



Change management: common failures and a checklist for improvement

Though the pharmaceutical and clinical supplies industries have improved their change management processes, there is still opportunity for improvement. In the absence of regulatory guidance on change control and deviation, inefficient and risky change management systems still exist and are evidenced by the issuance of many FDA Warning Letters. The trend towards electronic, automated and enterprise-wide change management systems will, however, see this situation continue to improve.

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In the pharmaceutical industry, a change and deviation management system (CMS) is a central part of the overall quality management system for drug product manufacture — often referred to as the pharmaceutical quality system. In accordance with the ICH Q10 guideline, also supported by the FDA, CMS is one of the four key elements that make up a pharmaceutical quality system (the remaining three elements include process performance and product quality monitoring system; corrective action and preventive action (CAPA) system; management review of process performance and product quality).

According to the FDA and International Conference on Harmonisation (ICH), a formal CMS should be established to evaluate all changes that could affect the production and control of the drug product, intermediate or API in a pharmaceutical

manufacturing company. In addition, some level of CMS is also expected by the FDA for the production of clinical supplies; any changes in the production process and product formulation after the production of the phase III clinical batch must be tightly controlled and carefully evaluated from a product equivalency perspective. Significant process, formulation or equipment changes after the production and use of the phase III clinical batch could result in the performance of lengthy and costly bioequivalency and safety studies, and cause a delay in FDA product approval.

FDA requirements and typical failures

Although the cGMP regulation for drug products (21 CFR 211) has no direct reference to change control, change control is implied in 211.100(a) and

211.160(a). 211.100(a) requires that changes in production procedures and process controls be reviewed and approved by the appropriate organisation units and the quality control unit. This was a major component of Warning Letters issued by the FDA between 2007 and 2009. 211.160(a) requires a similar review and approval for changes related to laboratory controls, sampling plans, specifications, and analytical test methods.

The FDA considers change control a very critical GMP compliance issue; therefore it has been one of the main criteria used by the agency in determining their drug inspection depth and coverage, and their decision for follow-up regulatory actions (e.g., Warning Letter issuance). The FDA's strategy for drug inspection and follow-up is evidenced in their systems inspection programme introduced in 2002 for drug product inspection, and in 2006 for API inspection. The FDA compliance programme for drug product inspection (CP7356.002) instructs the FDA investigator to select the comprehensive inspection option when changes have been made that could impact cross-contamination control, or when there had been changes in technology, new facilities or equipment. The FDA compliance programme for API inspection (CP7356.002F) has the same requirements for the performance of a comprehensive inspection, along with additional criteria for changes related to starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials or computer software. Both compliance programmes instruct the FDA district office to recommend regulatory actions when there is a

pattern of the failure to establish or to follow a CMS.

Typical major GMP deficiencies related to CMS include:

- The failure to evaluate FDA filing requirements; i.e., whether to file for a prior approval or changes being effected, or to report the change in the next annual report.
- The failure to file changes with the FDA.
- The failure to evaluate and/or justify whether equipment/system requalification is needed to support an equipment/system change, and whether process revalidation, stability studies or equivalency studies are required to support a process and/or processing parameter change.
- The inadequate review and approval of the change by the quality control unit.

The FDA expects the intimate involvement of the quality control unit in the change control review and approval process, and usually holds the quality control unit responsible for deficiencies regarding change control, which again can be evidenced in several Warning Letters issued in the past years. One example of this FDA expectation was documented in a Warning Letter issued by the FDA in 2003. A company performed a routine replacement of the filling pump pistons, without filing a change request because it was a "like to like" replacement (which has been a typical industry practice). Although the replacement pistons had the same part number as the original pistons, they were slightly longer. This longer dimension caused the pistons to come into contact with the bottom of the filling blocks, resulting in the generation of metal particles, which contaminated the product batches. This metal contamination resulted in

the recall of several product batches and the FDA's issuance of a Warning Letter. The Warning Letter stated that: "Prior to changing the filling line pump parts on the...line, the quality control unit failed to properly assess the impact that the change may have on the product. It is the quality control unit's responsibility to review any change to your manufacturing process and to assure the change will not adversely affect the drug product".

CMS track record

When researching the subjects and the number of FDA Warning Letters issued, the pharmaceutical industry has, in the past decade, learned how to comply with change management and change control. Opportunity for improvement though still exists as Warning Letters as described above are still issued on this implied GMP requirement. No specific CMS guidance is mandated for pharmaceutical or clinical supplies companies, which leaves these companies to experiment with various approaches and systems; recent studies reveal that change is still tackled on a plant-specific and even project-by-project basis, a relatively resource-intensive and impractical approach.¹ In addition, change management processes are often still controlled manually, i.e., paper-based, or by a combination of both paper-based and digital CMS (i.e., hybrid) and with a decentralised solution compared with an enterprise-wide, centralised solution. This makes control, visibility and quality control unit action on change control and deviations rigid, if not impossible.

Paper-based quality management systems are fairly common especially in mid-sized FDA-regulated pharmaceutical companies as well as the clinical supplies industry.

Table 1: Application of CMS throughout product lifecycle.

Development	Technology Transfer	Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should increase as the product moves through development.	The CMS should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal CMS should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate CMS (i.e. backup procedures for archival etc.)

While such systems can successfully manage product and process quality, they can significantly increase the risk of GxP and especially GMP non-compliance. They also impede a pharmaceutical manufacturer's ability to implement continuous improvement initiatives in process and products. Finally, paper-based systems can potentially become a bottleneck to fast growth and capitalising on investments.

Overall, the pharmaceutical and clinical supplies industries still have difficulty in planning and executing GxP, and especially GMP-based change management practices according to their quality manual or equivalent documentation approach. In our opinion, depending on type and size, the number of changes in a pharmaceutical facility can range between 30 and 175 a month; these numbers stress the need for efficient management if randomness is to be removed. Randomness and lack of control exists, which causes non-compliance; approximately 40% of regulatory issues, including warning letters, regulatory inspection observations or compliance observations (CAPA etc.) are attributed to changes.²

How to implement an effective CMS

To properly evaluate, approve and implement changes, pharmaceutical and clinical supplies companies (after the production of the phase III clinical batch) should have an effective CMS

that ensures continual improvements are undertaken in a timely, prioritised and effective manner while providing a high degree of assurance that no unintended consequences of the change exists (In the absence of FDA guidance on CMS, however, valuable inspiration can be found at a rather untraditional federal agency — The US Occupational Health and Safety Administration using 29 CFR 1910.119, Process Safety Management, a section that offers a useful model for pharmaceutical companies for managing change).

The CMS should include the following as appropriate for the stage of the product lifecycle (**Table 1**):

- Quality risk management should be used to evaluate proposed changes (e.g., using ICH Q9³). The level of effort and formality of the evaluation should be commensurate with the level of risk and there should be an assessment to determine whether a change to the regulatory filing is required under regional requirements.
- All changes should be properly evaluated. Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. As stated in ICH Q8, movement within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's CMS.
- Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., pharmaceutical development, manufacturing, quality, regulatory affairs and medical) to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set.
- After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.
- Regional regulatory submission/approval requirements should be

assessed for a proposed change to a marketed product.

The CMS should ensure that the level of documentation and effort is matched to the level of risk associated with the change. Specifically, companies should ensure that the CMS:

- is linked (and thus fully integrated) to other quality systems such as CAPA, customer complaints, validation, etc.
- includes criteria to evaluate whether changes affect a regulatory filing
- includes evaluation criteria for determining if changes are technically justified
- contains procedures for confirming and validating that the change has occurred, the objectives were achieved and that there were no unintended consequences
- develops a change management tracking system to facilitate effective change control, e.g. on training (training is often not integrated with change).

Significant organisational and cultural barriers should also be addressed. Teams should meet often instead of once a quarter or less, and these teams should use an appropriate set of metrics to track changes and drive process improvements.

To effectively deal with these basic CMS requirements, life science companies need to be more agile and, as such, have a well-organised, enterprise-wide response to change. Ideally, effective management and structuring of product- and process-engineering change can lead to reduced cycle times, quick responses to changing market conditions and increased rates of product innovation. Companies applying an integrated approach to managing change can innovate more quickly, promote compliance with global and regional regulations and better support a profitable, enterprise-wide response to innovative and effective production processes as well as customer demand.

A new paradigm for managing change in an ideal environment is electronic-based CMS; a solution that smoothly complies with the above mentioned requirements and

The author says...

- A formal CMS should be established to evaluate changes that affect production and control of a drug product, intermediate or API.
- The FDA considers change control a very critical GMP compliance issue, but no specific CMS guidance is mandated for pharmaceutical or clinical supplies companies.
- Companies should have an effective CMS that ensures that continual improvements are undertaken quickly, while also providing assurance that no unintended consequences of the change exist.
- To effectively deal with basic CMS requirements, companies should seek to implement electronic, automated and, where applicable, enterprise-wide change management systems.

provides a means of bypassing potential barriers and obstacles.

IT-based CMS solution checklist

An electronic based CMS should:

- Digitise and centralise information so that associates can find the organised information they need, when they need it. It should also manage almost any type of file required throughout any of the GxP processes.
- Automatically route documents, seek the appropriate approvals/electronic signatures, have incorporated notification and escalation procedures, search for documents and retrieve them.
- Provide revision control that is automatic and centralised so that once submitted, documents can be routed and approved quickly and effectively. Change tracking will also be automatic. This will enable annual compliance reviews (CR-cases closed, logbooks reviewed, all complaints properly managed, internal audit reports closed etc.) to be done by a notification report.
- Professionals should look for a solution that is customisable to a company's needs and that requires form explanations for changes that are being made.

In summary

There has been a significant improvement in change management in the pharmaceutical industry over the last decade. The industry is on the right track and

performs relatively better than it did up to 5 years ago when ineffective change management was responsible for the issuance of a significant portion of FDA Warning Letters.

From a strategic point of view, however, there is still an opportunity for improvement. Fortunately, the changing dynamics of the pharmaceutical industry now reveal a trend towards a new strategic paradigm in favour of electronic, automated and, where applicable, enterprise-wide change management systems. The trend is also forecasted for the clinical supplies industry. This approach provides top management, quality executives and engineers with instant access to the status of any change request, i.e., real-time transparency on trivial but formerly time-consuming details (e.g., who has reviewed the revised document, who is sitting on the approval request and needs to be prompted, and who else needs to review it). The cycle time of review is therefore significantly reduced once the process is automated. Using this new approach also enables out-of-specification problems, non-conformance issues and corrective actions to be tracked automatically, allowing users to have full access to details relating to non-conformance issues that have not been resolved or corrective actions that are waiting to be implemented. [PTE](#)

References

1. European Compliance Academy
www.gmp-compliance.org
2. FDA
www.fda.gov
3. ICH, Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Quality Risk Management Q9
www.ich.org

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