Technical Report No. 91

Post-Approval Change Management and Implementation for Biologics and Pharmaceutical Drug Products — A User's Guide

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Post-Approval Change Management and Implementation for Biologics and Pharmaceutical Drug Products Team

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ISBN 978-1-945384-41-1
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1.0 Introduction

The complexity of global post-approval change/variation (PAC) processes and the time required to receive their approval presents a challenge for industry when it is working to implement needed changes and operating with a focus on continual improvement. Industry benchmarking shows that receiving approval for a PAC requiring global approval can take between two and five years, and the time it takes from original submission can vary from six months to several years depending on the jurisdiction and review pathway ***(1)***. For new products, where the amount of commercial process or product data at the time of the initial submission is limited, this timing can significantly impact the ability to implement necessary process improvements identified as more data becomes available. In specific cases, when a change is needed to ensure the product remains safe, efficacious, and of high quality or provides additional capacity based on high product demand, the global approval timing can result in drug product shortages.

The current regulatory pathway to implement change is highly complex. For each jurisdiction in which a product is licensed, the respective regulatory agency typically requires a notification based on its risk reporting category, or it must preapprove certain PACs for certain products. Differences in country- and region-specific requirements for PAC filings, filing procedures, and associated timelines can often make simultaneous implementation of changes problematic, necessitating a product be tested or produced using different processes based on where it will be distributed. Companies must consider this factor when deciding to implement a change.

These challenges were highlighted during the COVID-19 pandemic, as companies continued to manufacture lifesaving products despite the extreme strain on supply chains for raw materials, components, and manufacturing supplies. As alternative sources of supply or alternative materials were identified, the complexity of the global regulatory PAC process presented a significant challenge to product supply, highlighting the need for a harmonized approach to PAC implementation.

1.1 Purpose

This technical report expands on the latest concepts and tools for improving PAC management, as published in ICH Q12. It provides a practical guide for the pharmaceutical industry on how to implement PACs within the framework of an effective pharmaceutical quality system (PQS) and in alignment with ICH quality guidelines. It recognizes the challenges that the limited amount of global harmonization among regulators presents with respect to PACs and attempts to provide some insight on how industry can work with regulators to improve in this area. Though TR-91 aligns with ICH Q12, it also provides guidance for non-ICH regions. It suggests how to implement the tools described in ICH Q12 and provides examples of the concepts that can facilitate aligned industry understanding for PACs.

TR-91 highlights the benefits of some of the tools described in ICH Q12 that are already available in certain jurisdictions, specifically, PAC management protocols (PACMPs, or comparability protocols) and established conditions (ECs). These concepts were acceptable for use by several regulatory agencies prior to ICH Q12; that is, ECs and comparability protocols by the U.S. Food and Drug Administration (FDA) ***(11,12)*** and comparability protocols by the European Medicines Agency (EMA) ***(13)*** and WHO ***(4,5)***.

Section 10.0 (Appendix 1) and **Section 11.0** (Appendix 2) provide examples of PACs common in industry that are presented as representative frameworks for consideration, presented as hypothetical PACMPs (or comparability protocols) that can be leveraged for similar changes. These examples, although not all-inclusive, do offer insights into the types of documentation and the scientific justification that may be required for implementation. They are intended to be illustrative, but they do portray how negotiation with regulators, where existing requirements may be disproportionate to risk given either knowledge gained through development or process experience, could be demonstrated using a PACMP approach.

1.2 Scope

The information in this technical report focuses on chemistry, manufacturing, and controls (CMC) changes that can be applied to PACs for both small-molecule and large-molecule pharmaceutical products.

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