

A Comprehensive Study on the Global  
Regulatory Requirements for the  
submission of a Post-Approval Change,  
specifically a Change in Manufacturing Site



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A Comprehensive Study on the Global Regulatory Requirements  
for the submission of a Post-Approval Change, specifically a  
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## ABSTRACT

Regulatory requirements for post-approval changes vary for different countries around the world. It is a challenging and costly process for pharmaceutical companies to manage changes to the approved regulatory dossier over the lifecycle of the product when it is registered in many countries. In practice the process can be complex, unpredictable and time consuming because of regional differences and frequent changes in regulatory procedures, requirements and timelines. The global regulatory requirements for the submission of a post-approval change, specifically a change in manufacturing site, were reviewed for six jurisdictions for this study. These include United States of America (US), Europe (EU), South Africa, Brazil, Russia and China. The study centred on the differences in the documentation required when submitting a post-approval change for a change in manufacturing site in these countries. The study compared and contrasted the differences and similarities between the jurisdictions. An analysis of the challenges for implementation of the change was performed. The study also examined what resources a company may need in order to meet the requirements. Some notable similarities but also many differences in the post-approval submission requirements between the countries were identified. Some of the similarities included classification of the type of variation, the submission application process, and the requirement to provide supportive stability data and updates to the common technical dossier (CTD). Differences highlighted were the types of application forms required, the amount of stability data required to support the change and the time lines for review of post-approval changes in each jurisdiction. The challenge for pharmaceutical companies arises in the effective management of these differences. Investment in a robust regulatory change management team is an essential resource requirement for pharmaceutical companies. Adoption of a QbD approach and careful consideration of the global requirements during the product development phase could potentially be of use in strategic planning within a company in order to ensure continued product access globally.

## DECLARATION

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

I agree to deposit this thesis in Hibernia College's institutional repository and the University of Western Cape's library or allow the library to do so on my behalf, subject to Irish and South African Copyright Legislation and Hibernia College Libraries and the University of Western Cape's conditions of use and acknowledgement.

Signed: Barbara Hoey

Dated: 21 April 2017



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## TABLE OF CONTENTS

TITLE.....	ii
ABSTRACT .....	iii
DECLARATION .....	iv
ACKNOWLEDGEMENTS.....	v
TABLE OF CONTENTS .....	vi
LIST OF ABBREVIATIONS .....	vii
Chapter 1: Introduction .....	1
Chapter 2: Literature Review.....	3
2.1 Introduction .....	3
2.2 United States (FDA) .....	3
2.3 Europe (EMA).....	4
2.4 South Africa (MCC) .....	6
2.5 Brazil (ANVISA).....	8
2.6 Russia (MOH) .....	9
2.7 China (CFDA) .....	10
2.8 Conclusion .....	11
Chapter 3: Methodology .....	12
3.1 Aims and Objectives .....	12
3.2 Rationale for the Study.....	12
3.3 Research Methodology.....	12
3.4 Study Design .....	13
3.5 Limitations .....	13
3.5 Ethical Considerations .....	14
Chapter 4: Results.....	15
4.1 Assumptions .....	15
4.2 Comprehensive Review of Documentation Requirements.....	15
4.3 Comparison of Stability Data Requirements .....	22
4.4 Comparison of Approval Times .....	23
Chapter 5: Discussion .....	24
5.1 Interpretation of Results .....	24
5.2 Recommendations.....	26
Chapter 6: Conclusion.....	29
REFERENCES AND BIBLIOGRAPHY .....	30
APPENDICES.....	35
Appendix 1: Research Proposal .....	35

## LIST OF ABBREVIATIONS

ANVISA	Brazil National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária)
API	Active Pharmaceutical Ingredient
CDER	Centre for Drug Evaluation and Research
CFDA	China State Food and Drug Administration
CGMP	Current Good Manufacturing Practices
CMDh	Co-ordination group for Mutual Recognition and Decentralised Procedures – Human
CMC	Chemistry, Manufacturing and Controls
CTD	Common Technical Dossier
DP	Drug Product
DS	Drug Substance
eCTD	Electronic Common Technical Dossier
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration, United States of America
FP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
GDUFA	Generic Drug User Fee Amendments
HCR	Holder of Certificate of Registration
HCP	History of Changes to the Product
ICH	International Conference on Harmonization of Technical Requirements for Registration of Biopharmaceuticals for Human Use
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MCC	Medicines Control Council
MOH	Ministry of Health

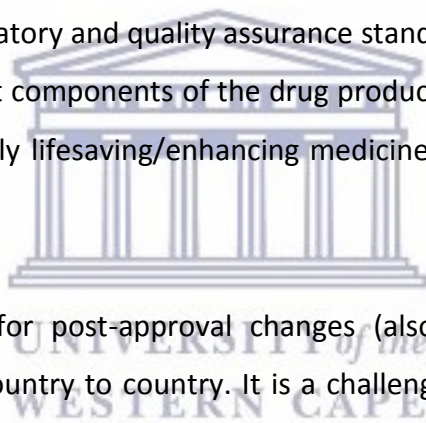
NDA	New Drug Application
OECD	Organisation for Economic Co-operation and Development
PAS	Prior Approval Supplement
PIC/S	Pharmaceutical Inspection Convention and Co-operation Scheme
QbD	Quality by Design
RMP	Risk Management Plan
SAPC	South African Primary Council
SUPAC	Scale-Up and Postapproval Changes
US	United States
WHO	World Health Organization





## Chapter 1: Introduction

The goal of every pharmaceutical company is first and foremost to get its drugs to market. It is a huge accomplishment to finally gain regulatory approval to licence and manufacture a pharmaceutical product (Baradaran, 2008), considering that the estimated average cost per new prescription drug approval is \$2.558 billion (DiMasi, Grabowski and Hansen, 2014). Once a drug has been approved by the regulatory authorities of a given country the focus changes to ensuring continued approval of the site of manufacture to supply the drug throughout its lifecycle. As part of the drug product lifecycle management, an applicant may propose postapproval CMC (chemistry, manufacturing and controls) changes to the product registration dossier. These changes are required for various reasons, such as continuous improvement, compliance with new regulatory and quality assurance standards, and new suppliers or manufacturers for different components of the drug product (Christensen et al, 2014). This ensures that potentially lifesaving/enhancing medicines remain accessible to the public.



Regulatory requirements for post-approval changes (also known as variations or amendments) vary from country to country. It is a challenging and costly process for applicants to manage changes to the approved regulatory dossier over the lifecycle of the product when it is registered in many countries. In practice the process can be complex, unpredictable and time consuming because of regional differences and frequent changes in regulatory procedures, requirements and timelines. The literature review that follows in Chapter 2 will look at the general requirements for postapproval changes in the following jurisdictions; US, EU, South Africa, Brazil, Russia and China. As part of the literature review some the challenges and opportunities proposed by the individual regulatory agencies or in peer-reviewed articles will be discussed.

Jaberidoost et al (2013) describes how most of the reported risks to the supply of pharmaceutical medicine are related to supply and supplier issues. The drug supply chain can be subject to many risks. These risks disturb the supply of medicine in many

ways, such as their quantity and quality and their distribution to the right place and customers and at the right time. Therefore risk identification and risk mitigation in the supply chain activities of pharmaceutical companies is highly recommended. In the evaluation of risk mitigation, pharmaceutical companies will often decide that in the interest of continued supply of medicine, that a new or second site of manufacture is deemed necessary. This could be due to risks associated with the region in which the manufacturing site is situated, for example, its susceptibility to bad weather and natural disasters, political and/or economic instability, security problems or terrorism (Jaberidoost et al, 2013). The site may have experienced quality and safety challenges, legal issues, or regulatory and environmental compliance concerns. It could also be simply due to a site requiring an upgrade to a more modern facility. The global regulatory requirements for the submission of a post-approval change, specifically a change in manufacturing site, are reviewed for six jurisdictions for this study. These include US, EU, South Africa, Brazil, Russia and China. The study centres on the differences in the documentation required when submitting a post-approval change for a change in manufacturing site in these countries. The study also compares and contrasts the differences and similarities between the jurisdictions with respect to documentation required, review timelines, accessibility to information pertaining to applications and cost of variations. An analysis of the challenges for implementation of the change was also performed. The study also examined what resources a company may need in order to meet the requirements, esp. when different data has to be generated for the various jurisdictions. It is hoped that this information could potentially be of use in strategic planning within a company in order to ensure continued product access globally.

## Chapter 2: Literature Review

### 2.1 Introduction

Global regulatory change control requirements in the lifecycle management of the CMC dossier can be challenging for pharmaceutical manufacturers (Moore, 2013). Obstacles to managing changes in a global environment include, differing regulatory requirements for changes, costs of filing changes and different timing for approval of changes from multiple health authorities (Moore, 2013). However post-approval changes are essential for companies to stay current and innovative. The literature survey will take each jurisdiction under review and discuss the general process for making postapproval changes to the marketing authorisation. It will examine some of the strategies that the regulatory agencies have proposed or begun to employ to make the postapproval change management process more efficient and easier for applicants.



### 2.2 United States (FDA)

In accordance with US statutory and regulatory guidance, a sponsor must notify FDA of a change to an approved application beyond the variations already provided for in the application (FDA CDER, 2004). All postapproval CMC changes are categorized into one of three categories; major, moderate or minor as per Code of Regulations 21 CFR 314.70 'Supplements and other changes to an approved application' (FDA CDER, 2004). Section 506A of the Food and Drug Modernisation Act lays out the requirements for making and reporting these changes. Major changes require a Prior Approval Supplement (known as PAS) from the FDA before they can be implemented. For moderate changes, the mechanism that is generally used is a CBE-30 supplement, where the applicant notifies FDA at least 30 days in advance of the distribution of the product. The applicant without prior approval or notification can implement changes that are considered minor. However FDA must be subsequently notified of all minor changes as part of the Annual Report, which is submitted each year on the anniversary of application approval date (FDA CDER, 2014). FDA recommends that SUPAC (Scale Up

and Postapproval Changes) guidance documents (FDA CDER, 1995) should also be consulted when assessing CMC postapproval changes. These documents provide guidance on the type of data to be generated as part of the assessment on change.

FDA appears to be committed to make the process less burdensome. Part of their approach is to allow more changes to occur using the Annual Report system and assessing the changes using a risk based approach (FDA CDER, 2014). FDA states that using this approach, CMC regulatory review should be based on an understanding of product risk and how best to manage that risk. With this in mind FDA published guidance for industry in 2014 outlining changes that could be considered as annual reportable changes (FDA CDER, 2014). FDA are asking applicants to use appropriate scientific data and risk analysis to support whether the change should be submitted in a PAS, CBE-30 or annual report. The goal here is to reduce administration costs and time to implement changes that are considered to be low risk to product quality and public safety (FDA CDER, 2014). In this study the requirements for a change to manufacturing site will be specifically studied. While this change is not considered to be an annual reportable change (reviewed in detail in Chapter 4), allowing more minor changes to go through the annual report system, should free up reviewers to deal with PAS and CBE-30 supplements in a more efficient way. However with the emergence of the biotech industry and biosimilars shaping the future of the pharmaceutical industry, this will only help to reduce the number of annual changes for conventional medicine. These molecules have complex manufacturing processes. Changes to the manufacturing process will likely require more scrutiny and in turn FDA review resource. The FDA initiative is commendable however and definitely a step in the right direction.

### **2.3 Europe (EMA)**

The process for the submission of postapproval changes in the European Union (EU) is very similar to that in the US. The terminology is different however and it can be further complicated by whether the original application is by the mutual recognition

procedure, purely national procedure or the centralised procedure. The Variations Regulation (Commission Regulation (EC) No 1234/2008) governs the procedures for the amendment of a marketing authorisation (MA). The European Medicines Agency (EMA) provides comprehensive procedural guidelines on the handling of variations (European Commission, 2013). The European Commission guidance details the classification, submission and processing of variations. To facilitate the classification of various types of changes, the variation guide is composed of 4 annexes. Annex I lists the minor changes and Annex II contains the definition and examples of major changes. Annex III and IV detail extensions and additional safety concerns (Annex III and IV are not in the scope of this review). Variations are categorised into three types, Type IA, Type IB and Type II. Type IA notifications are considered very minor changes. Examples of this type of variation would be administrative changes such as a change in the name and/or address of the MA holder or deletion of a manufacturing site that will no longer be used. Type IA variations do not require prior examination by the authorities before being implemented. Similar to the US system, the applicant must inform the authorities within 12 months from the date of enactment. Type IB variations are also considered minor variations but do require notification to the authorities before implementation. Similar to the CBE-30 in the US, the MA holder must wait a period of 30 days before implementing a Type IB change. Known as the 'Tell, Wait and Do' approach. Major variations are classified as Type II. Major variations are those changes that may have a significant impact on the quality, safety or efficacy of the drug product. Notification for all types of variation must be submitted simultaneously to all Member States concerned, to the national competent authority and to the EMA.

The Variation Regulation and guidelines also give detailed instruction with regards to how to submit a change application as per the mutual recognition, purely national or centralized procedures. The Co-ordination group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has also published additional guidance in respect of variations for products authorised through the mutual recognition or

decentralised procedures. Article 20 of the Commission Regulation (EC) N° 1234/2008 allows for a sponsor to submit the same Type IB or Type II variation or group of variations from the same Marketing Authorisation in one application. In order to avoid duplication of work in the evaluation of such variations, a work-sharing procedure has been established under which one authority (the 'reference authority') reviews the variation. The reference authority is chosen amongst the competent authorities of the Member States and the Agency and reviews the variation on behalf of the other concerned Member States. This is a positive approach to ensuring that variations are managed efficiently and approval is gained in all jurisdictions at the one time. According to Leivers (2014), however there are some frustrations and areas for improvement with the work-sharing procedure. For example the procedure can be too long for minor changes and there is a call to further streamline communication between national competent authorities and EMA during work-sharing process where EMA is acting as the reference authority (Leivers, 2014).

#### **2.4 South Africa (MCC)**

The Republic of South Africa (ZA) is the largest market on the African continent and is a member of the 'BRICS' (Brazil, Russia, India and China) group of the emerging world economies (Chorley, 2014). Therefore successful lifecycle management of medicine that has received approval for marketing in South Africa is very important to pharmaceutical companies wishing to continue to supply their drug product there. The Medicines Control Council (MCC) in South Africa is the authority that enforces the principles laid down by the Medicines and Related Substances Act, (Act 101 of 1965), which was established to govern the manufacture, distribution, sale, and marketing of medicines. A holder of a Certificate of Registration (HCR) for a drug product may submit an application to amend an entry made into the medicines register to the MCC. Changes to a registration dossier in South Africa are known as 'amendments', and are classified into one of three categories, Type A, Type B or Type C (there is also a Type D category, but these are considered new applications). Type A amendments are minor changes that are unlikely to affect the quality and performance of the medicine and



they can be implemented without intervention or prior notification (MCC, 2012). These are recorded in the product quality review and must be available during inspection (MCC, 2012). However, unlike in the US and EU, applicants are not mandated to notify MCC within 12 months of the date of implementation of Type A amendments (Chorley, 2014). In theory it might take several years for the dossier to be updated with MCC. It is important that the company keeps records of the amendments in the 'amendments schedule' and by updating the relevant sections of Module 2 and Module 3 of the dossier. This procedure could lead to being out of compliance with regulatory dossier if an effective regulatory and change management system is not employed by the pharmaceutical firm.

The opportunity to file Type A notifications with the MCC normally arises when a Type B or Type C amendment is required. Type B amendments are those that could have a more significant impact on quality or performance. Type B changes require written notification to MCC. Similar to CBE-30 and Type IB variations in the US and EU respectively, Type B amendment notification should be sent 30 days prior to implementation. Type B amendments cannot be made with amendments that do require prior approval (MCC, 2012). Amendments that require prior approval from MCC are classified as Type C. These are defined as changes that likely to significantly impact product quality or performance. Written approval from MCC must be obtained before proceeding with the change (MCC, 2012).

Chorley (2014) discusses that one of the main challenges for the post-approval CMC landscape in South Africa is the time taken to review and approve Type C amendments. It is reported that it can take up to two years to receive approval to implement a major change. Pharmaceutical manufacturers would need careful planning to allow time for approval and to ensure that they can continue to manufacture during the review period. Depending on the change however this could mean that manufacture would need to cease for a period while awaiting approval e.g.

addition of a new manufacturing site where an old manufacturing site can no longer supply the market.

Another factor that has reportedly contributed to the slow process for post-approval submissions is the requirement to convert older dossiers to the CTD format by 1<sup>st</sup> June 2016 (Chorley, 2014). The use of 'paper-only' CTD is also still commonplace in South Africa. It is hoped however that post-2016 that use of the electronic CTD (eCTD) will be routine (Chorley, 2014), thus aiding all types of submissions to the agency and allowing easier access for review and comment. Chorley (2014) reports that 'blocking of variations' is also something that occurs in South Africa. This occurs because unlike in the EU, parallel assessment of changes is not permitted i.e. a new Type C change cannot be filed while a pending Type C is still under review. This could be very inhibiting for products that are undergoing rapid CMC development and also present risks to not being in compliance with the certificate of registration during the long review approval time lines (Chorley, 2014).

## **2.5 Brazil (ANVISA)**

Brazil's pharmaceutical market is one of the largest in the world. So it is understandable why pharmaceutical companies are eager to gain approval in this lucrative market. The regulatory framework in Brazil has considerably improved since ANVISA, the federal regulatory agency, was established in 1999 (Handoo et al, 2012).

In March 2016, ANVISA sanctioned the amendments of Regulation RDC 48/2009, which refers to the post approval changes of drug products (Moeller IP Advisors, 2016). The amendments establish a new regulatory framework for post-approval changes. This meant the creation of a new Resolution (the term used for regulatory guidelines in Brazil), Resolution RDC No. 73, which replaces the older Resolutions RDC No. 48 and No. 49. Information is not so readily available on the ANVISA website, especially for English speaking nations. In order to review Resolution No.73, the author had to request an English translation from regulatory colleagues who have vast



experience with dealing with the Agency and interpretation of the Brazilian regulatory guidance. While this is not the official English translation, it is deemed suitable for the purposes of this review. The purpose of Resolution RDC No.73 is to classify post-marketing authorisation changes and establish the criteria and documentation required for the implementation of the changes (ANVISA, 2016). The classification of post-approval CMC changes in Brazil are similar to those outlined for the US, EU and South Africa, in that the changes are classified according to the impact on the quality, safety, and efficacy of the product. The changes are not given titles like Types A, B, C. They are simply defined as (1) being for immediate implementation, (2) with or without an individual protocol and (3) subject to prior approval from ANVISA. Changes for immediate implementation must be listed in the History of Changes to the Product (HCP), which is essentially the annual product review document filed at the company. Changes that require prior approval must await analysis and a favourable outcome from the review at ANVISA. ANVISA specify that the company have up to 180 days to implement the approved modification. ANVISA do allow changes to be made in parallel or concomitantly and outline the requirements for performing this exercise in the guidance. Resolution RDC No.73 provides a detailed Annex I listing examples of modifications, the conditions to be met, the documentation required, and the type of application needed. The ANVISA website is in Portuguese. English translations of the regulations and guidelines do not appear to be available on the website. This is a definite criticism for globalization, as a local agent or consultant company would be required in order for companies to interpret/translate the legislation. All the other regulatory agencies reviewed for this literature survey had English versions and in general the websites were easy to navigate, with the exception of the Russian Roszdrnadzor website discussed below.

## **2.6 Russia (MOH)**

All pharmaceutical products must receive a Certificate of Product Registration before the product can be manufactured, imported or sold in Russia (Sheftelevich and Tripathi, 2010). The State Regulatory Authority is called 'Federal Service on

Supervision in Sphere of Public Health Services and Social Development' (called Roszdranador). Roszdranador review and approve drug product marketing authorisation applications and issue the Registration Certificate. Roszdranador must also approve any changes required to the Licence Authorisation. There are 2 types of variations: Type I (minor changes) and Type II (major changes) (Chorich, Unknown). The guidance documents provided by Russian Ministry of Health do not stipulate whether minor changes can be implemented without prior approval. All potential changes are listed along in the guidance with the required documentation for each change, which suggests that even where there are minor changes, notification is required. This can be with or without expertise review from Roszdranador. Roszdranador website is in Russian. English translations of the regulations and guidelines do not appear to be available on the website. In fact the website is not free to navigate at all without completing an approval process. Here once again the author relied on reputable unofficial English translations of the guidance obtained from regulatory colleagues in order to complete the review (Russian Ministry of Health, 2012). It was also difficult to obtain peer-reviewed papers on the Russian post-approval process. However a number of sources did reiterate the information cited here (Chorich, Unknown), (Natarajan, 2012), (Van Arnum, 2014). It is understood that Russia is undergoing huge regulatory evolution and since it is also set to become one of the major players in pharmaceuticals, it stands to reason that improvements will come in time.

## **2.7 China (CFDA)**

China is reported to be in 9<sup>th</sup> largest pharmaceutical market in the world and is set to become the largest by 2020 (Kumar and Gupta, 2015). Despite the long arduous process for drug approval in China, pharmaceutical companies are increasingly pursuing approval in this market. The China State Food and Drug Administration (CFDA) are responsible for regulation of drugs. Supplement applications to drug registration are categorised according to three Categories or Registration items. (1) Supplemental applications to be approved by CFDA, these are the major change items

and include change of the location where the import drug is manufactured (2) Supplemental applications to be approved by PDA (provincial office for domestic drugs) and to be filed for record at CFDA – moderate changes for domestic drugs (3) Supplemental applications to be filed for record at PDA only – minor changes for domestic drugs (Lu, 2015, p294). CFDA website is easy to navigate and guidance is readily accessible. However the guidance was difficult to read and to follow. For the novice, it would require direct dialogue with CDFA or perhaps with a consultant with expertise in dealing directly with the Chinese authorities to understand exactly what is required.

## 2.8 Conclusion

The literature review has shown that the system for making post-approval changes to the CMC regulatory dossier is in theory quite similar across the different countries examined. Table 1 provides an overview of Global Post-Approval Change Classification, which highlights the similarities. In practice however, pharmaceutical companies complain the process is not similar. The study herein will examine where the differences lie and will try to see where improvements could be made to make the process more globally accessible.

**Table 1: Overview of Global Post-Approval Change Classification**

Type	Classification in each Country					
	US	EU	South Africa	Brazil	Russia	China
Minor	Annual Report	Type IA	Type A	Immediate Implementation	Type I	Lists 7 minor changes
Moderate	CBE-30	Type IB	Type B	Immediate Implementation but requires individual protocol	-	Lists 11 moderate changes
Major	PAS	Type II	Type C	Requires Prior Approval	Type II	Lists 18 major changes

## **Chapter 3: Methodology**

### **3.1 Aims and Objectives**

The purpose of the research conducted here is to perform a comprehensive review of global regulations and guidelines for the submission of post-approval manufacturing change, specifically a change in manufacturing site. Pharmaceutical companies have their drugs registered in many countries. All of which have different documentation requirements, differing opinions on the criticality of change and different time lines for review. For these reasons regulatory change management is a complex and costly process for the pharmaceutical industry. This research evaluates the differences and similarities between the requirements for global submissions.

### **3.2 Rationale for the Study**

By evaluating the requirements of the regulatory authorities from six of the largest pharmaceutical markets in the world (US, EU, South Africa, Brazil, Russia and China) it is hoped that this will provide the basis for creating procedures to manage global change control and to streamline the process as much as possible. But more importantly it will allow companies to plan their regulatory strategy for a change in manufacturing site by having this information collated. There are many changes to the CMC dossier that a company may need to make over the lifecycle of the drug product. For all countries reviewed, a list of the likely changes is specified in the guidance documents provided by the regulatory agency. This project will focus on one specific change however in order to highlight a mechanism for evaluating global change. A change in manufacturing site is considered by most of the authorities to be a major change. By evaluating a major change, it will encompass majority of the requirements needed for a global amendment submission.

### **3.3 Research Methodology**

The research for this dissertation was a literature-based review with the aim to provide qualitative analysis on a specific research topic that has practical relevance to

regulatory affairs. This is a qualitative study that is aimed to identify themes and patterns. The documentary analysis involved obtaining data from existing regulatory documents. Current regulatory guidance documents from a number of different countries were reviewed and analysed for differences and similarities. Other types of material used in the research were books, peer-reviewed articles, grey literature, press reports, and internet based materials i.e. presentations from global regulatory agencies or regulatory experts. The aim here was to design a research project where existing literature is the population. The basis of literature research methodology is to read through, analyse and sort literatures in order to identify the critical attributes. The primary difference from other methodologies is that it does not directly deal with the study topic, but to indirectly access to information from a variety of literatures, which is generally referred to as "non-contact method" (Lin, 2009).

### **3.4 Study Design**

The study design was based around the selection of the post-approval change to be evaluated i.e. major change to CMC dossier. Influential factors were examined and compared. These were change reporting category and documentation required, timelines for approval, requirement for stability data and other supporting data.

### **3.5 Limitations**

Research conducted in this way has its limitations. Since there were only a limited number of peer-reviewed articles on the topic, particularly when it came to reviewing the requirements in Brazil, Russia and China, the use of the Internet grey material (i.e., material that has not been through a peer review process) was required. In these cases however, the information was usually backed up by a number of sources (triangulation). Care was taken to interpret this information in the scope of the overall project and not to rely on it to complete the research. One other limitation was that the Brazilian and Russian regulatory agencies websites were in Portuguese and Russian, respectively. Here I looked to my regulatory affairs colleagues who have many years of expertise working with the registration of drug products in these countries.

English translations of the relevant guidance were obtained in order to complete the comprehensive review.

### **3.5 Ethical Considerations**

Ethical approval from the Ethics Review Board was not required for this project. The research as conducted solely by the author.



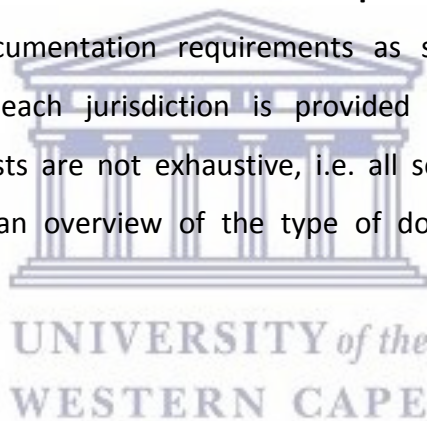
## Chapter 4: Results

### 4.1 Assumptions

For the purposes of this review a manufacturing site change is classified as the addition or replacement of a finished drug product manufacturing site for small molecules. Biological/immunological medicinal products are not in the scope of the review. A change in secondary or primary packaging site is also not in the scope. In order to compare the requirements between the jurisdictions, a change to manufacturing site will be considered as a Major Change. Some of the countries allow for a more moderate classification depending on the criticality of the site changes.

### 4.2 Comprehensive Review of Documentation Requirements

A description of the documentation requirements as set out in the individual regulatory guidance for each jurisdiction is provided below for a change to manufacturing site. The lists are not exhaustive, i.e. all sections of dossier are not described. Table 2 gives an overview of the type of documents required by the regulatory agencies.



#### **United States:**

A Prior Approval Supplement (PAS) is required for a major change in the US. The Code of Federal Regulations 21 CFR 314.50 outlines the content and format of a submission application. FDA classifies a move to a different manufacturing site as a major change requiring a prior approval supplement. SUPAC (Scale Up and Postapproval Changes) guidance documents (FDA CDER, 1995) are also consulted when assessing CMC postapproval changes. The following documentation is required for a PAS:

- Cover Letter
- Application Form
- Three copies of the application are required: An archival copy, a review copy, and a field copy.
- Appropriate Technical Sections: Update or amendment to the relevant sections



of the CTD. For a change to manufacturing site this is primarily Modules 1-3.

- Supporting stability data
- Dissolution data showing equivalence as per Case B in SUPAC guidelines

### **EU:**

A major change in the EU is classified as a Type II change. European Commission Variations Regulation guideline (2013) details a comprehensive list of the documentation required in order to submit such a change. The application must be presented in the EU-CTD format. Variations are submitted electronically. The following is required:

- Cover Letter
- Completed EU Variation Application Form
- Reference to the variation code as laid down in the Annex to the guideline<sup>1</sup>. In the case of a major change to manufacturing site this code is B.II.b.1 (c) or B.II.b.1 (d)
- Supporting data relating to the proposed variation<sup>2</sup>
- Update or amendment to the relevant sections of the CTD. For a change to manufacturing site this is primarily Module Modules 1-3
- If the competent authority requests new data to be submitted as part of the application, a copy of the request should be attached to the cover letter.
- Updated labelling and package leaflet detailing the new site of manufacture is required as well as the relevant translations.
- Additional documentation regarding notification to member states and acknowledgement of fees paid to the relevant authority are required depending on whether the variation is by the mutual recognition procedure, purely national or by the centralised procedure.

### Notes:

<sup>1</sup>The guideline also outlines examples where classification as a Type IB change (where notification is required 30 days prior to implementation) is deemed appropriate. These



include sites that have been previously authorised to manufacture similar dosage forms and have been inspected in the last 3 years by one of the Member States of the EU/EEA or where an operational GMP mutual recognition agreement exists between countries.

<sup>2</sup>Supporting data: This would normally include comparative dissolution data to show equivalency, a copy of the process validation or report, plus supporting stability data for drug product manufactured at the new site or with API from new API manufacturing site.

### **South Africa:**

A major post-registration change in the South Africa is classified as a Type C amendment. Medicines Control Council Amendments guideline (2012) provides an Annex that details the documents that may be affected or required for the change in manufacturing site. There are also some general requirements listed in the guidance document titled 'Implementation of the Post-Registration Amendments Guideline' (MCC, 2003). The application must be presented in the ZA-CTD format from June 2016. It is notable however that South Africa has still not fully adopted the electronic CTD (eCTD). Therefore paper submissions are still in operation. Specific instructions on the application package can be found in the guidance i.e. how the amendment should be bound. Submissions to MCC are written in English.

The following documentation is required:

- Amendment Schedule which entails:
  - Cover Letter
  - Old Circular 6/96 form
  - Forms MRF3 and MRF 3B
  - Other information relevant to the amendment application
  - Correct coding of the amendment is required
- Completed Forms MRF1 Part 1A including 1Ac – Amendment History/CTD Module 1.2.1
- Update or amendment to the relevant sections of the CTD. For a change to

manufacturing site this is primarily Modules 1-3.

- If the dossier has not been updated in 5 years, a fully updated dossier in CTD format should accompany the application for a change in manufacturer.
- The original medicine registration certificate should accompany amendments to registered products for a change in manufacturing site
- Copy of SAPC and Registrar of Companies registration certificates
- Latest inspection report (for manufacturers outside South Africa in recognised countries)
- A copy of the manufacturing licence or a GMP certificate and a WHO GMP Certificate (for manufacturers outside South Africa in recognised countries)
- Proposed process validation protocol or validation report
- Stability protocol and data to support change
- Proof of efficacy – dissolution data

**Brazil:**

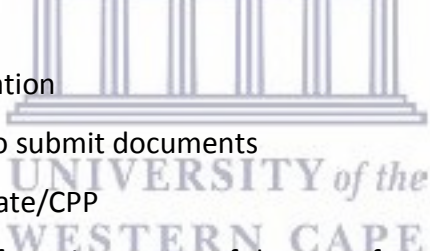
The documentation required for a modification to the regulatory dossier in Brazil is described in Annex I of Resolution RDC No.73. The following is required by ANVISA for a major change.

- Payment Slip relating to the Health Surveillance Inspection Fee
- Duly completed application forms
- Justification for the request
- Company Technical Analysis Opinion (PATE) - opinion prepared by the company Registrant that covers at least all the criteria and documents provided this Resolution and related regulations. ANVISA provides additional guidance on the preparation of the PATE.
- Stability Protocol in support of the change and any data generated to date
- Copy of Certificate of Good Manufacturing Practice issued by ANVISA
- Case file validation protocol
- Production Order and comparative table B of Annex IV – completion of this table allows a comparison of the production process to be made.

- Analytical Reports for one batch made at the existing approved site and for one batch made at the proposed site.
- Comparative dissolution profiles of batches manufactured at the approved and proposed sites.
- Validation reports for the analytical methods
- Technical report on relative bioavailability/bioequivalence of the medicinal product

**Russia:**

The guidelines provided by the Russian Ministry of Health detail the documents required in order to register 'changing of participants of production' i.e. new production site. All documents must be submitted in Russian or have a Russian translation, duly certified. All pages of the application are signed by the authorised person and stamped applicant. Hard copies of documents are submitted. The set of documents required for a change in manufacturing site in Russia are as follows:

- 
- Explanation Letter
  - Application for Variation
  - Power of attorney to submit documents
  - Registration Certificate/CPP
  - Place of Drug Manufacturing – copy of the manufacturing license or copy of the GMP certificate or other permits allowing the production of medicines
  - Manufacturing Scheme
  - Draft of Normative Documentation – drafts of relevant sections of the dossier
  - A copy of the approved regulatory documentation
  - Analytical data proving drug quality – Certificates of Analysis for at least 3 batches
  - Supportive stability data
  - Two copies of draft layouts for packaging
  - Copies of the existing layouts packages
  - Draft instructions for use
  - Copy of the current instructions for use

### **China:**

Supplemental applications must be approved by China's State Food and Drug Administration (CFDA) as per Annex 4: Registration Items and Applications Information Requirements of Supplemental Application of Drug Registration. The following items are required to register a change in the location where an import drug is manufactured.

- Supplementary Drug Application Form
- Copies of the drug approval certificate and appendices – includes all the approval documents related to the application
- Copies of the drug manufacture certificate, business licenses and GMP certificate
- The certified documents, notarized documents of the approval of the changes of the drugs issued by the competent drug administration authorities at local country or region and the Chinese translation should be provided.
- Draft of amended design of the insert sheet of the drugs, attached with detailed notes for amendments
- Draft of the amended design of the packaging and label of the drugs, attached with detailed notes for amendments
- Pharmaceutical study information – part or all experiment information of - Pharmaceutical study and necessary global literature hold be provide respectively for the different registration category
- Chromatograms from the stability programme are required. Raw data and supporting documentation must be produced manually (paper)

In addition to the above documents registration inspection should be conducted on three batches of drug product. Registration inspection means that batches are sent to China for test – analytical method transfer is required for this activity from the method owner (usually the manufacturing site quality control laboratory).

**Table 2: Overview of Documentation Required by the Regulatory Agencies under Review for a Change in Manufacturing Site**

Document(s)	US FDA	EMA	MCC	ANVISA	Russia MOH	CFDA
Cover Letter	✓	✓	✓	✓	✓	✓
Application Form	✓	✓	✓	✓	✓	✓
Updated Technical Sections of the Dossier	✓	✓	✓	✓	✓	✓
Supporting Stability Protocol	✓	✓	✓	✓	-	-
Dissolution Equivalency Report	✓	✓	✓	✓	-	-
Updated Labelling and Package Leaflet	-	✓	-	-	✓	✓
Additional application forms required by the agency	-	-	✓	✓	-	-
Process Validation Protocol	-	✓	✓	✓	-	-
A copy of the GMP manufacturing licence	-	-	✓	✓	✓	✓
Latest Inspection Report	-	-	✓	-	-	-
Original Registration Certificate issued by the Agency	-	-	✓	✓	✓	✓
Company Technical Analysis Opinion (PATE)	-	-	-	✓	-	-
Analytical Reports (Certificate of Analysis) for 1-3 Batches	-	-	-	✓	✓	-
Power of Attorney Documents	-	-	-	-	✓	-
Registration Certificate/CPP in country of origin	-	-	-	-	✓	-
Raw Data (Copies Produced Manually)	-	-	-	-	-	✓

### 4.3 Comparison of Stability Data Requirements

Table 3 gives the stability requirements as part of variations approval at the six agencies under review.

**Table 3: Comparison of stability data required for a change in Manufacturing Site**

Country	Stability Requirements	Maximum Time Needed	Reference
United States	<p>Significant body of data available: one batch with three months accelerated (40°C/75% RH) data in supplement; one batch on long term stability with data to be reported in the annual report</p> <p>Significant body of data not available: up to three batches with three months accelerated (40°C/75% RH) data reported in supplement; up to three batches on long term stability with data to be reported in the annual report</p>	3 months	(SUPAC, 1995)
Europe	<p>Conventional Dosage Forms: 6 months 25°C/60% RH and 40°C/75% RH on at least two batches of at least pilot scale are recommended</p> <p>Critical Dosage Forms (modified release): 6 months 25°C/60% RH and 40°C/75% RH on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.</p>	6 months	(EMA, 2014)
South Africa	9 months data from at least one pilot batch stored at 25°C/60% RH, plus 3 months data at 40°C/75% RH should be submitted with amendment. Study would continue for shelf life of drug product.	9 months	(MCC, 2012)
Brazil	Long term stability of 3 batches (30°C/75% RH) to be included in the HMP. One batch to be submitted in the application and the first 2 production batches after approval is implemented.	Not specified Assume data to cover shelf life - minimum 12 months	(ANVISA, 2016)
Russia	No specific stability requirements listed	Not specified Assume data to cover shelf life - minimum 12 months	N/A
China	No specific stability requirements listed	Not specified Assume data to cover shelf life - minimum 12 months	N/A

#### 4.4 Comparison of Approval Times

Table 4 gives the timelines for the review and approval of variations at the six agencies under review. Review times were taken from the regulatory agency websites unless otherwise referenced.

**Table 4: Comparison of Approval Times**

Country	Agency	Review Time
United States	FDA	6 months
Europe	EMA	6-9 months
South Africa	MCC	2 years <sup>a</sup>
Brazil	ANVISA	24-30 months <sup>b</sup>
Russia	MOH	6-12 months <sup>c</sup>
China	CFDA	24-36 months <sup>d</sup>

<sup>a</sup> Reference Chorley (2014)

<sup>b</sup> Oblessuc (2014)

<sup>c</sup> Reference Chorich (unknown)

<sup>d</sup> CFDA Guidance specifies different time lines for different stages of the review process. This total is estimated from the times given.



## Chapter 5: Discussion

### 5.1 Interpretation of Results

A comprehensive review was carried out examining the documentation that is required for a post-approval change application in six of the major global pharmaceutical markets. It was hoped that the study would highlight the similarities and differences in the documentation requirements. As can be seen from the text in Chapter 4.2 and in the overview provided in Table 2, there are some notable similarities but also many differences between the countries. By comparing and contrasting the documentation required some ideas for developing an effective regulatory strategy to manage post-approval change have emerged. This is discussed throughout the text below and further expanded in Chapter 5.2.

In general all the regulatory authorities require a cover letter, application form and appropriate updates to the regulatory technical dossier. When examining this deeper however each agency had its own format of cover letter and application forms, so work will always be duplicated here for multiple global applications. Some agencies, most notably South Africa's MMC, requires very detailed application forms to be filled out. A criticism here might be that information is over processed. However the MCC provides very clear guidance on post-approval requirements when compared with some of the other agencies. This is very commendable and helpful towards establishing a global regulatory strategy.

All the agencies reviewed appear to accept the CTD format of the dossier. Although not compulsory in Russia, Russia will accept the EU dossier, once it has been converted to Russian and duly verified. Adoption of the CTD is still not yet a global phenomenon. Harmonisation groups such as The Global Cooperation Group (GCG) are working towards bringing ICH and the CTD to the rest of the world (ICH, 2010). While this project only analyses six countries it should give some insight into the differences that would be experienced with the documentation for other countries. The CTD has



dramatically reduced the burden on global regulatory filing in the past decade. Future improvements will be facilitated through the implementation of ICH Q12 and the introduction of the next generation of information technology platforms for the eCTD.

Many of the agencies require supportive analytical data in the form of stability data for batches manufactured at the new site and/or dissolution equivalency testing between the batches manufactured at the old site and new site. FDA SUPAC guidance provides clear guidance on how to demonstrate dissolution equivalency. This is a good basis for designing a study that will meet the requirements for all countries and avoid duplication later. Table 3 provides a comparison of the stability data required to support a change to a manufacturing site. Looking at the differing length of stability studies in conjunction with Table 4, which shows the review timeline for submission approval, it is clear why the time for approval of submissions can vary dramatically for different countries. Most pharmaceutical companies will file the change as soon as the necessary documentation is available. The US for example only requires 3 months stability data. It is unlikely that a company will wait for the additional 6-9 months required by South Africa and others to file applications simultaneously. This could lead to a loss of revenue from gaining approval in the US earlier. One of the difficulties with the long and different approval time lines for pharmaceutical companies wishing to register a new manufacturing site is that some countries will have to be supplied from the old factory until such time as approval is granted in all territories. This is a costly enterprise.

Notably (see table 4) the review time in the United States is the shortest. This is most likely because PASs are subject to performance and review goals under GDUFA, which are intended to make sure FDA reviews applications quickly. In return, industry helps fund FDA through the submission of fees. The time line for review in the emerging countries is quite long, up to three years for China. This makes the change management extremely difficult for companies.

## 5.2 Recommendations

The pressure on companies to file the initial application can sometimes mean that the requirements for the US and EU are met first and foremost, without consideration for the global registration programme later. This is understandable for smaller companies with limited resources, especially since approval of the drug in the US and EU has many important advantages. Firstly these are two of the biggest markets with the most established regulatory systems, which provide the fastest review turnaround at present. Secondly many other non-ICH countries will only approve a drug if it has been already approved in these territories. However as the emerging countries develop their regulatory systems, many modelling them on the US and EU systems, it stands to reason that companies should have a more global outlook from the beginning of the development phase.

This could include for example, performing global stability studies to support Zone III and IV from the beginning of the product development, adoption of a Quality by Design (QbD) approach as per ICH Q8-10 and incorporation of the principles from ICH Q12 on lifecycle management. A global stability programme to support Zone III and IV would include long term stability conditions of 30°C/35% RH (relative humidity) and 30°C/75% RH, in addition to the traditional 25°C/60% RH required for Zone I and II countries. Often stability programmes for these conditions are only initiated later in the product lifecycle, when the data is required to register outside the ICH countries United States, Europe and Japan. Inclusion of these conditions earlier in the lifecycle would mean data is more readily available when the time comes to register in the rest of world. This would aid a simultaneously submission approach. ICH chapters Q8-11 place emphasis on obtaining better knowledge of products and processes through quality-by-design (QbD). A key goal of ICH Q11 is to harmonise the common technical dossier (CTD) submissions globally (Drakulich, 2012). Risk analysis, assessments linking material attributes to process parameters, critical quality attributes, design space, and process control strategy are all required as part of the enhanced QbD approach. The Q11 guidance attempts to provide examples on how to include some of the QbD

concepts in the CTD (Drakulich, 2012). The next chapter for ICH is the implementation of the Q12 guidance on Lifecycle Management (ICH, 2014). ICH recognises the lack of a harmonised approach for lifecycle management. The concept paper (ICH, 2014) proposes that the new guideline will provide a framework to facilitate the management of post-approval changes.

The use of post-approval change management protocols is also a step in the right direction. This is where the company provides a protocol to the regulatory agency during the initial submission, which will outline what changes a company would like to introduce during the lifecycle of the product (EMA, 2012). The protocol outlines how the changes would be implemented and verified should they be required. This risk based approach means that agreement is received from the agency up front. If the time comes that the change is required, it can be submitted as part of the Annual report.

In an ideal regulatory scenario there would be one global set of CMC requirements, one risk-based review of application for an efficient global approval, and one site regulatory inspection (Chang, 2014). However this dream is a long way off from reality. In the interim companies must plan their regulatory strategy with efficiency to reduce the cost burden. It begins with understanding the different global regulatory requirements. A more intensive study than the one performed here, which includes more countries and regions, would be beneficial for devising a company's strategy. The initial investment into such an exercise would require resource. However it would enable the design of an appropriate regulatory database that could be used as reference for submissions. The limitation with this of course, is that regulatory guidance is constantly evolving. It is important to ensure the guidance is regularly reviewed and the database maintained as a consequence.

EMA and MCC have impressive detailed guidance on exactly what documentation is required for a post-approval submission. This means that templates could be created and managed by the Regulatory Affairs department in the pharmaceutical company.

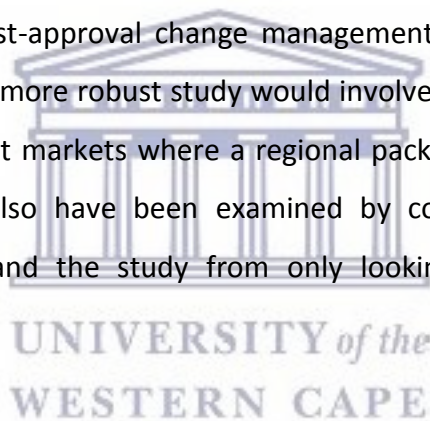
An effective regulatory system needs investment by the pharmaceutical company in order to ensure it is adequately resourced to manage global registrations. Software packages to develop regulatory documentation and manage Marketing Authorization Applications Postapproval could be employed to achieve this goal.



## Chapter 6: Conclusion

The postapproval change process should not hold back change for the better. This study has served to highlight the similarities and differences in the documentation required for a global post-approval amendment to the CMC dossier. Recognising the limitations that only six countries were examined here. However these are considered six of the largest pharmaceutical markets in the world. Growth from the emerging countries is also represented by the BRICS group members China, Russia and Brazil and South Africa. The study also underlines the complexities that arise in global post-approval change management and how these intricacies require large investment from pharmaceutical companies in both time and monetary terms.

Many countries model post-approval change management on that of the countries reviewed here. However a more robust study would involve more countries. Had time allowed, perhaps looking at markets where a regional pack is used. The cost of post-approval changes could also have been examined by comparing the fees in the different regions; to expand the study from only looking at the documentation requirements.



One thing that is evident in this study is that investment in a robust regulatory change management team is an essential requirement for pharmaceutical companies now and in the future. It is hoped that with the implementation of ICH Q12, that global harmonisation in the lifecycle management of medicines ultimately means continued supply of medicines for the patient.

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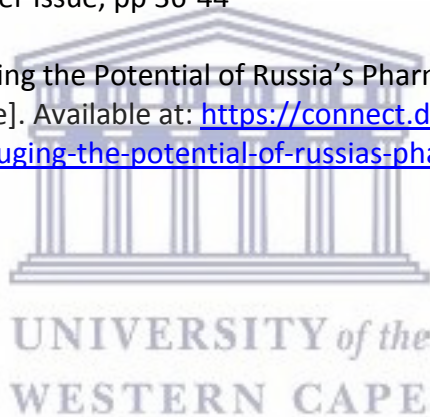
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## **APPENDICES**

### **Appendix 1: Research Proposal**

#### **Title:**

A Comprehensive Study on the Global Regulatory Requirements for the submission of a Post-Approval Change, specifically a Change in Manufacturing Site

#### **Introduction:**

Regulatory requirements for post-approval changes vary for different countries around the world. It is a challenging and costly process for pharmaceutical companies to manage changes to the approved regulatory dossier over the lifecycle of the product when it is registered in many countries. In practice the process can be complex, unpredictable and time consuming because of regional differences and frequent changes in regulatory procedures, requirements and timelines.

The global regulatory requirements for the submission of a post-approval change, specifically a change in manufacturing site, will be reviewed for at least five jurisdictions for this study. These will include EU, US, South Africa, Brazil and Russia. The study will be centred on the differences in the documentation required when submitting a post-approval change for a change in manufacturing site in these countries. The study will compare and contrast the differences and similarities between the jurisdictions. An analysis of the challenges for implementation of the change will be performed. The study will also examine what resources a company may need in order to meet the requirements, esp. when different data has to be generated for the various jurisdictions. This information could potentially be of use in strategic planning within a company in order to ensure continued product access globally.

#### **Methodology:**

The research for this dissertation will be a literature-based review with the aim to provide qualitative analysis on a specific research topic that has practical relevance to regulatory affairs. This is a qualitative study that is aimed to identify themes and patterns.

#### **Ethical Consideration:**

Ethical approval from the Ethics Review Board will not be required for this project. The student will solely conduct research for this mini-thesis.