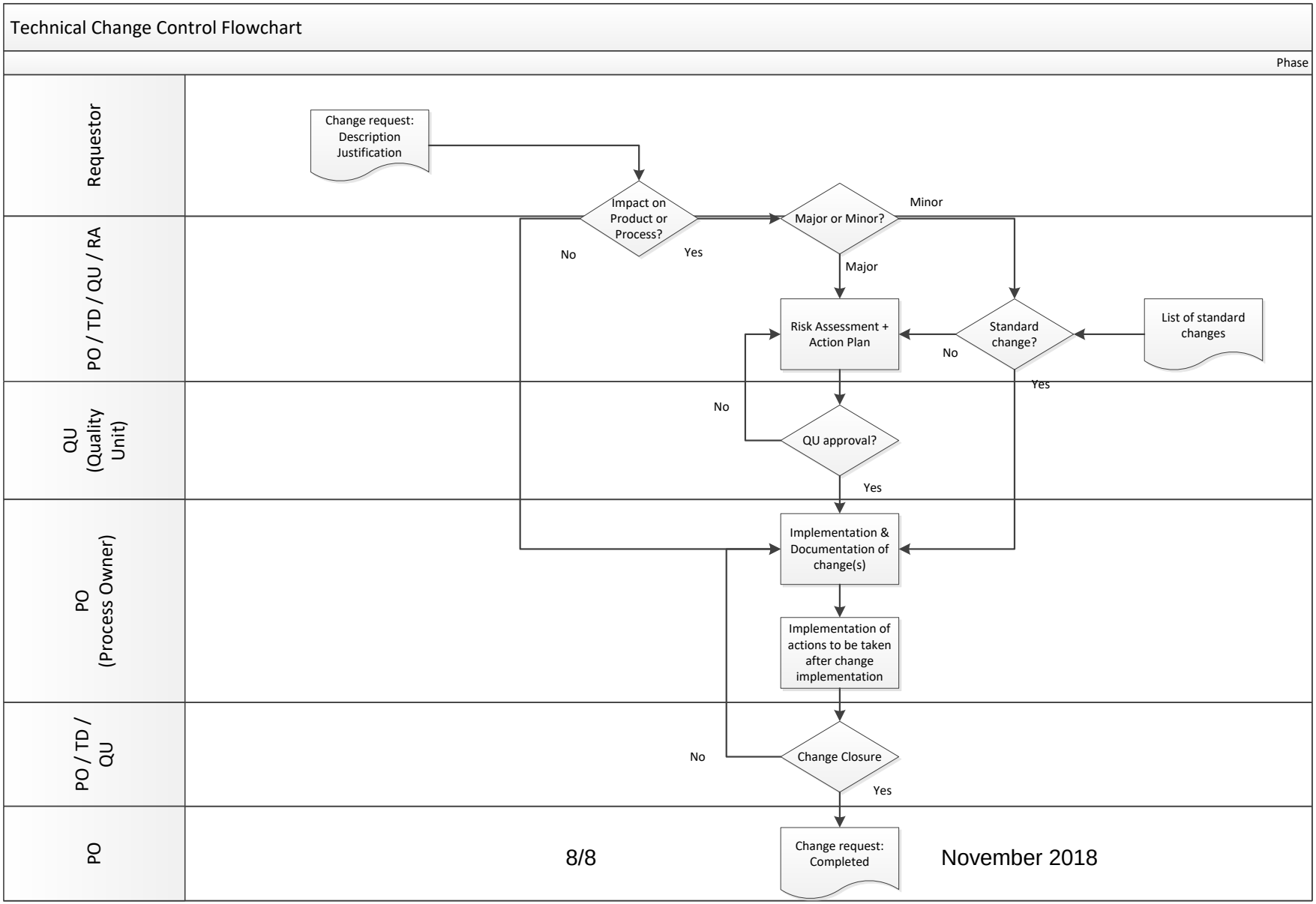
1. ICH, GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS Q7 (CPMP/ICH/4106/00), 2000
2. ICH Q7 Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients - Questions and Answers, June 2015
3. Pharmaceutical Inspection Co-Operation Scheme PIC/S PI 006-3, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S Secretariat, Geneva, September 2007.
4. ISPE Commissioning and Qualification Baseline Guide Volume 5.

9.2 List of Abbreviations

- API = Active Pharmaceutical Ingrdient
- CIP = Cleaning in Place
- DCS = Distributed Control System
- EHS = Environment Health & Safety
- HVAC = heating, ventilation, air conditioning
- PO = Process Owner
- PLC = Programmable Logic Controller
- QU = Quality Unit
- RA = Regulatory Affairs
- SIP = Sterilisation in Place
- SME = Subject Matter Expert
- TD = Technical Department

9.3. Enclosure

Scheme of the procedure


Technical Change Control Flowchart
Phase
Requestor
PO / TD / QU / RA
QU (Quality Unit)
PO (Process Owner)
PO / TD / QU
PO
Change request: Description Justification
Impact on Product or Process?
No
Yes
Major or Minor?
Minor
Major
Risk Assessment + Action Plan
Standard change?
No
Yes
List of standard changes
No
QU approval?
Yes
Implementation & Documentation of change(s)
Implementation of actions to be taken after change implementation
No
Change Closure
Yes
Change request: Completed