Guideline for the Establishment of a Control Procedure for Technical Equipment, including related Utilities, Computerised Systems and Facilities used in the Manufacture of API's

1. Introduction

The accepted international guideline for the production of API's, ICH Q7A, 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 paper 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 intermediate or API. There should be a written procedure in place to evaluate the impact (e.g., regulatory 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 signature of the responsible persons (mandatory for the process owner, optional for the quality unit, QU [1]).

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

In case there is an impact on the qualification documentation, it should be reviewed and updated (e.g. IQ, OQ, PQ). In this case, QU release can be required before using the equipment after change.

All documents should be archived as necessary to demonstrate the history of the changes that took place on the equipment.

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[1] see section 8 "Procedure"

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 Distribution and Control Systems (DCS)] and facilities for the manufacturing of active pharmaceutical ingredients (APIs). In the following text, this is referred to as "technical equipment".

This guideline is based on the requirements of the ICH Q7a and practical experiences. Other relevant publications (see Appendix) were taken into account.

This document provides examples 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 for use in human drug (medicinal) products. It does not include Analytical Equipment.

4. Definitions

Change Control

A system to evaluate, document, approve and implement changes to technical equipment used in the manufacture of APIs to ensure a constant qualified status of the systems concerned.

Technical Change

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

Major impact changes

A change expected to have an 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.

"Like to 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).

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.

Process owner:

The person who has the ultimate responsibility 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.

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[2]-systems) may result in changes in the process and as a consequence, revalidation/re-qualification may be necessary.

[2] see section 9 "Abbreviations"

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 prepares a list of changes with no impact expected on product quality (standard changes).

6.2 QU

6.2.1 The involvement of the QU is required if the change is thought to have, or potentially 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 has to approve the standard changes list.

6.3 Process Owner and QU

6.3.1 Every technical change with major impact should be assessed at least by the Process Owner and the QU. They should decide about the measures to be taken to document the change appropriately.

7. Criteria for criticality.

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

If the component to be changed…

- can directly contact the product or product components and the change is not a "like to like" one;
- 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;
- 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;

...then, the change may have an impact on product quality and should therefore be carefully assessed and reviewed before implementation.

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, and be signed.

8.2 The request triggers the question of the impact of the change on the product quality. It can be necessary to define several levels of impact on the product quality but there should be at least two categories: major and minor impact. The treatment of these two options should be clearly different.

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 8.6 and 8.7).

8.4 For the management of changes, an early decision is required of who should be involved. The decision should be taken 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. Depending on the company's procedure, the QU can be involved as an approver (to check the decision about product quality impact) or to check periodically by self inspection audits.

8.5 If the owner has decided that the change is minor and there is no likely impact on the quality of the product, it can be implemented. The change should be adequately documented.

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

8.7 If the decision has been taken that the change can or will have an impact on the quality of the product (Major Change), the QU has to be 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 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 after the completion of qualification. This will ensure that the qualified status is maintained.

8.10 Change control before completing qualification need not possess the same degree of formality as it can be easier regulated and can proceed without the formal and immediate involvement of the QU. The required activities in this case are adequate documentation of the changes and a periodical adaptation of the documentation.

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. International Conference on Harmonisation, Good Manufacturing Practice for Active Pharmaceutical Ingredients (CPMP/ICH/4106/00), 2000
2. EC Guide to Good Manufacturing Practice for Medical Products and Active Pharmaceutical Ingredients, compiled and edited by Gert Auterhoff, 4th. ed., Editio Cantor Verlag Aulendorf, 2002
3. Pharmaceutical Inspection Co-Operation Scheme PIC/S PI 006-1, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S Secretariat, Geneva, August 2001.
4. Deutscher Inspektionsleitfaden – Aide Mémoire – Inspektion von Qualifizierung und Validierung in Pharmazeutischer Herstellung und Qualitätskontrolle (07121103), EFG 10, Dez. 2001.

5. ISPE, Guides for New Facilities, Vol1, Bulk Pharmaceutical Chemicals, 1st. ed, June 1996.

9.2 List of Abbreviations

- API= Active Pharmaceutical Ingredient
- CIP= Cleaning in Place
- HVAC= Heating, Ventilation, Air Conditioning
- IQ= Installation Qualification
- OQ= Operational Qualification
- PQ= Performance Qualification
- QU= Quality Unit
- SIP= Sterilisation in Place
- SOP= Standard Operation Procedure

Enclosure: Scheme of the procedure

Scheme for Technical Change Control