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A Critical Analysis of Technical Changes and the Corresponding Documentation Required for Global Post-approval Submissions

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INTRODUCTION

Upon regulatory approval of a new medicinal product, a marketing authorization holder may propose post-approval changes to this product, which must be communicated to or even approved by the respective Health Authorities.[1] However, managing the regulatory approval process on a global level is complicated, unpredictable, and time-consuming.[2] Furthermore, the current European Union (EU) Variations Regulation (which is the most representative of the guidelines used by Health Authorities worldwide with respect to documentation requirements) provides a comprehensive guideline for specific minor change requirements affecting the Quality section of the regulatory dossier, but none for major changes.[3] Therefore, an understanding of requirements in different countries is important for document standardization and improved efficiency.

This project served as an analysis of documentation that had been submitted to Health Authorities worldwide by F. Hoffmann-La Roche (Roche), in support of post-approval changes concerning the Quality section of the dossier (technical changes). The post-approval changes used for this project spanned various change types commonly used within the organization, for a variety of biotechnology products. The aim of the analysis was to subsequently generate a proposal of the documentation required for the submission of selected change types. The primary goal was to harmonize, shorten, and ultimately simplify the Roche process (Figure 1) of gaining global approval for and implementing post-approval changes.

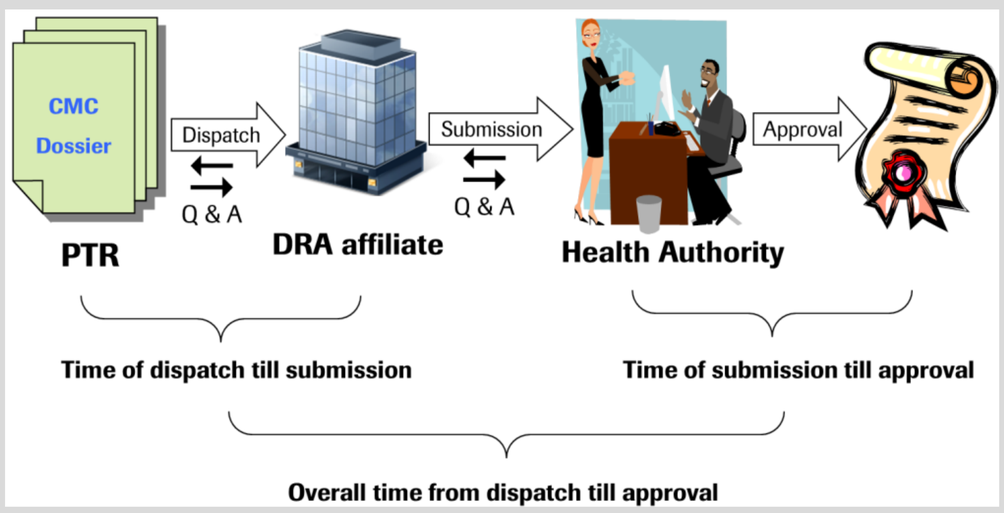

Figure 1: Overall Roche process for submission of Quality-related, post-approval changes worldwide

CMC = Chemistry, Manufacturing, and Controls (US term for the Quality section of the dossier); DRA = Drug Regulatory Affairs (local regulatory contact, located in different worldwide countries); PTR = Pharma Technical Regulatory (Roche technical regulatory headquarters)

The steps illustrated in this simplified graphic can be multipled by 100+ times for a given regulatory submission, depending on the worldwide marketing of the medicinal product.

CONCEPT

Data listing all Quality-related, global, post-approval changes made at Roche in the last few years was acquired from Roche databases. Each change was then assigned a change type, which were selected from a pre-established list from a Roche-internal Work Instruction document. Selection was then made of the most frequently-utilized change types to biotechnology products; changes that were specific to the United States (US) and/or Canada were excluded, since those countries have special documentation requirements which are not representative of the rest of the world. Post-approval changes that were associated with the eight selected types were searched in a different Roche database to create a retrospective list of document names that had been presented to Health Authorities in support of each change at the time of the submission process. A thorough analysis was then conducted to identify not only the most frequently-appearing documents across changes within a change type, but also the ones that were the most relevant to the change type in question. Documents that had only been submitted to specific countries were taken into account as well. Based on this analysis, a proposal was generated listing all of the documents required for submission of a particular change type, and any country-specific document versions (Figure 2).

Change Type 161 – Change in Test Procedure for Drug Substance, Minor Change to an Approved Test Procedure

Submitted Documentation	b-dossier	EU	Japan	Serbia	Montenegro
Administrative documents					
Application Form		X			
Cover letter	X	X	X	X	X
Table of Contents	X	X	X	X	X
TRIC Questionnaire	X	X	X	X	X
Statement of Reliability			X		
Statement of availability of raw data, incl. raw data list			X		
Change-specific documents					
List of Changes (if complex or concomitant changes)	(X)	(X)	(X)	(X)	(X)
Rationale for the change	X	X	X	X	X
Comparative table of changes			X		
QOS Update	X	X	X	X	X
CTD Module 3 Documents					
3.2.S.4.2 Analytical Procedures				Same documents as approved in EU	
All analytical procedures which are impacted by the change must be updated	bi-	bi-	JAP-		
3.2.S.4.3 Validation of Analytical Procedures					
Corresponding sub-sections to 3.2.S.4.2	bi-	bi-	bi-		

Figure 2 : Document requirements proposal example for one of the seven change types

b-dossier = basic dossier (Roche-specific designation); bi- = the version of a document that meets the requirements of both basic and international dossiers (Roche-specific designation); CTD = Common Technical Document; EU = European Union; JAP- = Japan-specific document version; QOS = Quality Overall Summary document; TRIC = Technical Regulatory Intelligence Center (Roche-specific designation)

RESULTS

For the eight selected change types, lists of submitted documentation proved to be less abundant than expected, mostly due to the complexities of internal database organization. As a result of insufficient documentation, one of the eight change types had to be excluded from the final proposal. On the other hand, for those change types that did have an adequate amount of data for analysis, most was not relevant to the technical change in question (e.g. editorial changes). Guidance in distinguishing the appropriate information was sought from the Rationale document frequently included in submitted dossiers.

An additional side finding showed that the majority (64%) of changes made to biotechnology products were submitted exclusively in the US and/or Canada. This observation could be explained by the difference in assessment of minor versus major changes across countries and regions, as well as worldwide differences in the regulatory reporting system of such changes.

CONCLUSION

For the seven analyzed change types, a large impact is expected to be made in terms of shortening the time required for post-approval change submissions at Roche. Such a standardized documentation package will ultimately help in the organization's collaboration between its technical regulatory headquarters, its local regulatory contacts in specific countries, and the respective Health Authorities (Figure 1). By reducing the uncertainty of the documentation required for submission, the overall process will be made more efficient.

In general, examination of varying change requirements and their associated timelines across different countries and regions revealed that convergence of the regulatory requirements for Quality-related changes worldwide would facilitate the life cycle management of medicinal products. More specifically, a number of suggestions can be made for future project improvement, including better standardized document templates and use of additional software for data collection.

Despite the encountered challenges, such a detailed evaluation is extremely valuable to an organization: not only does it result in the development of document standardization, but also a great deal can be learned about improving company-internal processes and standards.

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