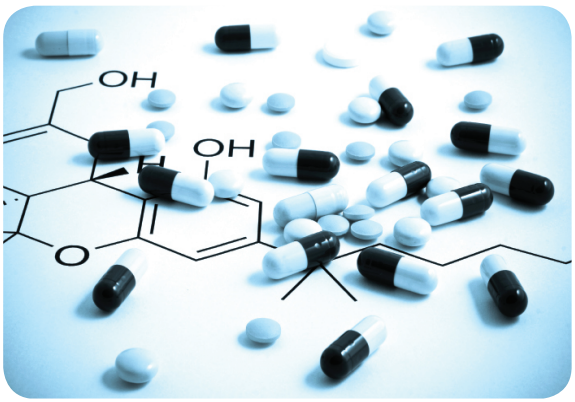


NMR in Pharma: The Principles of Change Control

Ian Clegg, Regional Market Manager
Bruker BioSpin

Change is an inevitable phenomenon especially in the pharmaceutical industry where, with the advent of new technologies and know-how, machines and manufacturing processes drive improvement in manufacturing and operational efficiencies.

Change refers to any modification of equipment, manufacturing materials, facilities, utilities, design, formulations, processes, packaging/labelling systems, computer systems and all associated documentation (e.g. SOPs, the quality manual, quality policy documents…etc.).

Many changes typically occur during operations, in late stage development, and also during manufacturing, and all of these changes need to be formally assessed and approved by an expert team, prior to implementation. The change control process overall, together with the details of any individual change, are subject to review by regulatory authorities. In manufacturing, some changes are considered to be post-approval changes (or variations) and they need to be approved by the respective regulatory authorities; if this is not done properly, it puts the marketing authorization holder and/or manufacturing license holder at risk.

Proper management of change(s) is critical, and proper change management reduces the risk of suspension of licenses and the issuing of a warning letter by the regulatory authorities.

Definition of Change Control

Change control (CC) is a cGxP (Current Good laboratory / Manufacturing Practice) concept that focuses on managing all changes made to a product or a system to prevent unintended consequences. The purpose is to ensure that a change to a system is introduced in a controlled and coordinated manner, that all changes are documented, and that resources are used efficiently.

A useful formal definition of CC is available in the glossary to Annex 15 of the EU GMP Guidelines[2]: "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 and processes. The intent is to determine the need for action to ensure that the system is maintained in a validated state".

A well-established requirement for companies that operate under GxP conditions, is that a robust change control system is implemented and maintained. Pharmaceutical companies are required to control any change to established processes, meaning the changes must be reviewed, recorded and approved by the QA/QC (Quality Assurance/Quality Control) department.

[1] In this documents, the term GxP is used, and this may mean either Good Laboratory Practice (GLP) or Good Manufacturing Practice (GMP)
[2] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf. Retrieved January 2019

For any proposed change, a risk analysis is performed to determine what action(s) need to be taken in order to mitigate any potential effects of that specific change. Proposed changes should be evaluated by expert teams contributing appropriate expertise and knowledge from relevant areas (e.g. Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs) to ensure that the change is technically justified.

Classification of Changes

Changes may be classified as Major or Minor, depending on the nature and extent of changes and the potential impact on the process overall. Changes that are deemed to have no impact on GxP, should also be formally written up and the decision recorded.

At the other end of the scale, changes that are determined to have a higher potential for impact are dealt with by progressively more robust and detailed measures, included detailed risk assessments, experimental verification, and engineering changes.

The brief summary table below illustrates the basic principles of such an assessment, including how typical examples are graded.

	Classification		
	Major change	**Minor change**	**Change Control not required**
Example of Proposed Change	■ Change to the formulation of a product. ■ Relocation of the manufacturing unit to another site. ■ Major Change to the synthetic route. ■ Replacement of a piece of manufacturing plant with a new design.	■ Replacement of a pump with one of the same design. ■ Modification to an existing analytical system. ■ Modification to cleaning agents used for non-production areas. ■ Working with a new supplier of gowning materials (assuming they have the same specifications).	■ Modification of the Terms and Conditions of the employees. ■ Changes to an electrical drive in a non- production area. ■ Modification to an administration building. ■ Changes to a road layout on site. ■ Change in purchase procedure.
Basic concern(s) over the proposed change	Affects process robustness (reliability) and/or product quality	Affects a processing unit or support system	No relevance to GxP or authorization
Potential Actions	■ Seek regulatory approval. ■ Carry out a re-validation of the process	■ Review exiting documentation. ■ Amend the documentation as appropriate. ■ Re-write the documentation.	■ None required other than to document the decision taken

Key Benefits of the Change Control System

The following are the key benefits in using a change control system:

- Structured and consistent approach towards managing change
- Documenting the details of the change(s)
- Routing of change requests to appropriate individuals/ team(s) for approvals
- Documentation of change approvals and implementation
- Maintenance of change history and easy retrieval of information
- Tracking changes effectively and providing an audit trail
- Demonstrate compliance with FDA regulations

Examples from FDA Warning Letters

It is also clear that CC is a strong focus for the regulators during their on-site inspections, as shown by the general comments and negative findings that appear regularly in the warning letters that are publicly available on the FDA web site[3] (see below for typical extracts from a couple of recent warning letters).

Example extracts from a FDA warning letter (the calendar year is indicated in each document clip):

2018

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Your quality unit failed to exercise its responsibility to review and approve test results before batch release. Instead, your quality unit released your non-sterile over-the-counter (OTC) finished drug product, (b)(4), before you received assay (% content) results for the active ingredient, (b)(4), from your contract laboratory.

Further, your quality unit lacked adequate systems and documentation to oversee quality, including insufficient:

- change control;
- quality control testing practices;
- batch record review; and
- annual product reviews.

2016

3. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance (21 CFR 211.100(b)).

Our investigator discovered that your firm was destroying original batch records and backdating revised replacement pages. For example, our investigator found original pages from five (b)(4) batch records (batches (b)(4) to (b)(4)) discarded outside your facility. Your quality control unit approved revised and backdated master batch record pages that your firm created to replace the discarded pages. The original data were subsequently transcribed and backdated to the time of production. Quality and production managers allowed this practice.

Your response indicated that your firm would not permit backdating in the future and that you would revise procedures to ensure reissued batch record pages are documented in the incident report register and a change control would be initiated for any minor editorial changes. In response to this letter, provide copies of the revised procedures and an assessment of how widespread the practice of revising and backdating batch records is.

In FDA and ISO environments, strict adherence to approved policies and procedures is a key factor in keeping manufacturing operations in a state of control; it is what makes change control crucial. All changes should be made according to approved, written company policies and procedures.

[3] https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm. Retrieved January 2019

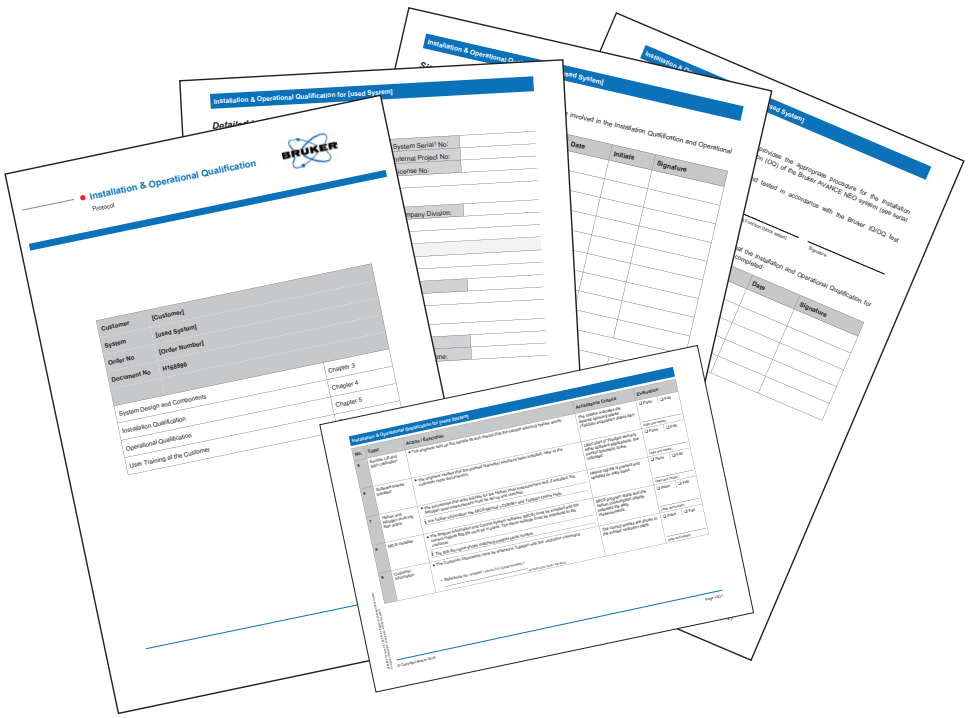
Bruker BioSpin "GxP Readiness Kit"

The fine details of the implementation of CC, together with the associated management oversight, vary between different companies, and it is therefore impossible for a vendor to be prescriptive about exactly how to actually deal with a change in an NMR system.

Bruker BioSpin has dealt with this situation by offering a "GxP change control assistance kit", which includes an Operational Qualification (OQ) Protocol and a Computer System Validation (CSV) Protocol. These are completed on site by a fully qualified Bruker BioSpin service engineer, working in close collaboration with the site-based team.

Typically, the trigger for purchasing the CC kit includes significant changes to the NMR system such as re-location of the system, software updates, console upgrade etc. Once completed and signed off by the installation team, QA and other individual and teams as defined by an SOP, these documents then form part of the documentation system that supports the compliance status of the NMR system employed on site.

Figure 1



Example pages from the Bruker BioSpin IQ / OQ protocols

www.bruker.com
Bruker BioSpin
info@bruker.com