

## PART II

### Post Approval Change Reporting Requirements to Regulatory Authorities, EMA and FDA

Inadequate management of deviations, not conducting adequate investigations and failure to identify probable root cause, remain near the top of the list of common observations in inspection reports and in warning letters. This has not changed much over the past decade. These observations or deficiencies are frequently followed by failure to implement corrective and preventive actions and to confirm that those actions are effective.

But for a moment, let's assume that deviations or trends requiring attention have been identified, appropriate investigations have been performed, and a root cause or probable root cause assigned. As appropriate, both corrective and preventive actions are identified with criteria and a timeline for measuring their effectiveness. Implementation of at least some corrective and preventive actions are accomplished through change control. Change control is also a component of continuous improvement expected in a modern pharmaceutical quality system. Changes may be made to decrease process and product variability, increase process robustness, increase purity and safety, or increase manufacturing efficiency. Thus, change control is a key process within the quality system.

Two high level considerations come into play when planning and implementing a change in pharmaceutical manufacture and testing:

1. What is the potential impact of the change(s) to drug safety, identity, strength, potency and quality?
2. Does the proposed change represent a change to the DMF / NDA / ANDA / BLA described site and process of manufacture and testing and how must the change be reported to regulatory authorities?

The two high level considerations is described below. This is not meant to provide an all-inclusive listing of considerations for making change but rather meant to provide a starting point for discussion and appreciation for the important part change control plays in a modern pharmaceutical quality system.

#### **1. What is the potential impact of the change(s) to drug identity, safety, efficacy and potency?**

So you want to make a change to address a corrective or preventive action, decrease process variability, increase product purity and safety or increase efficiency. What do you need to consider? At a minimum, changes should not be made "just because we can" but rather should be driven by a specific need. In all cases, firms should evaluate the return on investment remembering that the return is not only monetary, but can just as importantly address improvement in safety profile, occupational health and safety (OSHA) features, environmental protection (EPA) concerns or customer usability issues.

Manufacturers are expected to understand their product and processes and identify critical process parameters that have impact on the quality of the resulting product. This applies to both APIs and dosage forms. Unfortunately this is not a one-size-fits-all approach and a critical parameter for one product may be of only minor importance for another. Such knowledge is built over time during product development and commercial production and may change as more data are acquired. Any change should be expected to produce, at a minimum, a product that is no less pure, potent, or safe than the product prior to the change. Ideally, changes are made to

decrease process and product variability, increase process robustness, optimize safety profile, increase purity, or increase manufacturing efficiency. Changes may also be made to enhance occupational health and safety features and environmental protection.

A risk analysis supporting the change to a commercial product / process may be a component of the change justification. This risk analysis is a “living” document that incorporates new knowledge and is revisited periodically to determine whether new inputs, such as adverse events or customer complaints, identify previously unknown risk factors. As part of the change analysis the firm should consider the impact that the change may have on the validated state of the process. For example, does the process require re-validation to establish that it continues to operate in a state of control? Firms should remember to consider that a change in the source of excipient(s) or critical API raw material(s) may have unintended and unanticipated impact on the quality of the final product. For example, a change in supplier for a cell culture media component at the bioreactor / fermenter stage may negatively impact cell growth or product production rate or result in changes that dramatically modify pharmacokinetics.

Changes to drug testing schemes and methods need to consider that the new analytical method or process should be shown to be at least equivalent to or an improvement on the previous method. And where appropriate, the change in the method should be validated. Also, changes to the manufacturing process may require modification of in-process analytical methods and their requalification or re-validation.

Change in the pharmaceutical industry is never as simple as it might seem initially. The law of unintended consequences can become readily apparent.

## **2. Does it represent a change to the DMF / NDA / ANDA / BLA described process of manufacture and testing and how must the change be reported to regulatory authorities?**

The NDA / ANDA / BLA describe the manufacturing and testing process that is approved by regulatory authorities. Regulatory agencies expect manufacturers to comply with the conditions in their approved applications. Failure to do so is not something they take lightly and can result in enforcement actions.

Regulatory authorities provide guidance on the reportability of changes to manufacture and testing. In general, the major category of changes include those that represent a change to the site of manufacture or a significant modification to the method of manufacture provided in the regulatory filing. Some changes in the scale of manufacture may also be classified in this category. Major changes require approval by regulatory authorities before they can be implemented for commercial product. Firms would be well served to become familiar with the guidance provided by regulatory authorities for reporting of changes. Such guidance cannot address all possible changes but does provide the starting point for reportability decisions.

Further, changes are often bundled to minimize facility down time and the need to possibly repeat validation if each change was made in isolation. When a change that a regulatory agency has deemed to be in the prior approval category is made simultaneous with others that may be reported in an annual update report, they may all generally need to be reported in the prior approval submission. It is prudent to discuss the complex change(s) with regulatory authorities in advance and minimize compliance actions that may be taken for not manufacturing product consistent with the regulatory application or DMF.

Among the challenges for prior approval changes is the need to build adequate inventory of material from the existing process when the facility must be temporarily shut down to make the

change(s). Each regulatory authority has different timing for review and approval of such changes. This further complicates inventory planning so that drug shortages do not become an unintended consequence of the change.

Change analysis needs to include identification of all documents and processes that may be impacted by the change. For example, do cleaning SOPs need modification based on a manufacturing or equipment change? What changes if any need to be made to batch records? Does a change in manufacturing process require modification to sample plans or analytical methods? Sometimes this analysis is not sufficiently thorough and a regulator may identify this lack of consistency during an inspection, never an ideal situation. Evaluation of the effectiveness of the change(s) is not specifically a part of the change control process, but is necessary to consider for major corrective and preventive actions undertaken within the change control process.

In conclusion, effective use of change control is a key component of the pharmaceutical quality system ensuring safety, potency, strength and efficacy of products made consistent with relevant regulatory filing. The change control process is a key facilitator to document continuous improvement and should operate in accordance with a structured process. Each change should be carefully considered and approved in advance based on thoughtful evaluation of the scope of work required. Safety concerns should be important drivers in the change control process and should be considered as the most important “returns on investment”.

FDA and the EMA refine and update guidance addressing reporting of post-approval changes in manufacture and testing of products, including APIs. Often this is done in revisions to the GMP Q&A's published on their websites. While many of the documents below apply to drug product, the concepts are relevant to changes made in API manufacture and testing. Companies are advised to closely monitor agency publications and guidance to ensure they apply the most current guidance when evaluating the expectation to report the change to regulatory authorities. In fact, as this article was being written, FDA published a draft guidance addressing changes to “regulatory commitments”, the final document in the list of agency guidance at the end of this article.

Reliance only on the references listed below may not ensure the necessary level of GMP compliance. For example, it is generally expected that the concepts of ICH Q8, [9](#), [10](#) and [11](#) along with their respective implementation documents will be applied in the evaluations and documentations of changes. Also, agency specific guidance on the topic, and relevant ICH guidance such as those addressing impurities (ICH Q3A through D) and stability (ICH Q1A through F) determinations should be considered. [ICH Q7](#) specifically addresses GMPs for APIs, and section 13, along with other areas in the document address change control.

**The references below address changes that must be reported to regulatory authorities, not changes that must be communicated between the contract giver and contract recipient.** The later should be specified in the quality agreement and overlap between the two is common. For applications that make use of the design space concepts, post approval changes may be modified from the descriptions in the documents below, and will be specified and agreed to as part of the application approval process.

### [Questions and Answers on Post Approval Change Management Protocols](#)

**Regulatory Authority:** EMA

**Date of Publication:** 30 March 2012

**Comment:** This addresses the use of a protocol that is similar to the use of an FDA Comparability Protocol, which when approved, permits reduction in reporting requirements for the specifically approved change(s) that meet the pre-determined acceptance criteria. This does *not* decrease the nature of the evaluations or documentation necessary to support the change. This documentation should be available upon inspection by the authorities. Note that Section 4 describes the content of the protocol; the same criteria are similar to those that should be considered in the overall change control process and documentation even if not submitted in a Post Approval Change Management Protocol.

**Guideline** on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

**Regulatory Authority:** EMA

**Date of Publication:** 2 August 2013

**Comment:** Provides background to variations requirements including tabulation of potential changes, their classification and the data that must be submitted in support of the change. Note that this focuses on changes to the Marketing Authorization Application.

**Supplements and Other Changes to an Approved Application, 21 CFR 314.70**

**Regulatory Authority:** FDA

**Date of Publication:** April 2004 and subsequent amendments

**Comments:** This section of 21CFR 211 is the regulation that specifies post approval reporting to FDA for approved drug products.

**Guidance for Industry, CMC Post Approval Changes to be Documented in Annual Reports**

**Regulatory Authority:** FDA

**Date of Publication:** March 2014

**Comment:** This guidance represents FDA's current thought on changes that represent minimal risk to product quality that can be submitted in an annual report. Specific examples are provided.

**Guidance for Industry, Changes to an Approved NDA or ANDA**

**Regulatory Authority:** FDA

**Date of Publication:** April 2004

**Comment:** This 40-page guidance addresses reporting requirements for approved NDAs and ANDAs. A variety of examples are provided. Firms are to reference the relevant guidance for the data necessary to support qualification, implementation and reporting of specific types of changes and unlike the EMA guidance earlier in this section, the actions necessary and the documentation to be provided is not included in this guidance. Only the reporting categories are identified. Note that the March 2014 guidance immediately above updates the changes that may be submitted in an annual report.

**Guidance for Industry, Changes to an Approved NDA or ANDA, Questions and Answers**

**Regulatory Authority:** FDA

**Date of Publication:** January 2001

**Comment:** This set of Q&A is meant to provide clarification to the Guidance on changes that was published in November 1999.

**[Guidance for Industry, Changes to an Approved NDA or ANDA, Specifications --- Use of Enforcement Discretion for Compendial Changes](#)**

**Regulatory Agency:** FDA

**Date of Publication:** November 2004

**Comment:** Compendial changes to relax or delete a test may be submitted in an annual report, rather than as a CBE-type of filing and FDA will not take enforcement actions.

**[SUPAC-IR, Guidance for Industry, Post approval changes for Immediate Release Solid Oral Dosage forms, Scale up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In-Vitro Dissolution Testing and In-vivo Bioequivalence Documentation.](#)**

**Regulatory Agency:** FDA

**Date of Publication:** November 1995

**Comment:** This 30-page guidance describes the level of changes for immediate release solid oral dosage forms, the data that should be generated to support their implementation and the documentation that should be either submitted or available for review upon inspection. Firms are cautioned to continue to monitor FDA publications including new and revised Q&As published by FDA to address changes that are made in this area.

**[SUPAC-IR Questions and Answers about SUPAC-IR Guidance](#)**

**Regulatory Agency:** FDA

**Date of Publication:** February 1997, last update 2005

**Comment:** This represents the most frequent questions that FDA has received since publication of the original SUPAC-IR guidance in 1995. Topics covered include: component and composition changes, manufacturing site changes, manufacturing process changes, manufacturing equipment changes, in-vitro dissolution, in-vivo bio studies, stability and change in batch size, and miscellaneous topics.

**[Guidance for Industry, PAC-ATLS, Post Approval Changes – Analytical Testing Laboratory Sites](#)**

**Regulatory Agency:** FDA

**Date of Publication:** April 1998

**Comment:** This 5-page guidance addresses changes in the analytical testing laboratory sites.

**[Guidance for Industry, SUPAC-MR, Modified Release Solid Oral Dosage Forms. Scale up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In-Vitro Dissolution Testing and In-vivo Bioequivalence Documentation.](#)**

**Regulatory Agency:** FDA

**Date of Publication:** September 1997

**Comment:** This guidance identifies the levels of change, the tests that should be conducted and the documentation that should be available for submission or review during inspection for changes made to modified release solid oral dosage form products.

**[Guidance for Industry, Changes to an Approved Application for Specified Biotechnology and Specified Biosynthetic Products](#)**

**Regulatory Agency:** FDA

**Date of Publication:** July 1997

**Comment:** This 12-page guidance speaks to post approval changes made for specific categories of biotechnology of biosynthetic products.

**[Guidance for Industry, Established Conditions, Reportable CMC Changes for Approved Drug and Biologic Products](#)**

**Regulatory Agency:** FDA

**Date of Publication:** May 28, 2015

**Comment:** This 17-page draft guidance, published for comment, tackles the challenge of identifying what constitutes a “regulatory commitment”. Changes to these commitments are to be reported to FDA consistent with existing change-control guidance. The concept of “regulatory commitment” has been interpreted differently by various inspectors and from company to company. The guidance uses the structure and format of the eCTD to identify the sections that constitute a regulatory commitment.