TITLE

Risk based approach of Post- Approval changes in Central America and Dominican Republic, Identifying opportunities for Convergence with EMA and FDA

M.Pharm. proposal by

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DECLARATION

I declare that the mini-dissertation hereby submitted to the University of Limpopo, Medunsa Campus, for the degree of Master of Science (Medical) in Pharmacy, in the Faculty of Health Sciences, School of Health Care Sciences, has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

Nov 18, 2021

Trejos, AG **Date**

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ABBREVIATIONS AND ACRONYMS

ARSA	Medicines and Medical Devices Regulation Agency (Agencia de Regulación Sanitaria), Honduras
CA	Central America
CAC	Central America and Caribbean
CBE-0	Changes effective in 0 days (FDA)
CBE-30	Changes effective in 30 days (FDA)
CMC	Chemistry, Manufacturing and Controls
cGMP	current Good Manufacturing Practices
CTD	Common Technical Dossier
DIGEMAPS	General Direction of Drug Products, Food and Health Products (Dirección General de Medicamentos, Alimentos y Productos Sanitarios), Dominican Republic
DNM	National Directorate of Medicines (Dirección Nacional de Medicamentos), El Salvador
DP	Drug Product
DR	Dominican Republic
DS	Drug Substance
ECs	Established Conditions
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FyD	Pharmacy and Drugs (Farmacia y Drogas), Panama
FDA	Food and Drug Administration, United States of America
FP	Finished Product

ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MC	Minor Change
MOH	Ministry of Health
MSCR	Ministry of Health of Costa Rica (Ministerio de Salud de Costa Rica)
MINSA	Ministry of Health (Ministerio de Salud), Nicaragua
MSPAS	Ministry of Public Health and Social Assistance (Ministerio de Salud Pública y Asistencia Social), Guatemala
NDA	New Drug Application
NRA	National Regulatory Authority
OECD	Organisation for Economic Co-operation and Development
PA	Prior Approval
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PAS	Prior Approval Supplement
PQS	Pharmaceutical Quality System
RTCA	Central American Technical Regulation (Reglamento Técnico Centroamericano)
SICA	Central American Integration System (Sistema Centroamericano de Integración Económica)
SUPAC	Scale-Up and Post-approval Changes
US	United States
WHO	World Health Organization

ABSTRACT

Introduction: In Central American countries (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama) and Dominican Republic (DR) the approval timelines for major changes are described ranging from 12 to 18 months, these timelines are considerably extensive. Other countries or regions applying FDA post-approval change and EMA post-approval variation guidelines have timelines of 6 months or less (Hoath et al, 2016, Murray, 2016). The research aims to identify opportunities for alignment of the post-approval changes categories of Central America (CA) and Dominican Republic (DR) National Regulatory Agencies (NRA) with the risk-based categories of FDA and EMA as encouraged by the ICH. The FDA and EMA are considered reference authorities for many countries, as they are Stringent Authorities.

Objectives: The objectives of the study are to describe the PAC category classification by listing the PACs from each of the NRA´s regulation (MSPAS, DNM, ARSA, MINSA, MSCR and FyD), compare the information with the classification from FDA and EMA and propose PAC category recommendations for CA and DR regulations.

Method: A qualitative comparative approach was used. The data was collected through a literature-based review of Central American countries´ regulatory requirements with regards to post-approval changes and comparing these requirements to those of the FDA and EMA.

Results: Eight (8) PACs were compared with the reference country's NRA's (FDA and EMA). The proportion of Notifications for Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Dominican Republic is 3.7% and 7.4% for Panama while for FDA was 41 % and for EMA it was 37%.

Conclusion: The PAC categories in CA and DR regulations were identified. The CA and DR NRAs categories for seven (7) PACs differ from FDA and EMA risk-based categories.

Recommendations: Implement convergence with PAC risk-based categories from EMA and FDA, increasing the number of PACs to be notified. The recommendation of this research is to change the proportion of PACs in CA and DR to 48 % Notifications, 11 % Prior Approval (PA) and a more detailed classification is necessary for 41 % which can be classified as PA or Notification.

CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

In this chapter, introductory aspects about the background and study rationale, research question, aim, objectives and importance of the study will be covered in the following sections.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Post-approval changes (PACs) are an important part of the product lifecycle. Pharmaceutical Industry needs to implement these changes to improve the manufacturing processes or quality control analysis, introduction of state of the art technology in the sites and to respond to changes in regulatory requirements from Health Authorities (EFPIA, 2017). Even before the product is launched to the market, there are PACs that are already planned, for example, increase of batch size or additional manufacturing sites to be able to support the increase of product demand once the product is launched and expand access (Murray, 2016).

For products marketed worldwide, a company may have to submit a post-approval change to National Regulatory Authority (NRA) of about 140 countries (Hoath et al, 2016). The regulations for post-approval categories and requirements worldwide vary widely. Many PACs require regulatory approval and obtaining the worldwide regulatory approval may take long time, making the implementation of a post-approval changes very challenging (Murray, 2016).

1.3 RESEARCH QUESTION

The research question is: Can Central American (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama) and Dominican Republic national regulatory agencies´ post-approval change regulations be categorised according to ICH terminology and compared to EMA and FDA regulations.

1.4 AIM OF THE STUDY

The aim of this study is to identify post-approval changes from NRA policies within Central America and Dominican Republic aligned to the risk based approach recommended by ICH guidelines through a comprehensive review of the policies that apply to Chemistry, Manufacturing and Controls (CMC) variations for small molecules using as reference the classification from reference agencies (FDA and EMA).

1.5 OBJECTIVES OF THE STUDY

The objectives of the study are the following:

- Describe the PAC categories according to ICH risk-based approach in the CA and DR countries, FDA and EMA.
- List the PACs described in the CA and DR regulations related to finished product of small molecules and its categories according to ICH Q12 terminology.
- Compare the CA and DR list of PACs categories to the reference agencies' categories (FDA and EMA).
- Recommend a list of PACs that can change categories based on reference agencies (FDA and EMA).
- To compare the amount of post-approval changes that require a notification or prior approval on each regulatory association.

1.6 IMPORTANCE OR SIGNIFICANCE OF THE STUDY

In Central America (CA) and Dominican Republic (DR) the approval timelines for major changes are described ranging from 12 to 18 months, these timelines are considerably extensive considering other countries or regions where the timelines are of 6 months or less (Hoath et al, 2016). The management of PAC requests is also difficult for Regulatory Authorities. RA within CA and DR countries suffer resource constraints. Regulations that do not contemplate risk-based approaches, within this limited capacity setting contribute to the long approval timelines (Murray, 2016).

The high variability in the approvals of PACs worldwide leads to companies to have to manage multiple inventories according to the approval status, reducing their ability to respond to changes

of demand of the product, leading to a higher risk of noncompliance or to stock-out situations (EFPIA, 2017). For example, when a new molecular entity is submitted for approval for the first time all the product is manufactured under one process, once the product is approved by the RA agencies the MAH submits a change in process. The RAs approve the PACs at different timelines. The MAH starts implementing the change for the approved markets but has to keep the first process for the markets where the RA hasn´t approved the product and as the number of PACs submitted increase, the company may have to replicate this situation and have several different production batches depending of the PACs approval situation for every market. This situation hinders the ability to react if there is a change in demand and this can cause product shortages (Ramnarine, 2018).

This lead the researcher to explore the possibility of CA and DR NRA's to converge with reference agencies´ where CMC changes are categorised according to the potential risk to product quality, safety, and efficacy; with the aim of suggesting changes in the current categories to reduce the time to implementation of PACs that pose a low risk to patient safety. If taken into consideration by NRAs, these recommendations may have an important impact in the lifecycle management of the products and will benefit patients, NRAs and industry.

In this research, the reference agencies that will be used as comparison for NRA from Central America and Dominican Republic are the EMA and FDA. These agencies represent ICH Founding Regulatory Members (ICH, no date), are Stringent Regulatory Agencies according to the WHO and for the region under study are considered as reference agencies.

1.7 OUTLINE OF THE DISSERTATION

Chapter 2 will cover the relevant literature review for this dissertation, then Chapter 3 the Methodology including the aim and objectives of the research, Chapter 4 the Results and Discussions and finally Chapter 5 with the Summary of Results, Conclusions and Recommendations.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the literature review will go through the concept of risk-based approach to lifecycle management from ICH Q12 guideline and other important concepts mentioned in ICH documents. Implementation of post-approval changes to finished pharmaceutical products is important to support supply chain continuity and to facilitate innovation. The lack of a worldwide-harmonized approach towards lifecycle management of technical changes is affecting the industry capacity for innovation and continuous improvement processes (ICH, 2014). It´s important that the lifecycle of a product is seen with an integrated approach to quality risk management and science (ICH, 2014). The national regulatory authority, within each country, should formulate CMC regulatory reviews in accordance with the potential product risk (FDA, 2014).

Latin America has improved in the modernization of the public sector, however processes are still very bureaucratic affecting the timeliness and quality of the public services as happens with the process to obtain the drug approval or license that varies widely across the agencies from the region (PRO-COMPETENCIA, 2017).

As stated by the WHO (2015, p.204) 'The quality, timeliness and success of medical product application reviews are dependent on adequate RA review capacity'. The review capacity is having enough and adequately prepared personnel for the tasks under their responsibility (WHO, 2015). Given the long approval timelines in the Central American and Dominican Republic when compared with FDA and EMA, it´s important to contemplate that convergence with the risk-based categories and reliance in the regulatory reviews for PACs performed by these reference RAs could alleviate and improve the efficiency of the countries under scope. There is a lot of pressure for NRA due to the growing workload and the resources are limited, both in capacity and expertise and in a globalized world, international cooperation should be considered (WHO, 2016).

2.2 ICH RISK-BASED APPROACH

The scope of the ICH Q12 Guideline (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management) is pharmaceutical drug products (DP) and drug substances (DS) that require marketing authorization (MA). As mentioned in the ICH Q12 Concept

Paper (ICH, 2014, p.2) 'An ICH harmonised approach on technical and regulatory considerations for lifecycle management will benefit industry, regulators and patients by supporting continued quality assurance and supply of high quality product'.

One of the key elements mentioned in the ICH Q12 is the implementation of a risk-based approach towards quality of the products. It is encouraged that NRAs have a risk-based approach for the categories of changes that considers the potential to affect the quality of the DP, DS, manufacturing process, quality controls, the facility and equipment (ICH, 2017). The ICH Q12 (ICH, 2019) guideline encourages the following submission categories for post-approval changes: prior approval (higher risk changes to require RA review), notification (moderate to low risk changes) and suggests that some changes with very low risk are not notified to the RAs and are documented in the Pharmaceutical Quality System (PQS). The outcome of the review indicates that the implementation of this system can support opportunities to lowering of regulatory submission requirements and converge to the categories of other countries based on improved product and process knowledge (ICH, 2019).

Additional to post-approval change risk-based approach as part of the product lifecycle, ICH Q 12 also addresses topics covered in other ICH guidelines: the pharmaceutical quality system (ICH Q10) during commercial phase and complements and details on flexible regulatory approaches for CMC PAC described in ICH Q8(R2) and Q10 Annex 1 (ICH, 2019). ICH Q12 is under implementation step process by ICH members, EMA and FDA have guidelines and regulations in place with risk-based post-approval change categorization as described in 2.2.1 and 2.2.2.

From an industry perspective, the expectation with the adoption of this guideline is that the NRAs implement a risk-based approach and focus their resources on the evaluation of the major and moderate changes (EFPIA, 2017). Additionally, industry also considers it valuable to implement review timelines, ideally of less than 6 months and reliance to evaluations performed by Stringent Regulatory Agencies (SRA) (Murray, 2016). The journey of the preparation of a PAC by the Marketing Authorization Holder (MAH) for submission to around 140 agencies and timeline to approval are highly complex. For the MAH these processes have an economic impact, supply complexity increases, systems to track filings and regulatory compliance must be implemented, and the commercialization maybe interrupted due to increasing approval timelines affecting the patients and the company (Murray, 2016).

2.2.1 European Medicines Agency (EMA)

The European Commission is a Founding Regulatory Member in ICH, as mentioned in the ICH website (ICH, no date). The European Commission is legally responsible to authorize the centrally authorized products for the European Union based on the EMA´s recommendation (EMA, no date). Through the centralized procedure, the companies submit a one marketing authorization to the EMA. The EMA´s recommendation for a medicine for human use to be marketed or not is based on the scientific assessment performed by the EMA's Committee for Medicinal products for Human Use (CHMP) (EMA, no date). The centralized procedure is compulsory for human medicines with new active substances with indications for human immunodeficiency virus or acquired immune deficiency syndrome, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, viral diseases, medicines derived from biotechnology processes, advanced-therapy medicines, somatic cell-therapy or tissue-engineered medicines and orphan medicines (medicines for rare diseases) (EMA, no date). It is optional for other innovative medicines with new active ingredients. The scope of this investigation are the products approved though the EMA centralized procedure.

The submission of post-approval variations must follow the European Commission Regulation No. 1234/2008 (EC, 2008). In Chapter I, Article 2 includes the definitions for the types of variations: Minor variation type IA, Major variation type II, extension of a marketing authorization or extension and minor variation of type IB. This information is compared with the classification of other jurisdictions in Chapter 4 of the Results.

In the case of type IA variations, the MAH should submit the information complying with the requirements within 12 months of the implementation (IA) except in the case of minor variations requiring immediate notification (IAIN). Within 30 days of the receipt of the notification, the EMA should inform the MAH the outcome of the assessment (EC, 2008). Even though type IA variations are notifications “Do and Tell” procedure, the EMA reviews the application and issues an acceptance or rejection of the notification in 30 days. The EMA may require additional information but if the decision is to reject the notification, the MAH has to cease the implementation of the respective variation. (EC, 2013)

For type IB minor variations the MAH should submit the notification and the required supporting information. The EMA has 7 days to perform a ´validation´ of the classification of the change and its completeness, the MAH is informed if the application in receipt (EC, 2013). After the receipt the clock starts and the EMA will inform within 30 days if the notification is favourable or unfavourable, if the 30 days have passed it can be assumed the notification is favourable (EC,

2008). If unfavourable the MAH has 30 days to provide additional information and justifications and EMA has 30 days for the review (EC, 2013).

In the case of the variations of ´Prior approval´, classified as type II, the MAH should submit the variations and requirements and the EMA shall issue the opinion in 60 days after the receipt (EC, 2008). The period may be reduced in case of urgency or extended to 90 days in certain cases, for example when grouping variations. Additional information may be requested by the EMA and it must be fulfilled in the given timeframe, the clock stops usually for 1 month and if additional time is required to provide the information it should be justified for an additional. After supplemental information is provided by the MAH, the EMA will review it in a period of 30-60 days (EC, 2013).

According to Regulation No. 1234/2008, Chapter IV, Article 24 the implementation timelines for variations, in the case of type IA the implementation may be anytime (EC, 2008). Type IB variations may be implemented once informed that the notification is accepted (approximately 37 days) and in the case of the Type II the MAH must wait for the EMA approval (EC, 2008).

When a type IA, IB and II is approved and the MA needs to be updated, the Commission will perform the update within 12 months (EC, 2013). The MA is updated in 2 months for some cases of type II variations listed in the Guideline related to clinical or safety information not related with the CMC scope of this research. This may be a limitation for the implementation of reliance, if a requirement of a CA and DR NRA to apply reliance is the evidence of the updated MA approval and the updated document is not available.

The post-approval changes are listed in the Annex of the Guideline for Commission Regulation No 1234/2008 and are classified in a) Administrative Changes, B) Quality Changes for active substance and finished product (FP) and C) Safety, Efficacy, Pharmacovigilance Changes (EC, 2013). Given the scope of this research the review will focus on the administrative changes and quality changes for finished product. In this Annex each type of change and the conditions to be fulfilled are described, and the categories and documentation to be provided. The information will be described in Chapter 4 of the Results.

2.2.2 United States (FDA)

According to the Code of Federal Regulation, Title 21, part 314, Section 314.70 “Supplements and other changes to an approved NDA” the following are the categories for post-approval changes: major, moderate and minor (FDA, 2019a). In the case of major changes, the MAH must submit the change and wait for approval before the implementation; these are known as Prior

Approval Supplement (PAS). In the case of moderate changes, the MAH must wait either at least 30 days prior to implementation (CBE-30) or implementation may be after submission (CBE-0) and in the case of minor changes (MC) these can be included in an annual report (FDA, 2004).

The categories of changes is risk based, this means based on the risk of having an issue with the safety or effectiveness of the DP due to the effect of a change in the identity, strength, quality, purity or potency of the DP (FDA, 2019a). In the case of major changes, it may have a substantial potential, moderate changes have a moderate potential and in the case of minor changes a minimal potential.

There are several guidance documents for CMC post-approval changes for small molecules under the scope of this research; the recommendations include changes in components, composition, manufacturing sites, manufacturing processes, specifications, container/closure system and others. The Guidance for Industry document “Changes to an Approved NDA or ANDA” mentions that it provides recommendations on the reporting categories and these should be consistent with other published documents, if cases of inconsistency with previously issued documents, this guideline has the most updated considerations (FDA, 2004).

This is a list of the documents issued by FDA related to PAC (FDA, 2004), which may be supportive to the aim of this research:

• PAC-ATLS: Postapproval Changes – Analytical Testing Laboratory Sites, dated April 28, 1998

• SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, dated November 1995

• SUPAC-IR Questions and Answers about SUPAC-IR Guidance, dated February 18, 1997,

• SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum, dated January 1999

• SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, dated September 1997,

• SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, dated May 1997

• SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum, dated December 1998

• Changes to an Approved NDA or ANDA: Questions and Answers, dated January 2001

• Changes to an Approved NDA or ANDA, Revision 1, dated April 2004

• Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes, dated November 2004

The corresponding document will be referenced when describing the FDA category for the list of changes under study detailed in Chapter 4 of the Results.

In the case of PA changes, the MAH may request an expedited review to the FDA based on public health reasons or a situation that could not be foreseen. In the case of moderate changes if the change is not approved the FDA, the FDA may request to cease the distribution of the product with the change implemented (FDA, 2004).

2.3 CENTRAL AMERICA AND DOMINICAN REPUBLIC COUNTRIES

2.3.1 CENTRAL AMERICAN INTEGRATION SYSTEM (SICA)

Central America is a unique region, connecting North and South America, the population of the region is more than 40 million (OECD, no date). The Central American countries in geographical order are Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama. These countries are part of an Economical Integration Initiative created to stimulate the trade growth in the region.

According to FDA (FDA, 2019b), harmonization is a process where participating authorities develop technical guidelines to uniform the requirements between one another. In SICA, harmonization was implemented through the elaboration of Central American Technical Regulations (RTCA) to have harmonized requirements and to implement recognition procedures to stimulate the trade growth in the region. The RTCA regulations are supranational harmonized frameworks, meaning that the countries had to agree on a common standard for implementation in countries with different legal frameworks and health care systems (PAHO, 2019).

These countries have negotiated and agreed several harmonized regulations. The latest implemented regulation is RTCA 11.03.59:11 for the registration of pharmaceutical products. This regulation includes a list of post-approval changes and submission requirements. On December

12, 2013 the regulation was endorsed by the Council of Central American Ministers of Economic Integration (COMIECO) through the signature of Resolution No. 333-2013 (COMIECO-LXVI) and was implemented 6 months after, on June 12, 2014. Panama also signed the resolution however; according to Resolution No. 333-2013 there is a transitory timeframe for the incorporation of this country into the Economic Integration Subsystem (RTCA, 2013). Therefore, Panama has not implemented RTCA 11.03.59:11, the national regulation is part of the literature review for this country. The regulation and the resolution are available only in Spanish in the websites of most of the NRAs, given that this is the official language in these countries. According to the RTCA (RTCA, 2013), manufacturers located in a member country may register their products in the country where they are based and then request recognition in the rest of the countries. The mutual recognition process has simplified the commercialization processes; during 2016 the costs related to registration applications were reduced by 25 % (PRO-COMPETENCIA, 2017). Currently there are no transnational companies manufacturing in any country of the region. Therefore, transnational companies have to apply for registrations in each country individually for evaluation of quality, safety and efficacy.

In the case of post-approval changes, there is no recognition regulation in place. Therefore, all applicants have to submit to each of the member countries the post-approval changes for approval.

The classification and requirements for post-approval changes to the drug registration are included in Annex I of the RTCA 11.03.59:11. Annex I has two sections, Section A for modifications that require previous approval and Section B for notifications. Annex I includes 19 modifications in Section A and 4 notifications in Section B (RTCA, 2013).

The timeframes for evaluation and procedures are not part of the RTCA regulation given that it covers requirements only. The timeframes are part of the NRAs regulation. The following sub-sections will refer to the individual member regulations about revision timeframes.

COSTA RICA (MSCR)

Decree No. 38409-S of the Reform of the Regulation of the functioning and usage of the “REGISTRELO” portal regulates the review timeframes for the approval of the different types of submission for DPs (MSCR, 2014). REGISTRELO is the Costa Rican online platform for the submission, review and approval of applications for registration, renewal and post-approval changes for DPs, natural products, cosmetics and others. This system allows an efficient, safe and transparent product registration. (PRO-COMPETENCIA, 2017). The NRA is able to have a

standardized review process and monitor review timelines and the applicant can check online the status of their submission (PRO-COMPETENCIA, 2017).

In Decree No. 38409-S, recital III, it´s stated that the MSCR considers it´s appropriate to establish a resolution timeframe for the products of health interest. Article 43 of this regulation details the timeframes per type of process. Article 34.1.4.1 indicates that in the case of notifications, the MSCR has 1 month to approve or reject the request. Article 34.1.4.2 indicates that for post-approval changes that require evaluation the MSCR has up to 3 months to approve or reject the requests (MSCR, 2014).

The MSCR publishes a monthly report of average revision timeframes in “REGISTRELO” portal per type of process. According to the report from September 2019, the average review time for post-approval changes at that moment was 48 working days, less than the 66 working days established by Decree 38409-S (REGISTRELO, 2019).

The MSCR has a very efficient online platform for the submission of regulatory applications of health products. All the processes, follow-up of the status and communication between the authority and the applicant is online. As mentioned above, the MSCR has resolution timelines established per regulation and the system facilitates the control of this timelines through reports.

The NRA has the responsibility to monitor and control the timely resolution of processes according to the timelines established in the regulation. The established timelines and transparency though the system facilitate the predictability of regulatory processes.

El Salvador (DNM)

There are no timeframes established by regulation for post-approval changes.

Guatemala (MSPAS)

There are no timeframes established by regulation for post-approval changes.

Honduras (ARSA)

There are no timeframes established by regulation for post-approval changes.

Nicaragua (MINSA)

There are no timeframes established by regulation for post-approval changes.

2.3.2 Panama (FyD)

Executive Decree No. 95 (FyD, 2019) regulates the registration, renewal, post-approval changes and other topics related to DPs and other health products. Executive Decree No. 95 was signed May 14th, 2019 and supersedes Executive Decree No. 178 from July, 2001. According to the recitals of Executive Decree No.95, there was a need to update the former decree given the changes in science and technology (FyD, 2019).

This regulation includes in Chapter X the categories and requirements for post-approval changes to the drug product registration. The term modification refers to post-approval changes that require approval for implementation, while the term notification refers to post-approval changes that do not require approval for implementation. In this Chapter, Section I refers to modifications and Section II refers to Notifications. Section I include articles 115 to 140 and Section II include articles 141 to 156. Section I comprises 19 notifications and Section II comprises 6 notifications (FyD, 2019).

Even though the categories are in separate sections it´s important to review thoroughly both sections given that sometimes the information in one section is applicable for both, modifications and notifications. For example, Article 116 indicates that the applicant cannot submit modifications and notifications within the period of 6 months before the expiry date, that the applicant should bundle these modifications with the renewal application (FyD, 2019).

Executive Decree No. 95 doesn´t establish review periods for evaluation, it is only mentioned that if the product applies for the abbreviated registration procedure, the approval timeline will be reduced (FyD, 2019). Executive Decree No. 58 regulates the Abbreviated Regulation Procedure. To apply through this procedure according to Article 3, numeral 3, the applicant must submit evidence of approval of the modification by a high standard authority and a Free Sale Certificate issued by the foreign RA (FyD, 2017). Article 1 lists the high standard authorities as US, Canada, Japan, Australia, Switzerland, Sweden, Iceland, Norway, Spain, UK, Finland, France, Belgium, Austria, Germany, Denmark, New Zealand, Holland, Ireland, Italy and EMA (FyD, 2017). The categories of post-approval changes under scope is compared with other jurisdictions in Chapter 4 of the Results.

Executive Decree No. 58 establishes review periods for applications submitted through the abbreviated pathway. According to Article 3, numeral 4, the NRA will review the abbreviated procedure applications in 60 calendar days. If clarification or additional information is required, the applicant will have 2 months to provide it and once the response is submitted the NRA has 30

calendar days to review and issue a rejection or approval (FyD, 2017). The Ministry of Health (MOH) does not published the current average review timelines.

2.3.3 DOMINICAN REPUBLIC (DIGEMAPS)

Regulation Number 246-06 covers the manufacturing, quality control, distribution, commercialization, promotion, import, storage, dispensing, evaluation, registration and donation of DPs as well as raw materials. Within this regulation, Section V covers the modifications as well as transfers, suspensions and annulments of registration of a DP and Article 68 indicates every modification, transfer, suspension, cancellation or annulment of a registration either by request of the MAH or the NRA must be processed and approved.

In this regulation, Article 79 mentions that NRA must approve modifications to information and conditions of the DP when registered (DIGEMAPS, 2006). The list of requirements for each change are not part of this regulation, these are available online in DIGEMAPS website. Chapter 4 lists the requirements in detail.

Article 81 lists the modifications that may apply for simplified procedure, for example, substantial modifications to the manufacturing facilities, primary and secondary packaging materials, manufacturing process and controls, excipients when bioavailability is not impacted and labeling changes (DIGEMAPS, 2006). There is no further information about the simplified procedure in this regulation neither of the requirements for each type of change, therefore it is not possible to submit the modifications mentioned by simplified procedure.

On 2015, Article 81 from Regulation 246-06 was modified by Article 5 from Regulation 82-15, adding that NDA and renewals may also apply for simplified procedure (DIGEMPAS, 2015). Regulation 82-15 also requested that DIGEMAPS should put a procedure in place as well as requirements. On January 2016 the Minister of Health signed Resolution No. 000004, this document details the criteria to apply for the simplified procedure for new registration and renewals but not for post-approval changes (DIGEMAPS, 2016). There is no procedure in place to submit post-approval changes though the simplified procedure as of the finalization date of this research.

Resolution No. 000011 from July 2011 establishes the criteria to apply for the procedure of notification and automatic renewal. The resolution defines the notification as a sworn declaration of an update to a registered product maintaining the quality, safety and efficacy (DIGEMAPS, 2017). The changes that may apply through this procedure are an update to the design of the

primary and secondary packaging material, a change in the format of the product information, update to the specifications and quality control of the FP (DIGEMAPS, 2017). There is no procedure for notifications in place, therefore in practice it´s not possible to apply for simplified procedure for a modification.

DIGEMAPS establishes a review period of 90 days for the registration of DPs, it doesn´t establish review periods for post-approval change applications (DIGEMAPS, 2006). According to a survey from 2017, the registration timelines were of 5.5 months, longer than the 90 days established in the regulation (PRO-COMPETENCIA, 2017).

The human resources of DIGEMAPS are limited and insufficient for the number of registration processes that are submitted, this leads to a delay in the evaluation and approval (PRO-COMPETENCIA, 2017). Additionally, applicants receive rejections from the evaluators that reflect a need of training and specialization (PRO-COMPETENCIA, 2017). There are also technological limitations given that institutions is not able to obtain statistics from the platform (PRO-COMPETENCIA, 2017). The lack of trained and sufficient personnel and the lack of a supportive technological platform are threats that make difficult a timely evaluation process by DIGEMAPS.

The regulations and website are in Spanish given that this is the official language.

2.4 SUMMARY

The countries from Central America and Caribbean under review have regulations or guidelines with categories for post-approval changes. These countries include Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama and Dominican Republic. The information of the categories is in Chapter 4, Results.

Chapter 3, will describe the methodology used for the review of the list of PACs in the Central America and Dominican Republic countries, as well as the FDA and EMA regulations used as reference.

CHAPTER 3
METHOD

3.1 INTRODUCTION

This chapter presents a detailed description of the methodology used for this research project. The aim, objectives, rationale and importance are described in detail in Chapter 1.

3.2 STUDY DESIGN

The methodology used in this research is a qualitative comparative analysis. The data was collected through a literature-based review. This study design was used because this research centred on reviewing regulations from different regulatory agencies across different countries and comparing them to each other.

According to Onwuegbuzie, Leech and Collins (2012, p.12) the qualitative comparative analysis facilitates the systematical analysis of "similarities and differences across sources, typically being used as a theory-building approach, allowing the reviewer to make connections among previously built categories, as well as to test and to develop the categories further". The researcher identified this research method as the ideal approach to describe, list and compare different recommendations across different regulatory associations/agencies.

Facilitating the aim of creating recommendations for convergence with ICH terminology and reference countries requires the comparison of the existing regulations across all the included NRA´s. This comparison also allowed the terms of reference within each NRA to be standardised according to reference NRA´s.

During the literature review it was apparent to the researcher that there were differences between the requirements for PAC between various NRAs. Qualitative comparative analysis is often used to by researchers to explore differences in regulations or policies between different agencies/associations across different nations (Rihoux, Rezsöhazy and Bol, 2011).

3.3 STUDY SAMPLE

The documents under study are the regulations/guidelines on post-approval changes (PACs) from the regulatory agencies of Central America and Dominican Republic. Once the regulations were identified, the study sample consisted of the post-approval changes related to CMC variations for small molecules from each of these regulations

As mentioned in Chapter 1, the rationale for choosing FDA and EMA as reference agencies for this research is because of their representation as ICH Founding Regulatory Members and Stringent Regulatory Agencies according to WHO. Additionally, for the region under study these agencies are considered as reference agencies.

Once the sample was selected, meaning the list of CMC variations for small molecules from the policies of Central America and Dominican Republic. The same list of variations was searched in the regulations of the reference agencies.

The steps followed for the identification of the applicable policies related to post-approval changes CMC related for small molecules in Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Dominican Republic, EMA and FDA were the following:

- First step was to navigate the National Regulatory Agencies (NRAs) websites, searching for the regulations for post-approval changes. When a regulation was identified, the document and its link to the webpage was saved. The official language in Central America and Dominican Republic is in Spanish, therefore the website and regulations are available in Spanish. Translation of these documents wasn´t necessary given that Spanish is the researcher´s native language. All the regulations were located in the corresponding agency website.

- Search in Google® and Explorer® search engines. The words used were: country name and/or agency name and the words “post-approval change” in English for FDA and EMA and in Spanish “cambio post-registro” for CA and DR. When a regulation was identified, it was verified if it was the same found in the NRA´s website. There were no contradictions in the regulations found in the web searches.

- As a measure to cross check the validity of the regulations identified under the scope for this research, I approached regulatory affairs colleagues for confirmation.

Table 3.1. Summary of the information obtained in the internet research

Country	NRA Name	Webpage	Regulation for PACs (see References)
Costa Rica	Ministry of Health	https://registrelo.go.cr/cfmx/ms/normativas/index.cfm?categoria=1	RTCA, 2013
Nicaragua	Pharmacy Directorate, Ministry of Health	http://www.minsa.gob.ni/index.php/repository/Descargas-MINSA/Dirección-General-de-Regulación-Sanitaria/Dirección-de-Farmacia/component/content/	
Guatemala	Ministry of Public Health and Social Assistance	https://medicamentos.mspas.gob.gt/	
Honduras	Medicines and Medical Devices Regulation Agency	https://www.arsa.gob.hn	
El Salvador	National Directorate of Medicines	https://www.transparencia.gob.sv/institutions/dnm/documents/otros-documentos-normativos	
Panamá	Pharmacy and Drugs, Ministry of Health	http://www.minsa.gob.pa/normatividad	FyD, 2019
Dominican Republic	General Direction of Drug Products, Food and Health Products	https://www.msp.gob.do/web/Transparencia/baselegal/	DIGEMAPS, 2006; 2016 and 2017
US	FDA	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.70	FDA, 2004; FDA, 2019; CDER, 1995
EU	EMA	https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:en:PDF https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:223:FULL:EN:PDF	EC, 2008 and EC, 2013

3.4 DATA COLLECTION

The data collection period happened on the second half of 2019. In section 3.4.1 is a detailed description of the data collection process and instruments.

The inclusion and exclusion criteria are the following:

Inclusion criteria

- The post- approval changes included are those related to CMC variations for small molecules mentioned in the regulation of Central America and Dominican Republic, identified by the review process of the regulations.
- To include a PACs related to CMC variations for small molecules, it had to be listed in at least one of the regulations from Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama or Dominican Republic.

Exclusion criteria

- The post- approval changes related to administrative, clinical or safety information variations (non-CMC) were excluded from this investigation.
- Regulations in draft version or under review.

3.4.1 Data collection instruments

Upon reviewing sourced literature and documents, variables were captured in an instrument using Windows Microsoft Excel (trademark). The instruments are described in Appendices. These instruments were used to document specific information pertaining to the terminology and PAC categories within each NRA.

These tools where used in a chronological sequence to capture and categorise the information presented in the NRA guidelines of the various countries. This was done to create a standardized table that would enable comparison between the different NRA´s.

3.5 DATA ENTRY AND ANALYSIS

The collected data was included in the instruments 1 and 2 described in section 3.4.1. The classifications from each column (country) were compared and analysed and the recommendations were included in Instrument 3.

To standardize the terminology and create the sample list with all the post-approval changes (PACs) related to CMC the following methods were used:

- Review of the documents mentioned in Table 3.1 to identify the PAC terminology in each of the NRAs regulations, document the terminology according to the implementation timing and categorise according to the ICH Q12 terminology: Prior Approval (PA) or Notification (N). Introduce the information in Instrument 1.
- Identification of post-approval changes listed or included in each regulation for CMC changes for small molecules of Central America and Dominican Republic. Introduce the description of the change in the column “Type of change” in Instrument 2. These PACs are the sample under study. If a regulation included more than one sub-type of change description with its own requirements and category, it was included in the Instrument in subtitles.

To categorise each of the changes listed in Instrument 2 the following steps were followed:

- Inclusion of the category assigned by each agency as: “PA” and/or “N” or “-“. If the change is not included in an agency “-“ will be used. If in a reference agency the PAC may classified as PA and N, both letters were included. This step will be performed for all the under study and the reference.

For the recommendations of PAC categories the following method was used:

- Creation of the recommendation by merging the FDA and EMA category columns from Instrument 2 and summarized in Instrument 3. No formula or personal criteria were introduced.

To compare the current CA and DR situation with FDA and EMA the number of changes was inserted in Table 4.2 and Figures 4.1 and 4.2.

3.6 RELIABILITY AND VALIDITY

In order to facilitate the reproducibility of the results, research tools were based on reference agencies. The information from the documents was systematically classified and compared. The tools were developed by the researcher to facilitate the collection and analysis of the information and are not validated.

The list of policies used is facilitated in Table 3.1, as well as the internet link. It is expected that a reader or researcher wishing to replicate this research ends with the same conclusions by following the methodology described in this Chapter. It is also expected that this methodology is useful to apply to a different sample of post-approval changes from these countries or from other latitude by using the tool provided and the regulations of interest for the study and FDA and EMA as reference or introduce the information of other reference agencies.

All of the documents are in the public domain.

3.7 ETHICAL CONSIDERATIONS

Ethical approval was not required for this project given that there is no confidential information; there are no subjects or data from subjects used.

3.8 SUMMARY

Chapter 4 will comprise the results of the data collected and the discussion of these data.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 INTRODUCTION

The terminology and categories of PACs in EMA, FDA, RTCA countries (Guatemala, El Salvador, Honduras, Nicaragua and Costa Rica), Dominican Republic and Panama is described in this chapter as well as the results from the literature review of the post-approval CMC changes regulations. The results are presented in charts and figures.

4.2 CLASSIFICATION OF POST-APPROVAL CHANGES

The term used for the PACs in each country was classified according to ICH Q12 terminology and a description of the implementation timing according to each of the regulations. The information is summarized in Table 4.1. Each country has defined the concept of prior approval changes and notifications in the regulation, the terminology is described in Table 4.1.

According to ICH Q12 "Regulatory authorities are encouraged to utilise a system that incorporates risk-based regulatory processes for (a) requesting prior approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC changes, with associated information requirements and, where applicable, timeframes for decision" (ICH, 2019, p. 9). The countries under review have post-approval categories for prior approval and notification; there is not a category for recording CMC changes as encouraged by ICH Q12 guideline. The categories of changes under the scope of this research are included in table 4.3.

There are more alternatives of implementation timing for notifications in EMA and FDA regulations: implementation after report and wait period, implementation after report and report after implementation. In the case of the RTCA countries, Panama and Dominican Republic there is only one timing to implement after notification report.

Table 4.1 Terminology used for post-approval change categories in each country

ICH Q12[a]	Description of Implementation timing	FDA[b]	EMA[c]	RTCA[d]	Panama[e]	Dominican Republic[f]
Prior Approval (PA)	Implementation after approval	Major (PAS)	Type II	Modification		
Notification (N)	Implementation after reporting and wait period	Moderate (CBE-30)	Type IB	-	-	-
	Implementation after reporting	Moderate (CBE-0)	-	Notification		Notification
	Report after Implementation	Minor Annual Report	Type IA Type IA_{IN}	-	-	-

Source: [a]ICH Q12, 2019; [b]FDA (2004) and (2019a); [c]EC (2008) and (2013); [d]RTCA (2013); [e]FyD (2019); [f]DIGEMAPS (2006), (2016) and (2017)

In the following sections the ICH Q12 terminology will be used, Prior Approval (PA) and Notification (N) to facilitate the standardization of the concepts between each country´s regulation terminology described in Table 4.1.

4.2.1 Classification of PACs: Prior Approval (PA) and Notification (N)

Applying the methodology described from Chapter 3, specifically sections 3.4 and 3.5, the regulations were reviewed and the information of the CMC post-approval changes was gathered in Table 4.2. When a PAC was classified as Prior Approval, "PA" was included in the cell and when the PAC was classified as Notification, "N" was included in the cell. When the PAC was not included in one of the regulations of a NRA it was filled with "-". In some cases the cell indicates "NDA" referring to New Drug Application, this means in the regulation this type of change is not included as a PAC but the applicant must submit a complete new registration request.

Table 4.2. Classification of post-approval changes as encouraged by ICH Q12 categories: Prior Approval (PA) and Notification (N)

Type of change	FDA[a]	EMA[b]	RTCA[c]	Pana-ma[d]	DR[e]
1. **Discontinuation of registered presentations**					
1.1 Deletion of pack size(s)	-	N	N	N	-

2. **Change in the pack size (number of units, fill weight, fill volume)**					
2.1 For nonsterile drug products	N	N	PA	PA	PA
2.2 For sterile drug products	PA	PA	PA	PA	PA
3. **Changes in the primary packaging**					
3.1 Change in shape or dimensions for nonsterile and sterile FP	PA, N	PA, N	-	N	N
3.2 Change of the type of material or of the container-closure system of the FP	PA, N	PA, N	PA	PA	PA
3.3 Addition of a new primary package	PA, N	PA, N	PA	-	PA
4. **Change in shelf-life (SL) or storage conditions of the FP**					
4.1 Reduction of the SL of the FP	N	N	PA	PA	PA
4.2 Extension of the SL supported by real time data (based on approved protocol)	N	N	PA	PA	PA
4.3 Changes in the storage conditions of the FP or the diluted reconstituted product	-	N	PA	PA	PA
5. **Change in the composition and other markings to the DP**					
5.1 Deletion or reduction of a colouring excipient	N	N	PA	PA	PA
5.2 Changes in the qualitative and quantitative formulation	PA	PA, N	PA	-	PA
5.3 Excipients. Change or addition of imprints or addition of inks used for markings	PA, N	N	PA	-	PA
5.4 Change or addition of bossing or other markings to solid dosage forms, except modified release	N	N	-	-	PA
5.5 Changes in scoring/break lines intended to divide into equal doses to solid dosage forms, except modified release	N	N	-	-	PA
6. **Change in the packaging or manufacturing sites**					
6.1 Change of the primary packaging site (Replacement/addition)	PA, N	PA, N	PA	NDA	PA
6.2 Change of the secondary packaging site (Replacement/addition)	N	N	PA	PA	PA
6.3 Replacement or addition of manufacturing site (except packaging)	PA, N	PA, N	NDA	-	PA
6.4 Replacement or addition of manufacturing site (except packaging) for third party manufacturing	PA, N	PA, N	PA	-	PA
6.5 Change of the manufacturing site within the same country	PA, N	PA, N	PA	-	PA
7. **Change in the manufacturing process, including and intermediate**					
7.1 Minor change (MC)	N	N	-	-	PA
7.2 Substantial changes that may have a significant impact on the quality, safety and efficacy of the FP	PA	PA	-	-	PA

7.3 Introduction or increase in the overage that is used for the API	PA	PA	-	-	PA
8. **Changes to specifications and methodology of analysis of FP**					
8.1 Change/update of the specifications	PA, N	PA, N	-	PA	-
8.2 Tightening of specification limits	N	N	-	PA	-
8.3 Change/update of the specifications to comply with an official compendia	N	N	-	PA	-
8.4 Change in methodology of analysis	PA, N	PA, N	-	PA	-
8.5 Change in methodology of analysis to comply with an official compendia	N	N	-	PA	-

Source: [a]FDA (2004), FDA (2019a) and CDER (1995); [b]EC (2008) and (2013); [c]RTCA (2013); [d]FyD (2019); [e] DIGEMAPS (2006), (2016) and (2017)

In Figure 4.1 and Table 4.3 the total number of PACs is represented in columns with the respective category in Prior Approval (PA), Notification (N), a combination of both (PA, N) if specified in the regulation or (-) when not included in the regulations and NDA for new drug applications. The most frequent type of change in the FDA and EMA regulations is the notification while the most frequent type of change in the RTCA, Panama and Dominican Republic regulation is Prior Approval. The quantity of notifications in very low for the PACs reviewed for RTCA and Dominican Republic only one and two for Panama. Even though there are PAC categories, the risk-based classification for each change should be reviewed considering the low number of notifications (N) and high number of prior approval (PA) in comparison with reference NRAs.

Table 4.3 Number of PACs per category for each NRA

Category	FDA[a]	EMA[b]	RTCA[c]	Panama[d]	DR[e]
PA	4	3	14	13	20
PA, N	10	10	0	0	0
N	11	14	1	2	1
-	2	0	11	11	6
NDA	0	0	1	1	0
Total:	27				

EMA and FDA regulations are more comprehensive and detailed in the list of PACs reviewed in comparison with RTCA, Panamanian and Dominican Republic regulations. There are some

cases in EMA and FDA where the category is “PA, N”, meaning that the change can be a “PA” or a “N”, it is required to review more in detail the classification to define the applicable category. On the contrary, in CA and DR regulations the category is “PA” only, it is recommended to review and include more detail in the CA and DR regulation to contemplate possibilities for notification (N) in certain sub-types of PACs according to reference RAs. This is supported also by a high number of “-“ where not included in the regulation of CA and RD, given this higher level of detail in the reference NRAs regulation. For RTCA and Panama there is a change in each that is classified as NDA, given that reference RAs handle this type of change as “PA, N” or “N” is it recommended that this can be changed from NDA to a post-approval change according to reference RAs.

Source: Information from Table 4.2

Figure 4.1 Proportion of Post-approval change categories in each country under study

4.2.2 Recommendations for Classification of PACs

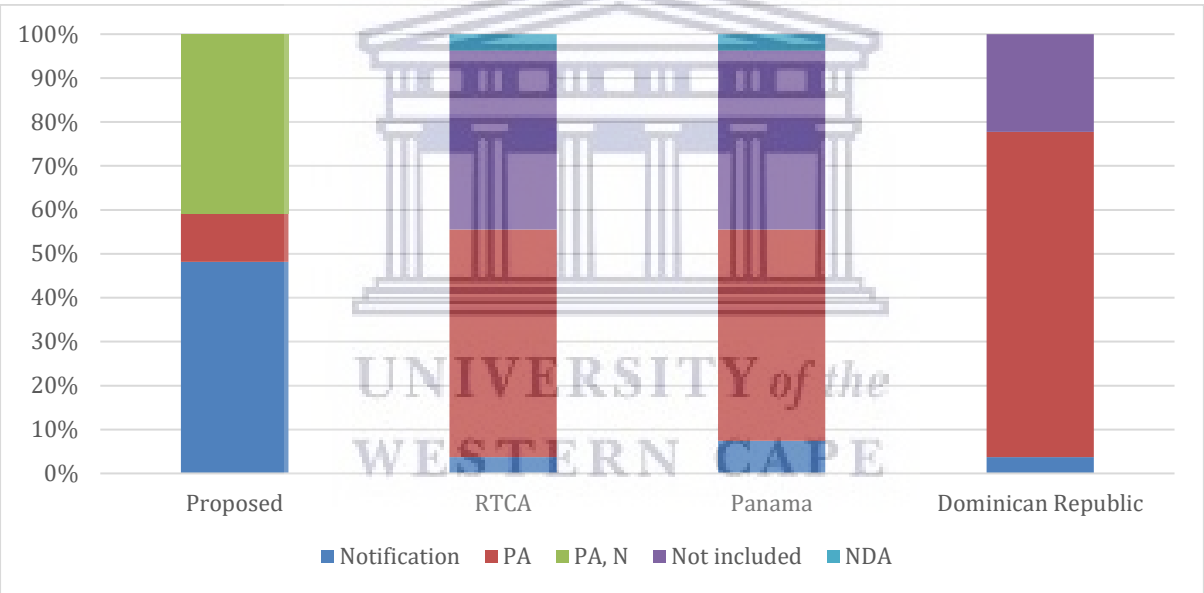
According to the information of the categories of PACs in reference agencies, FDA and EMA from Table 4.2, the following recommendations are gathered in Table 4.4 for CA and DR countries.

Table 4.4 Recommendations for convergence of the PAC categories for CA and DR countries according to reference agencies EMA and FDA: Prior Approval (PA) and Notification (N)

Type of change	Change category Recommendation
1. **Discontinuation of registered presentations**	
1.1 Deletion of pack size(s)	N
2. **Change in the pack size (number of units, fill weight, fill volume)**	
2.1 For nonsterile drug products	N
2.2 For sterile drug products	PA
3. **Changes in the primary packaging**	
3.1 Change in shape or dimensions for nonsterile and sterile FP	PA, N
3.2 Change of the type of material or of the container-closure system of the FP	PA, N
3.3 Addition of a new primary package	PA, N
4. **Change in shelf-life (SL) or storage conditions of the FP**	
4.1 Reduction of the SL of the FP	N
4.2 Extension of the SL supported by real time data (based on approved protocol)	N
4.3 Changes in the storage conditions of the FP or the diluted reconstituted product	N
5. **Change in the composition and other markings to the DP**	
5.1 Deletion or reduction of a colouring or flavouring excipient	N
5.2 Changes in the qualitative and quantitative formulation	PA, N
5.3 Excipients. Change or addition of imprints or addition of inks used for markings	PA, N
5.4 Change or addition of bossing or other markings	N
5.5 Changes in scoring/break lines intended to divide into equal doses	N
6. **Change in the packaging or manufacturing sites**	
6.1 Change of the primary packaging site (Replacement/addition)	PA, N
6.2 Change of the secondary packaging site (Replacement/addition)	N
6.3 Replacement or addition of manufacturing site (except packaging)	PA, N
6.4 Replacement or addition of manufacturing site (except packaging) for third party manufacturing	PA, N
6.5 Change of the manufacturing site within the same country	PA, N
7. **Change in the manufacturing process, including and intermediate**	
7.1 Minor change (MC)	N
7.2 Substantial changes that may have a significant impact on the quality, safety and efficacy of the FP	PA
7.3 Introduction or increase in the overage that is used for the API	PA
8. **Changes to specifications and methodology of analysis of FP**	

8.1 Change/update of the specifications	PA, N
8.2 Tightening of specification limits	N
8.3 Change/update of the specifications to comply with an official compendia	N
8.4 Change in methodology of analysis	PA, N
8.5 Change in methodology of analysis to comply with an official compendia	N

Figure 4.2 shows the proposed recommendation of PAC categories based on Table 4.4 in contrast with the current CA and DR categories. The proposed distribution of PAC in each category is: Notification (N) 48 %, Prior Approval (PA) 11 % and "PA, N" 41 %. The proposal increases the number of PAC for Notification to 48%, currently the percentages are RTCA 3.7 %, Panama 7.4 % and Dominican Republic 3.7 %.



Source: Information from Table 4.4

Figure 4.2 Proposed post-approval change categories vs the current situation in each country under study

4.3 SUMMARY

A discussion of the results, conclusion and recommendation is offered in the next chapter.

CHAPTER 5

SUMMARY OF RESULTS, CONCLUSION AND RECOMMENDATIONS

5.1 INTRODUCTION

The research project has met the aim and objectives proposed. The following section will describe the summary of results, the conclusion and recommendations.

5.2 SUMMARY OF RESULTS

- The CA and DR countries have a PACs´ categories of prior approval and notification as recommended in the ICH terminology and reference RAs. There is no category in the regulation of CA and DR for not-reported changes.
- Most of the PAC for CA and DR are classified as PA, while in the reference NRAs the proportion of N predominates. A risk-based review should be performed, convergence to reference NRAs should also be taken into consideration.
- The list of PACs from CA and DR should be reviewed in more detail to include different subcategories for each PAC, where some may be prior approval and other notification. This can facilitate the implementation of changes that can be notified.
- There is one PAC for Panama and another for DR classified as NDA, a risk-based review is recommended to determine if it can be changed to a category of PA or N as reference NRAs.

5.3 CONCLUSION

There is a PAC category in CA and DR countries. The current NRA regulations surrounding PACs are not adherent to ICH guideline and differ from the FDA and EMA about a risk-based approach. This research presents an opportunity to harmonise PAC categories of the reviewed countries with the reference NRA categories as encouraged by ICH Q12.

5.4 RECOMMENDATIONS

The following recommendations are based on the results of the study:

5.4.1 Converge the PAC categories

Converge the PACs categories in RTCA, Panama and Dominican Republic regulations with those of the reference authorities. This would increase the number of PACs that are classified as notification and lower the amount of PACs that are prior approval. Table 4.4 describes a change recommendation of classification of PACs for CA and Dominican Republic countries according to reference agencies.

5.4.2 Implement reliance in the prior approval categories of PACs

For PACs that are classified as prior approval, it is recommended that the NRAs from El Salvador, Guatemala, Honduras, Nicaragua, Costa Rica, Panama and Dominican Republic consider the implementation of reliance to reference regulatory agencies for the evaluation of the PACs. There are examples in the CAC region, for example Panama and Costa Rica, where reliance has been implemented for new registrations, broadening the application of reliance to PACs may alleviate the RAs workload and facilitate the management of PACs.

5.5 LIMITATIONS OF THE STUDY

El Salvador, Guatemala, Honduras, Nicaragua, Costa Rica, Panama and Dominican Republic countries have the limitation that none is an ICH member or ICH observer, therefore implementation of the ICH guidelines is voluntary. However, the ICH mission has a global scope, promoting to achieve harmonization to ensure the safety, efficacy and quality of medicines meet high standards as described in the website. It is expected that the ICH documents are considered as reference for NRAs worldwide.

As described in the methodology, this research did a review of the qualitative data obtained from the regulations of Central America and Dominican Republic under study and compared it with FDA and EMA regulation considering this as the reference. The instruments used were developed for this research by myself and are not validated. It may be an opportunity in the future the validate the tool. The information is taken from the NRAs regulations and cannot be externally validated.

As mentioned in the methodology, the regulations were searched in the NRAs website and in search engines and no discrepancies were found. To corroborate that these were the most current

regulations, I approached regulatory affairs colleagues for confirmation. The websites and regulations are in Spanish, this may be a challenge for non-Spanish speaking when reproducing the investigation.

5.6 CLOSURE

This research presents an opportunity to implement convergence in the categories for PACs from CA and DR with reference NRAs.

REFERENCES

CDER (1995). Guidance for Industry. Immediate Release Solid Oral Dosage Forms. Scale-up and Postapproval changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation. Center for Drug Evaluation and Research (CDER). November 1995. [Online]. Available at: https://www.fda.gov/media/70949/download (Accessed: 23 November 2019).

DIGEMAPS (2006). Decree No. 246-06. Drug product Regulation. 9 June 2006. [Online]. Available at: http://apps.who.int/medicinedocs/documents/s19014es/s19014es.pdf (Accessed: 28 October 2019).

DIGEMAPS (2015). Decree No. 82-15 that creates the General Direction of Drug Products, Food and Health Products, under the dependence of the Ministry of Public Health and Social Assistance. G.O. No. 10794 from 30 April 2015. [Online]. Available at: http://extwprlegs1.fao.org/docs/pdf/dom163802.pdf (Accessed: 28 October 2019).

DIGEMAPS (2016). Resolution No. 000004 that stablish the criteria for the application of the registration through the simplified procedure and the recognition of the Free Sale Certificates and Good Manufacturing Practices of Establishments issued by the Stringent Regulatory Authorities (WHO) and/or the Regional Reference Level IV Regulatory Agencies (ARNr) from PAHDRA/PAHO. 27 January 2016.

DIGEMAPS (2017). Resolution No. 000011 that stablish the criteria for the application with the aim to apply for the notification procedure and the automatic renewal. 25 July 2017.

EC (2008). Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. [Online]. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:en:PDF (Accessed: 20 July 2019).

EC (2013). Guidelines 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 authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those products. [Online]. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:223:FULL:EN:PDF (Accessed: 20 July 2019).

EFPIA (2017). ´Optimising Post-Approval Change Management for Timely Access to Medicines´. 8 February 2017. Version: 1.0. [Online]. Available at: https://efpia.eu/media/25953/efpia-post-approval-change-position-paper_final_feb2017.pdf (Accessed: 20 July 2019).

EMA (no date). Available at: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines (Accessed: 26 September 2019).

FDA (2004). Guidance for Industry. Changes to an Approved NDA or ANDA. April 2004. [Online]. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda (Accessed: 20 July 2019).

FDA (2014). CMC regulatory review should be based on an understanding of product risk and how best to manage this risk. March 2014. [Online]. Available at: https://www.fda.gov/media/79182/download (Accessed: 23 November 2019).

FDA (2019a). CFR - Code of Federal Regulations Title 21. [Online]. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.70 (Accessed: 20 July 2019).

FDA (2019b). Regulatory Harmonization and Convergence. [Online]. Available at: https://www.fda.gov/vaccines-blood-biologics/international-activities/regulatory-harmonization-and-convergence (Accessed: 3 November 2019).

FyD (2017). Executive Decree No. 58. Procedure for Abbreviated for the Registration. Gaceta Oficial Digital No. 28248. 30 abril 2017. [Online]. Available at: http://www.minsa.gob.pa/sites/default/files/publicacion-general/decreto_58_del_28_de_marzo_de_2017_medicamentos_de_alto_estandar_0.pdf (Accessed: 28 October 2019).

FyD (2019). Executive Decree No. 95. Regulates Law 1 of January 10th, 2001, on Medicines and other Products for Human Health. Gaceta Oficial Digital. 17 may 2019. [Online]. Available at: http://www.minsa.gob.pa/sites/default/files/publicacion-general/de_95.pdf (Accessed: 28 October 2019).

Hoath, C., Chang, L., Ramalingam Iver, K, Kutza, J., Murray, S., Smith, H and Payne, R. (2016). ´Postapproval Changes for Biopharmaceutical Drug-Substance and Drug-Product Manufacture: Regulatory Complexity and Impact. Bioprocess International´. 13 December 2016. [Online]. Available at: https://bioprocessintl.com/business/regulatory-affairs/postapproval-changes-biopharmaceutical-drug-substance-drug-product-manufacture-regulatory-complexity-impact/ (Accessed: 12 August 2019).

ICH (no date). Available at: https://www.ich.org/page/members-observers (Accessed: 26 September 2021).

ICH (2014). Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. Final Concept Paper. 28 July 2014. [Online]. Available at: https://database.ich.org/sites/default/files/Q12_EWG_Concept_Paper.pdf (Accessed: 24 July 2019).

ICH (2017). Technical and Regulatory considerations for pharmaceutical product lifecycle management Q12. Draft Version. 16 November 2017. [Online]. Available at: http://www.ich.org/products/guidelines/quality/quality-single/article/technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-management.html (Accessed: 16 August 2019).

ICH (2019). Technical and regulatory considerations for pharmaceutical product lifecycle management Q12. Final version Adopted on 20 November 2019. [Online]. Available at: https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf. (Accessed: 16 October 2020).

Murray, S. (2016). Presentation 'An Industry Perspective: The Complexity of Post-approval CMC Changes and Proposed Regulatory Strategies', BiPhorum Operations Group. [Online]. Available at: https://cdn.ymaws.com/www.casss.org/resource/resmgr/cmc_no_am_jul_spkr_slds/2016_CMCS_MurraySuzanne.pdf (Accessed: 6 November 2019).

MSCR (2014). Decree No. 38409-S of the Reform of the Regulation of the functioning and usa of the "Registrelo" portal. Signed on 9 April 2014. [Online]. Available at: http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=77262&nValor3=96735&strTipM=TC (Accessed: 28 October 2019).

OECD (no date). Programa Regional de la OECD para América Latina y el Caribe. http://www.oecd.org/latin-america/regional-programme/Iniciativa-Centroamericana-ESP.pdf (Accessed: 2 November 2019).

Onwuegbuzie, A., Leech, N, Collins, K. (2012). Qualitative Analysis Techniques for the Review of the Literature. *The Qualitative Report* 2012 Volume 17, Article 56, 1-28. 7 September 2012. [Online]. Available at: http://nsuworks.nova.edu/cgi/viewcontent.cgi?article=1754&context=tqr/ (Accessed: 29 October 2019).

PAHO (2019). Regulatory Reliance Principles: Concept Note and Recommendations. 9th Conference of Pan American Network for Drug Regulatory Harmonization (PANDRH). San Salvador, 24-26 October 2018. [Online]. Available at: http://iris.paho.org/xmlui/handle/123456789/51549 (Accessed: 3 November 2019).

PRO-COMPETENCIA (2017). Propuesta sobre la simplificación de los trámites de obtención de registro sanitario en la República Dominicana. [Online]. Available at: http://procompetencia.gob.do/Docs/Estudios/Informe%20de%20Simplificaci%C3%B3n%20de%20Tramites%20para%20la%20Obtenci%C3%B3n%20Registro%20Sanitario.pdf (Accessed: 2 November 2019).

Ramnarine, E. (2018). Presentation ´Post Approval Changes & Product Lifecycle Management´. PDA West Coast Chapter Meeting. 22 February 2018. [Online]. Available at: https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/west-coast/post-approval-changes-and-product-lifecycle-management.pdf?sfvrsn=6 (Accessed: 2 November 2019).

RTCA (2013). Reglamento Técnico Centroamericano. Productos Farmacéuticos. Medicamentos de Uso humano Requisitos de Registro Sanitario. Annex I of Resolution No. 333-2013 (COMIECO-LXVI). 12 december 2013. [Online]. Available at: http://www.minsa.gob.ni/index.php/repository/Descargas-MINSA/Dirección-General-de-Regulación-Sanitaria/Dirección-de-Farmacia/Resoluciones-COMIECO/Resolución-333-2013-(COMIECO-LXVI)-Registro-y-RUA-Medicamentos/Resolución-No.-333-2013/ (Accessed: 28 October 2019).

REGISTRELO (2019). Plazos de registros por tipo de producto. 18 September 2019. [Online]. Available at: https://registrelo.go.cr/cfmx/ms/documentos/estadisticas/inf_mensual_plazos_atencion_tramites/Plazos%20por%20Tipo%20de%20Producto.pdf (Accessed: 28 October 2019).

WHO (2015). Annex 9. Good review practices: guidelines for national and regional regulatory authorities. WHO Technical Report Series No. 992, 2015. [Online]. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex9-TRS992.pdf?ua=1 (Accessed: 3 November 2019).

WHO (2016). ´Good regulatory practices: guidelines for national regulatory authorities for medical products´. Working document QAS/16.686. Draft for comment. October 2016. [Online]. Available at:

https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf (Accessed: 16 August 2019).

This instrument collects the information about the terminology used for the categories for post-approval changes in each country, according to the description ICH Q12 classification and the description of implementation timing in each regulation/guideline.

Instrument 1. Terminology of Categories of post-approval changes in each country

ICH Q12	Description of Implementa-tion timing	FDA	EMA	RTCA	Panama	Dominican Republic
Prior Approval (PA)						
Notification (N)						

This instrument collects the types of CMC post-approval changes described in the regulations of Central America and Dominican Republic and the categories according risk-based categories: Prior Approval (PA), Notification (N) or "–" where not included in the regulation of FDA, EMA, RTCA, Panama and Dominican Republic.

Type of change	FDA	EMA	RTCA	Pana-ma	DR
1. **(Type of change)**					
1.1 (Description of the type of change)					
2. **(Type of change)**					
2.1 (Description of the type of change)					
2.2 (Description of the type of change)					

The following instrument collects the recommendation of classification. The change category recommendation is obtained from the information from the reference authorities (FDA and EMA) collected in Instrument 2. The change recommendations are to Notification (N) and Prior Approval (PA).

Type of change	Change category Recommendation
1. **(Type of change)**	
1.1 (Description of the sub-type of change)	

2. **(Type of change)**	
2.1 (Description of the sub-type of change)	
2.2 (Description of the sub.type of change)	