"COMPARATIVE REGULATORY ACCOUNT ON POST APPROVAL COMPLIANCE OF US, SOUTH AFRICA AND GCC COUNTRIES"

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MASTER OF PHARMACY

IN

REGULATORY AFFAIRS

BY

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CERTIFICATE

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I hereby declare that the dissertation entitled "COMPARATIVE REGULATORY ACCOUNT ON POST APPROVAL COMPLIANCE OF US, SOUTH AFRICA AND GCC COUNTRIES", is based on the original work carried out by me under the guidance of Dr. Nagja Tripathi, Assistant Department, Designation under the Department of Pharmacognosy, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that Ms. Shravani Wagh a student of Institute of Pharmacy Nirma University, Ahmedabad has undergone Project training at our R&D Centre, Taloja from 06/06/2019 to 05/02/2020.

During the above training period, she has shown keen interest while carrying out the given job responsibilities and she has acquired adequate practical knowledge in the referred area.

We wish her very best in future endeavours.

for, Alkem Laboratories Ltd,

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LIST OF ABBREVIATIONS

Abbreviation	Full form
NDA	New drug application
ANDA	Abbreviated new drug application
CDER	Centre of drug evaluation and research
CMC	Chemistry, manufacturing, control
SAHPRA	South Africa Health Product Regulatory Authority
GCC	Gulf cooperation council
SFDA	Saudi food & drug authority
UAE	United arab emirates
NDoH	National department of health
MCC	Medicine control council
DRC	Directorate of Radiation Control
CTD	Common technical document
PSUR	Periodic safety update report
REMS	risk evaluation and mitigation strategies
PALM	Post approval lifecycle management
PACMP	Post-approval change management protocol
MAH	Marketing authorisation holder
PQS	pharmaceutical quality system
CQA	Critical quality attributes
CPP	Critical process parameters
API	Active pharmaceutical ingredient
RLD	Reference listed drug
ICSR	Individual case study reports
NDA	New drug applications
ANDA	Abbreviated new drug applications

CBE-0	Changes Being Effected
CBE-30	Changes Being Effected in 30 days
PAS	Prior approval Supplement
ICH	International conference on harmonization
NDC	National Drug Code
MOHAP	Ministry of Health and prevention
Mfg	Manufacturing
IR	Immediate release
IPI	Inactive pharmaceutical ingredient.
FPP	Finished pharmaceutical product
CCS	Container closure system

Abstract

The study gives the idea of comparative view of various post approval compliance activities of semi-regulated regulatory authorities of South Africa, Saudi Arabia and United Arab Emirates with regulated USFDA authority. The study involves regulatory view on post approval change management, post approval changes, annual reports, renewals of dossier and post marketing safety surveillance i.e periodic safety update reports. USFDA is stringent regulatory authority and have well established guidelines for every activity. In June 2017, the MCC has upgraded to the SAHPRA. SAHPRA has recently moved towards electronic submission and updating their guideline trying to be a stringent regulatory authority. GCC countries have reference of European guidelines. This study mentioned the post approval submission, annual report and PADER report which give the practical view of submission report. And study gives the idea about requirements to fulfill and documents required to submit while submitting the application. This study gives overview of USFDA, SAHPRA, SFDA and MOHAP regulations in one study. USFDA is founder member of ICH committee and SAHPRA, SFDA and MOHAP follows ICH guidelines for quality and safety. But still every regulatory authority has their own guideline for regulatory activities.

Key words: post approval changes, annual report, renewals, periodic safety update report.

CHAPTER 1

Introduction

Role of Pharmaceutical Industry

The living organism goes through different phases of their respective lifecycle. The unhealthy and diseased conditions can lead to misbalancing of the ration of healthy stage of living organisms. Diseased state in human beings always has been the basics for various researches. Disease can be transmitted through carriers. And it can be transfer from animal to human being, human to human and worldwide also. The many factors of human life stages are considering factors for the disease incidence in the population. Study findings say that to cure the disease and for survival of the human beings, it is necessary to counteract basics of disease causing vectors mainly their evolution history and genetic mutations. The technological procession and consummate knowledge in science make it possible to find the molecules which have the ability to cure the diseased condition of the subject. Here is where pharmaceutical industries enter and play important role to have healthy population.

Scientists utilise their knowledge to discover treatment for diseases. And pharmaceutical industries use this knowledge as a baseline to their drug development process and it is the process to convert drug discoveries into effective medicines. Medicines discovery process is long, steady, time consuming and extravagant. It directly involves human health hence strict monitoring at each and every step is necessary. (Barker & Darnbrough, 2007)

Here regulatory affairs department involves. Basically each step in the medicine development process should follow similar processes and should fall within specific parameters. This is important to create specific tests, parameters, specifications for the drug product and this whole responsibility is of regulatory authorities. The authority names International Conference on Harmonisation of Technical Requirement for Pharmaceuticals for Human Use which develops guidelines and pharmaceutical industries are expected to follow them. United States, Europe and Japan are the ICH countries. The aim of ICH guidelines is to develop common specification for drug products with respect to safety and quality. The main role of regulatory affairs is to ensure the compliance with the guidelines. (Bhavsar et al., 2010)

A mainly regulatory affair is the interface between the pharmaceutical industries and regulatory authorities to fulfil all the requirements which are demanded and necessary according to particular regulatory authority. Rules and legislations is the bold part of the department. Regulatory affairs should have controls over all steps of drug development process including clinical studies, manufacturing, analytical testing, registration of product and post approval compliance (Elizabeth & Moyer, 2006). The documentation of each step is the core part and proof for the safety and quality analysis. Regulatory affairs people collect process generated data and check if they fit into the particular regulatory authority's requirements and guidelines for which country they are seeking the approval for candidate drug product. Regulatory affair has prime role on the international level and proper governance of regulatory affairs activities play vital role in company's financials (Harsha et al., 2017).

CHAPTER 2

Aim & Objective

Aim:

To study product post- approval change compliance concept and comparative review in US, South Africa and GCC Countries.

Objective:

To analyze the similarities and differences of all three regulatory authorities regarding the conditions and documentation requirements and to bring them in a single document for the easy assessment of all three regulatory authorities by reading single document and can have a brief idea and they don't need to refer respective authority's guidance documents. To harmonize all three authority's respective post- approval requirements which will lead to reduced shortage / stock outputs, faster product access through process improvements, ease of manufacturing and inventory control, a common harmonized regulatory strategy to encourage and optimize resources and time, A more efficient landscape for handling post-approval changes to MAs worldwide will contribute to improving global public health by ensuring continuous patient access to state-of-the-art medicines and up-to-date information on product safety.

CHAPTER 3

Literature Review

Literature Review

- **Changes to an Approved NDA or ANDA**

In conformance with 314.70 part of 21 CFR and federal food, drug and cosmetics Act section 506A above guidance is published by FDA which provides basic guidance to applicant or application holder of 'New Drug Application' (NDA) and 'Abbreviated New Drug Application' (ANDA) who is aspiring to do deliberate changes in dossier after approval. This document takes over all reportable categories of finished product post approval changes. This document defines appropriate type of the change and also elaborates the general considerations of the particular change. Reporting categories defined by documents are (1) components of formulation and its composition, (2) site of manufacturing, (3) process of manufacturing, (4) specifications of the ingredients and product, (5) suitable container closure system for the product and many other changes.

- **Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation**

This document is issued in judgment of CDER for immediate release dosage form which gives outline and guidance for those who are seeking approval for changes after approval of NDA and ANDA. This document is a guidance document focuses on reporting categories which mainly defines chemistry, manufacturing and control changes. Reporting categories defined by documents are 1) components of formulation and its composition, (2) site of manufacturing, 3) scale-up or scale-down of manufacturing batch, 4) process of manufacturing.

- **2.08_Amendments_Jul12_v6:**

This guideline is prepared as guidance document for the applicant or holder of certification of registration who is aspiring to make changes in dossier after approval. This guidance document is representing the expectations of South Africa Health Product Regulatory

Authority with respect to safety, efficacy and quality should be consider if holder is willing to submit amendment application.

- **The GCC Guidelines for variation requirements (version 5.0):**

GCC authority built this guideline to provide the recommendation for the marketing authorisation holder of registered product who is willing to make some changes in registered product. Guideline describes the classification, general considerations and documentation need with respect to safety and quality. The guideline purpose is to aid the marketing authorisation holder to prepare and submit the variation application in accordance with legislations of Saudi Food and Drug Authority.

- **Minor Variation for Registered Pharmaceutical Product in UAE:**

The guidance provides the guidance for minor variations with description of change and documentation need. Provide the list of which changes should be documented. Also provide general provisions for submission of variation. If the change not described in the guidance, according to UAE authority, it has substantial impact on quality, safety and efficacy of product and has to submit new application.

CHAPTER 4

Introduction of Regulatory Authorities

US Food and Drug Authority

The authority which innards of Health and Human Services Department is greatly known as 'Food and Drug Administration'.

The target mission of food and drug administration is to protect health of population of humans as well as animals by securing safety of public and quality and efficacy of human, veterinary and biological products as well as medical devices, cosmetics and food supplements also. It has four directorates along with Office of the Commissioner taking over the basic functions of authority viz. Foods and Veterinary Medicine, Medicinal Product and Tobacco, Global Regulatory Operations and Policy, and Operations.

FDA consists of six of product centers, one research centre, and two offices:

- Office of the Commissioner: the purpose is to promote strategies and planning and to appraise the functions of the offices and centers.
- Center for Biologics Evaluation and Research: the purpose is to regulate vaccines, gene therapy and blood products.
- Center for Drug evaluation and Research: the purpose is to regulate over-the-counter drugs and prescription drugs.
- Center for Device and Radiological Health: the purpose is to regulate medical devices and electric products that give off radiations.
- Center for food safety and Applied Nutrition: the purpose is to regulate food except meat and poultry which comes under Department of Agriculture, food additives, infant formulas, dietary supplements and cosmetics.
- Center for Tobacco Products: the purpose is to regulate tobacco and tobacco products like cigarettes.
- Center for Veterinary Medicine: the purpose is to regulate feed of animals, drugs and medical devices which are going to use for the animals.

- Office of Regulatory Affairs: the purpose is to inspect the registered products and manufacturing facilities along with manufacturing process and analyses of the drug products (*U.S. Food and Drug Administration*, n.d.).

Code of Federal Regulation:

United States Federal Government has published the codification of rules and regulation of general and permanent with the help of administrative departments and agencies in the federal register is widely known as Code of Federal Regulation (CFR).

CFR has wide representing areas classified into 50 different titles representing different subjects according to primary roles and functions of federal regulation.

21 CFR is for subject food and drug which is useful for pharmaceuticals and generally referred by pharmaceutical industries.

CFR is the annually published codified document. And electronic version of CFR is available online which update regularly on daily basis (*CFR - Code of Federal Regulations Title 21*, n.d.).

South Africa Health Product Regulatory Authority

Government of South Africa built an authority named SAHPRA which represents the National Department of Health to secure health of public and animals by assuring safety and quality of medicinal, veterinary and biological products along with medical devices.

Role of SAHPRA is to look after market of medicinal drugs and medical devices. Previously SAHPRA was known as Medicines Control Council as health regulatory authority. In June 2017, the MCC has upgraded to the SAHPRA. The reason behind this up-gradation is to become the stringent regulatory authority. SAHPRA will regulate the medicinal drugs and medical devices as upgraded rules and legislations are expected to follow, although SAHPRA is assigned to take over accountability of MCC and Directorate of Radiation Control (Andrea Keyter et al., 2018).

South Africa has comparative around 45 billion Rand (US$3.2 billion) in market of pharmaceuticals in the year of 2015. South Africa has great demand for generic drugs. The economical status of Pharma sector of South Africa is exclusively dependent on generic drug production as well as domestic market for generic drugs. According to statics of the year 2013, generic drug products hold about 63% accounts of pharmaceutical market in private sector whereas generic product share in market of South African government pharmaceuticals is around 80%. (V. et al., 2018)

Currently SAHPRA is facing backlog submission load as it got converted into eCTD format from ZA-CTD. According to numbers, SAHPRA receives nearly 4700 applications in a year although SAHPRA could make assess the applications up to 2550 applications annually. Recently SAHPRA is under load of nearly 16000 applications which are submitted up to 31 January 2018 adding the assessment and final approvals of these submitted applications are still pending. The current goal of SAHPRA is to clear the backlog submission coming year as soon as possible. This will be ease for the process because of eCTD implementation. (A Keyter et al., 2018)

Now SAHPRA follows few key recommendations and try to build stringent legislative structure by considering measuring and monitoring the processes, facilitated regulatory pathways, strong and robust technologies, information and communication system and quality management system. (Andrea Keyter et al., 2019)

The SAHPRA health system based on three pillar system which mainly emphasizing on

- Safety
- Efficacy
- Quality

SAHPRA consider public health as a priority and SAHPRA's goals, vision and mission reflects the purpose. (*SAHPRA | Who We Are*, n.d.)

Saudi Food and Drug Authority

Saudi Arabia, Kuwait, Bahrain, Qatar, United Arab Emirates, Oman and Yemen all together formed Gulf Cooperation Council which was founded in 1981. The purpose behind this foundation is to harmonize rules and legislations among the member states. (Al-Jazairi et al., 2011)

Saudi Food and Drug Authority (SFDA) was demonstrated representing an individual regulatory body under the Council of Ministers which expected to report to The President of Council of Ministers directly. The purpose of SFDA is to focus on public health along with the safety of products involve in the therapy of human as well as animals with their feed. Also SFDA has legislative regulations on biological and chemical products and electronic products also. (Alsager et al., 2015)

The pharmaceutical market of the Kingdom of Saudi Arabia is one of the affluent markets among the Middle East and North African region. Also it is believed to be growing economy. The annual rise of year 2014-15 of healthcare market is about 16 % according to statistics. On the other hand at the same time pharmaceutical market got rise by total 12 %. This growth helped to built up the international status and economical stability. The study said that this rise in the market of healthcare and pharmaceuticals is mainly due to great rise in population and also increase in incidences of unhealthy and diseased condition. This increase in demand of pharmaceuticals, SFDA take charge on drug pricing policies and make them more stringent in collaboration with drug pricing plan of GCC in these circumstances. (Hashan et al., 2016)

SFDA follow the following objectives:

- To comply with the safety, quality as well as efficacy specifications of the final pharmaceutical products which are used for humans & animals.

- To comply with the safety and quality specifications of biological as well as chemical products along with cosmetics and pesticides.
- Take charge of safety of medical devices and its influence on health of public.
- Provide accuracy and extreme safety for medical devices.
- Create different rules and construct policies which are necessary to maintain the safety.
- Stick to the policies and try to implement the policies while processing.
- Create departments according to the need. Assign the staff. Check on the employment necessary for the task.
- Create the new analytical methods, specifications, guidelines in point of view of research and evaluation expecting more stringent and enriched quality product.

SFDA believes in strategic planning for efficient results. Up till now, SFDA has been executed two strategic plans. First strategic plan was executed in year 2006-2011 which ensured the responsibility of pharmacovigilance department. Second strategic plan was execute in year 2012-2016 which were focusing on development of technology to enhance the investment of stakeholders'. The SFDA is currently having 3rd strategic plan of year 2018-2022. The aim is to promote advance safety and secure the health of public. (*Sfda.Gov.Sa*, n.d.)

United Arab Emirates

Ministry of Health and Prevention

'United Arab Emirates' is a member of Gulf Cooperation Council. Ministry of Health and Prevention is the healthcare regulatory authority of UAE. Ministry of Health of UAE consists of 'Health Authority of Abu Dhabi (HAAD)' of Abu Dhabi, 'Dubai Health Authority (DHA)' of Dubai and 'Emirates Health Authority (EHA)'. These authorities are helpful to Public health services to ensure the safety of public health.

In the gulf region, UAE pharmaceutical market is on second position of the list of large market of pharmaceutical medicines and it is growing constantly with the time. The exact value of pharmaceutical market is approximately US$ 1.8 Billion. The UAE has strong government support. Previously UAE used to import generic medicinal products in large amount. Due to UAE's government support local manufacturing of the generic drugs is purposely enhanced. The use of generic products is increased greatly. Government has promoted the production of generic drugs as to reduce the cost of medicines due to import. Due to this step, many pharmaceutical companies start looking towards UAE as opportunity and show interest in investing for UAE market. The numbers indicate , the UAE market of pharmaceuticals was approximately $ 2.4 billion in the year 2013 and up to 2020, it is expected to cross the market value $ 3.7 billion. (Article et al., 2015)

CHAPTER 5

Post Approval Compliance

Post approval compliance

The pharmaceutical finished drug product goes through many stages of its development period until it gets registered authorisation status by particular health and regulatory authority. The many concepts and theories are applied for the development of one drug. Actual drug development process is the collaboration of many researches and study findings as well as need of treatment. All these events lead to develop a medicine. One drug development is a joint venture of various departments for a successful and effective outcome.

Firstly, the drug doesn't remain same at the end of the pharmaceutical product process. The active part of the pharmaceutical product which is responsible for the pharmacological action should be formulated with some excipients which are suitable for the formulation as well as for the human body. Here it is start the product development process. The pharmaceutical industry has particular department which is responsible for head start of the product. The drug development process mainly relies on human need and market demand.

The new drug product life cycle is very distinctive. Generally each type of product goes through same stages with some particularities. Predominantly, there are three key stages of drug life cycle:

1. The research and development of the pharmaceutical drug up to regulatory approval
2. The time period between approval and the loss of marketing exclusivity of registered drug
3. After the loss of marketing exclusivity where many generic drugs step into market for competition.

In the first stage, an innovator company finds out the doable search for new drug entities for the specific physiological conditions. And perform different actions to get

the approval for the mew chemical entity. For the approval of new drug product, regulatory authority demands the results and date generated at the time of performing steps as regulatory document requirement for granting an approval.

There are post approval requirements to fulfill defined by every regulatory authority. The phase IV reports i.e post-marketing safety surveillance is the main document of post approval requirement. And to maintain the approval of product, there are provisions like annual reports, renewals of approvals. This is part of post approval compliance. Generic drug lifecycle is also same as of new drug entity. Industries prefer generic drug production over the new drug product for two specific reasons 1)generic drugs get approved in around 1-3 years approximately, where new drug product approval process takes around 15 years and 2) generic drugs are reasonable where new drugs are very costly. (CIOT 2015)

The regulatory need of documents in the lifecycle of drug is generally classified as preapproval documents and post approval documents.

Pre-approval stage required following documents:

- Drug development reports
- Chemistry, manufacturing, control results
- Analytical tests reports
- Data showing stability, safety as well as efficacy of the pharmaceutical drug product
- CTD format required document
- Forms necessary for submission application
- Administrative documents according to particular regulatory

Post-approval documents required to maintain the approval status:

- Post marketing surveillance

- Periodic safety update reports
- Dossier updation with committed CMC data
- Annual reports
- Variation filing if any changes in approved regulatory application
- Renewals of dossier
- Facilities and other license renewals (*Pre & Post Approval CMC · G&L Scientific*, n.d.)

Post approval safety is the prime component of post marketing safety surveillance. This data helps to build up safe design and draw risk management plan. The drug post marketing surveillance and risk analysis is long term and consistent process. This requirement leads to born pharmacovigilance department which main motive is to implement the risk evaluation and mitigation strategies of pharmaceutical drug product. Pharmacovigilance database is responsible to generate public experienced data and any risk found with generated data the actions like labelling changes according to new information should be done. And on major call regarding safety product recall can be proceed. (*Post-Approval Compliance | Ropes & Gray LLP*, n.d.)

After a finished pharmaceutical product obtain a approval, then it means the holder of application get permission to distribute his product commercially in the market. However, to maintain the status of the approval, holder of application must make sure to fulfill the post approval requirements meeting regulatory standards. These maintenance activities collectively frame as post approval compliance.

To retain the approval status of product, holder of application must update dossier and information in a way described by regulatory requirements:

- Updation of dossier i.e quality part as more information is obtained.
- Continuation with phase IV clinical i.e post marketing safety surveillance study.
- Submission of PSUR reports regularly.
- Preparations of annual reports and submit annually.

- Renewals of dossier if marketing authorisation period is going to expire.
- Post approval changes i.e variation filing if applicant wants to change in the approved application. (*Post-Approval / Maintenance - PharmaLex*, n.d.)

The requirements of post approval compliance are the need of approval maintenance which is also the part of consent at the time of approval submission. The guidelines suggest the needful actions which should be followed published by particular regulatory authority by their official portal or websites. These guidelines state that the consent conditions must accurately follow the requirements after approval of dossier with respect to retain the authorisation.

The post approval compliance reporting mainly follows 2 component systems:

- Compliance monitoring and reporting: in which the phase IV studies are conducted. The post marketing surveillance is the requirement for approval and commitment of applicant or holder at the time of submission. This monitoring program is public case studies to observe and study the adverse effect reporting. Program develops various strategies and methods to analyze the submitted data and to collect the evidences.
- Schedule of reporting: To report the adverse events, public need an appropriate portal to submit the feedback. Also to comply with post approval requirement applicant should follow and should reach the timelines. (*Compliance Reporting Post Approval Requirements*, n.d.)

The regulatory perspective highlights three main elements in post approval compliance. Pharmaceutical industries follow these 3 elements in practice of post approval compliance:

- Post approval changes i.e variation filing practice
- Annual reports
- Renewals of dossier

- Periodic safety update reports

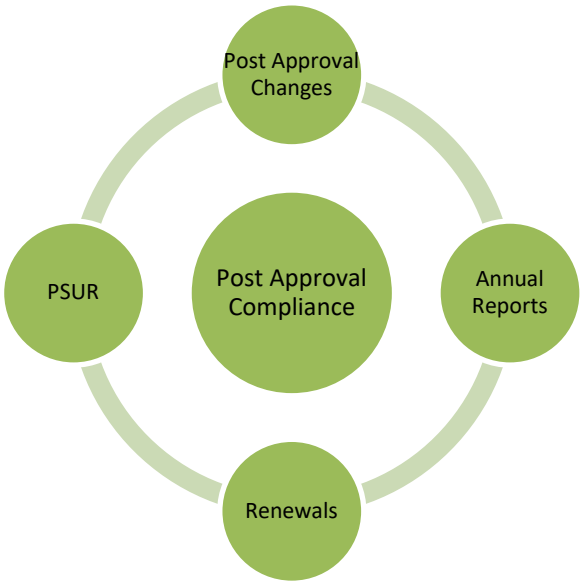


Fig (1). elements of post approval compliance

Post approval changes/ management:

Every drug product goes through many changes during throughout complete lifecycle. So the original version of registered product keep updating end evolved. There are many factors behind the change generated. It is imperative to evaluate the significance of implemented changes. The proposed new change should be evaluated for quality, safety and efficacy of that change. Here where post approval change submission process starts. (Ramani et al., 2011)

The post approval change is the major and important element of post approval compliance. It mainly represents the changes in the approved pharmaceutical finished product. Post approval changes are defined as the change has been deliberately implemented after the approval of the pharmaceutical mainly to improve product's

whole quality which ensures the safety also. These changes revolve around CMC changes, administrative changes including formulation changes also. If the holder of marketing authorization want to do change in the finished drug product, to implement that change he should submit an application to file a change before the distribution of that improved product. Again, post approval change varies as intensity level changes with appropriate application. (Langer et al., 2020)

Evaluation of the change to approved finished product is necessary as it has influence on quality, safety as well as efficacy of the product. Every change has specific degree of intensity of the change which is the basis of classification of post approval changes. According to degree of change impact the requirements of testing to ensure safety and quality varies. To register the change, the application should be submit which require the documents showing the proof of safety of the changed product. For the evaluation of change, regulatory authorities have published a guidance document for industries. Post approval change management has a vital role to play in pharmaceutical product lifecycle. It specifies the necessary changes need to implement in product to maintain status of approved application.

Post-approval change management protocol:

To submit the application for implementing changes ICH guideline suggest to seek the approval of protocol of required testing to justify the change in terms of safety as well as to maintain the transparency between the regulatory authority and holder of marketing authorisation. PACMP is the protocol tool which is part of PALM. Protocol helps in designing the accurate procedure to implement change, verification of that change including the evaluation of the change.

ICH Q 12: Technical and regulatory considerations for pharmaceutical product lifecycle management suggests pharmaceutical industries to do the application of PACMP.

PACMP follows 2 steps:

First Step: To submit the PACMP to the respective regulatory authority.

The protocol should give the scenario of proposed change, justification of that proposed change, risk analysis of that change, tests, specification and acceptance criterion required to prove the safety of proposed change. Also, PACMP should state the reporting category of that specified change. Supportive information is suggested to give. And PACMP documents are submitted in Module 3.2.R.3 of CTD dossier format. Respective regulatory agency will review the protocol and documents supporting protocol and assessment results will approve the protocol.

Second Step: to perform the tests to justify change.

Once the regulatory authority assesses the protocol and gives the approval then MAH starts with the second step. In this step, the study should start by performing the tests mentioned in the protocol. The MAH should make sure that tests results are meeting the acceptance criterion and each result should be documented. At the time of submission the documents generated as test results are submitted as a proof of safety of proposed change. The tests need to perform and documents which need to submit are mentioned in the guidelines of post approval changes published by respective regulatory authority.

Elements of PACMP:

The protocol of PACMP is designed by considering following elements for the complete assessment to justify the safety of proposed change:

- Description of proposed change: The PACMP should include the detailed description of change with justification of change which MAH wants to implement. And a tabulated table differentiating the approved and proposed change with clear high lightened difference.

- New risk analysis should be done by considering the previous risk assessment. On the basis of this evaluation, the study design, tests required to perform, specifications and acceptance criteria of tests are made to justify the safety. If any new tests are add for the newly proposed change, then the MAH should also give the analytical procedures and standard operating procedure of that new tests. Each CMC parameter related to proposed change should be tested with given appropriated conditions.
- Need to check the validity of proposed change. Discussion and assessment should be done of control strategy with respect to proposed change.
- Other confirmatory tests and qualifying tests to meet the criterion of new tests, their validation and verification should be done.
- At relevant places, previous data which could be helpful for the proposed change regarding any CMC step can be referred just to mitigate the risk.
- Discussion over the reporting category of proposed change. The appropriate category should be selected as it is the question of safety as well as according the reporting category the requirement of testing and submitting data varies.
- The evaluation of impact of proposed change along with its adverse effect on quality of product should be done. Hence the verification of proposed change should be performed as a part of maintaining PQS (pharmaceutical quality system).
- Monitoring of each change and its results should observe and should be noted for further reference. Also the profit analysis of the proposed change should also be done in aspect of quality and to widen the exposure in various markets. (Ahmed, 2018)

The PALM is the bridge between the development stage of product and commercial phase of product. And the basis of PALM stands for the safety of human health and the products position in the market i.e commercial status. With respect to the quality of pharmaceutical indirectly the position in the market throughout the lifecycle of product, the MAH should be taken care of various control strategies, risk analysis, critical

quality parameters even after the approval of drug product. These actions are set importance in the post approval lifecycle management.

The PALM is part of dossier which is generally submitted in the regional document part of dossier as per the requirement of the particular health authority as it is the agreement document demanded at the time of submission as a part of dossier requirement. PALM builds with the following:

- Critical quality attributes and Critical process parameters should be evaluated to have post approval control to ensure the quality and safety.
- Design space should be designed by considering the CQA and CPP to manage the risk assessment in complete lifecycle period of the drug.
- Control strategies should be ready and keep them regularly updated as development progress further and more information is available.

The PALM is an integral part of dossier requirement.

PALM has key elements:

- Design space
- List of tests and strategy of testing
- Critical quality attributes and Critical process parameters
- Control strategy information and implementation
- Risk analysis (Ohage et al., 2016)

A change management system has important role in the implementation of proposed change as it mandatorily has the change plan, protocol for change and appropriate strategy. PALM system helps to achieve the objective of the proposed change in systematic controlled manner and control strategies. This leads to safe and secure change implementation with accurate documentation for post approval change submission to health authority. The PALM system also considers the Pharmaceutical

Quality System mentioned in ICH Q 10 guideline and Quality Risk Management described in ICH Q 9 guideline. Every regulatory authority has developed and published a guidance document and guidelines of post approval changes. These guidelines make sure that they should provide the guidance regarding the reporting category of the proposed change, tests need to be performed to assure the safety, established required condition associated with proposed change and documents requirement at the time of submission. The development of protocol and maintaining the lifecycle of the product is a part of PALM system. To deal with the PALM more comprehensive actions to justify the need of change is required. PALM system focuses on effectiveness of proposed change and its consequences by evaluating the risk analysis which can be done on the basis of generated data at the time of testing, risk based analysis of proposed change, analysis of established conditions and all other relevant aspects to evaluate the potential effect of change.

Post approval changes set timeline criteria to submit the application, time for regulatory authority to evaluate the change, and time for industry to implement the change. Though every regulatory authority variations in the reporting category, documentation requirement and also timeline for the evaluation. But all guidelines stick to the safety and quality requirement.

The monitoring of post approval change system is whole n sole responsibility of pharmaceutical industry as it builds the company's profile at the regulatory authority and has impact on reputation. The monitoring activities should be précised for long or short term as per the proposed change requirement.

Post approval changes are meant to be done to improve the quality of product. The evaluation of the PACs is important as they are imparting for better quality for whose safety is necessarily should check. (Ramnarine et al., 2017)

Clarification on reporting post-approval changes:

Generally the guidance published by regulatory authority categorizes the changes into different categories.

The types of changes are:

- Administrative changes
- Quality changes
- Changes in active pharmaceutical ingredient (API)
- Changes in finished pharmaceutical products

These main categories further classified into:

- Facility, manufacturing site
- Manufacture
- Stability
- Container closure system etc.

Determining the reporting category:

Every change has different aftereffect on the quality & safety of the pharmaceutical. The proposed may have adverse effect on quality hence evaluation of that change is required. Evaluation is done on the basis of potential risk to the quality. The guidelines published for the guidance to the industry categories the change according to the risk and impact on quality.

Generally change reporting category is divided in 3 categories:

- **Minor change:** These types of changes have negligible impact on products quality. And the minor changes don't require agency assessment but need to inform to the agency and submit annually.

- **Moderate change:** These types of changes have moderate impact on products quality. And moderate changes don't require the agency assessment but agency should be notified by the MAH.
- **Major changes:** These types of changes have significant impact on products quality. And major changes need to be assessed by regulatory authority for quality check and MAH require the approval of authority before implementing the proposed change.

Process for submitting changes:

According to the reporting category of the proposed, every change has different impact on quality hence there is difference in submitting change to the agency. Applicant should follow the appropriate submission pathway as per reporting category of change. Minor changes have negligible impact on quality hence they just need not take any approval or don't require separate application. Moderate changes need to notify agency about the change. And major changes require a prior approval hence application need to be submitted. Every regulatory authority has their own specific procedures for submission of applications. Application should contain all information, data of tests and documents as per particular agency.

Risk analysis:

The proposed change might have adverse effect on other factors of drug which affect the quality of product. Hence risk analysis of the proposed change should be done. It depends on the different type and intensity of change. According to the type of change, control strategy should implement to mitigate the risk.

Assessment of the change:

The PACMP and PALM system plays consequential role in the assessment of the proposed new change. Protocol designs the plan of work need to assess the new change. PALM system of industry cope up with the quality requirements.

The changes related to active substance & pharmaceutical products more probably to have influence on quality.

Drug substance: The proposed as well as present specifications should be given. According to the change intensity, more tests are needed to perform. Each new addition should be submitted with proper rationale.

Drug product: the equivalence study should be checked as product should be as equivalent as previous and reference listed drug.

Documents required submitting:

Every regulatory authority required documents according their guidelines. Also it depends on reporting category. At the time of submission, application should contain required forms, cover letters like administrative documents as per particular authority.

And the documents showing the testing performed to prove the quality as per requirements and comparative tabulated format o change and justification of proposed change. (*Looking for Clarification on Reporting Post-Approval Changes to a Drug Substance to the FDA? You Are in Luck. | Camargo*, n.d.)

Periodic Safety Update Reports

The MAH have the responsibility and commitment to assure and keep an eye on the profile indicating safety of pharmaceutical after the marketing of the approved pharmaceutical product. Periodic safety update report is part of post marketing surveillance. To assure the safety of product MAH is continuously involve in the conversation with the regulatory authority discussing the regulatory strategies and hoe to indulge the strategies to maintain the risk-benefit ratio.

Post marketing surveillance is a commitment given by MAH to the regulatory authority at the time of submission of the dossier of pharmaceutical product. Post marketing surveillance is the last phase of clinical studies which is stand on the basis of practical field study. It is the tool of raw experience of huge public who is using the product. PSUR should submit on regular basis to the agency. The purpose of PSUR is to monitor drug risk-benefit ratio and safety profile of drug. PSUR helps to note the drug adverse effects. PSUR is a spontaneous, direct and advertence studies along with other safety information. At the development stage, product is evaluated for many human unpredictable, predictable effects like hypersensitivity. Also risk analysis is also a part of product safety. These studies are done before the submission of dossier. But PSUR's aim is to note down the all effects other than they studied before the submission. The adverse events are noted, then they are evaluated, analyzed and to take the decisions if there is any need to make changes in the approved pharmaceutical product as human health's safety concern. (Waring & McGettigan, 2011)

PSUR is the commitment of the MAH given at the time of submission of dossier. PSUR is the requirement of each regulatory authority. But the slight difference is there as per different regulatory authority. Some regulatory authorities have their own portals to register the observed adverse effects. And then it gets registered in the data base. This information is then utilized to analyze the risk and to decide the control strategy to initiate the change in approved pharmaceutical product. (Ridley et al., 2006)

Components of PSUR:

- Title page:
  Title page should give the idea of the content and it must be appropriate heading.
- Executive Summary:
  This must include the summary of whole report and general description of all noted events.
- Introduction:
  It should give the name of products noted in the PSUR and clear perspective of the PSUR.
- Status of product in market worldwide:
  Scenario of all markets where product is authorised describing product's different indications should be given in the PSUR.
- Safety actions taken by MAH or regulatory authority:
  Description of the safety majors taken by the MAH after the distribution of the product are noted in PSUR. The time is covered by the PSUR reporting.
- Changes in the registered information:
  After the approval of product, if the MAH wants to change in the information like contraindications, adverse drug reactions, side effects, and precautions as more knowledge regarding this gets available. This information should be should be updated and these changes should be reported in PSUR.
- Exposure to the patients:
  This is the information and observations regarding any adverse event which are not found by study at the time of submission. This should cover the results reported by patient. Also this should give the methods of collecting and evaluating the collected data.
- Individual case study reports:
  For the better evaluation of post marketing safety, individual case study is the prime strategy to evaluate the danger and rebuild the safety profile. This information

includes the information reported by consumers, doctors, pharmacists and also a literature base.

- Study:

  This includes the study performed to take the safety measures, study to analyse the reports, study to do the necessary changes after getting the appropriate information and ongoing market study.

- Other information:

  The information other than the registered reports which get by the literature, discussions with the team, risk management plan, risk-benefit ratio should be considered.

- Overall safety evaluation:

  The submitted information is then categorised into types of effects. On that basis, new risk evaluation is done and new safety profile is generated. This information should highlight the changes in the submitted data.

- Conclusion:

  According to the new safety profile generated and risk-efficacy evaluation based on reported data industry decides the safety actions to be taken and changes to be done according.

- Appendices:

  This should include the tests results, data sheets; other tabulated information supported the safety action and change. (Ebbers et al., 2013)

As preclinical trials are important for the drug, like wise post approval safety surveillance is also important. And industry should develop the strategies for that. And tested and valid tests and methods should develop to evaluate the reported data. (Gibbons et al., 2010)

Annual Reports

Annual report is the main component of the post approval compliance. As it is the regulatory document, there are many concepts, considerations and regulatory requirements are associated with annual reports. The annual reports are now a day evolution as it is not practiced since earlier. The annual reports are designed after the concept of eCTD dossier format.

Initially the dossiers were used to submit in CTD paper format to the respective authority. At that time renewals of dossier were practiced. The concept behind the renewals is to keep the dossier updated as it is submitted in paper format. So the new information used to submit in either variation format and summarized all in final dossier renewal.

Initially all countries were following CTD dossier format set by the ICH guidelines. Now regulated authorities like USFDA, EMEA are following eCTD format and some authorities are still stick to the CTD format. The eCTD format generally reduces the paper work and ease of review of the documents. An eCTD software stores the data in the database hence there is no exact need to update the dossier. Hence health authorities develop a annual report concept. Annual report is the summary of all implemented changes done to the product in the whole annual time span.

The regulatory authorities which are still following CTD format have renewal provision in practice. This varies with the regulatory authority. And the guideline and requirements are provided by particular authorities.

Renewals of dossier

Renewal of drug product dossier is also the component of the post approval compliance. As it is the regulatory document, there are many concepts, considerations and regulatory requirements are associated with annual reports.

Initially the dossiers were used to submit in CTD paper format to the respective authority. At that time renewals of dossier were practiced. The concept behind the renewals is to keep the dossier updated as it is submitted in paper format. So the new information used to submit in either variation format and summarized all in final dossier renewal.

The regulatory authorities which are still following CTD format have renewal provision in practice. Generally for renewals, only module 1 and module 3 i.e. administrative information and quality information respectively are going to submit to the agency. Hence if any changes done to the product, then the changed information, data and tests results are submitted in module 3. The renewals are as similar as annual reports. (Bhavya et al., 2018)

CHAPTER 6

USFDA Post Approval Compliance

USFDA

POST APPROVAL CHANGES

USFDA provides the guidance for industry for those applicants of new drug application or abbreviated new drug application who wants to make some changes in the approved dossier. These changes should be in accordance with the Federal Food, Drug, and Cosmetic Act section 506A and subpart 314.70 of 21 CFR. These changes are known as post approval changes.

The post approval changes are designated as levels of changes based on the intensity of new change and its impact on the quality and safety. USFDA also published guidance on the designation of intensity of change.

USFDA divided the change intensity into three categories:

- **Level 1 changes:** these changes generally have no impact or negligible impact on the quality and performance of pharmaceutical formulation. Level 1 changes having negligible impact on quality generally reported in annual reports.
- **Level 2 changes:** these changes have moderate to significant influence on the quality as well as performance of pharmaceutical formulation. Level 2 changes are generally reported in CBE-0 and CBE-30.
- **Level 3 changes:** these changes have influence on the quality as well as performance of pharmaceutical formulation. The level 3 changes are reported in prior approval supplement. ("Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation," 2004)

Level of changes should be placed in appropriate reporting category while submitting the application. Section 506A and § 314.70 (21 CFR 314.70) have given the classification of reporting category. There are total 4 different reporting categories mentioned in the guidance document.

- **Minor changes:**

  "Minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."

  These deliberate changes are less dangerous and most likely to have negligible impact on the pharmaceutical quality & safety as these deliberate changes have adverse impact on product's identity, strength, purity or potency.

  These new changes should be submitted in the annual reports by the applicant as per the 21 CFR 314.70 (d).

- **Moderate changes:**

  "A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."

  These new changes are less dangerous and most likely to have moderate influence on the pharmaceutical's quality & safety as these new change have adverse effect on pharmaceutical's identity, strength, purity or potency.

  Again moderate changes are classified into two different categories.

  - **Supplement- Changes Being Effected:** These types of changes have less to moderate influence on the quality, safety and effectiveness of pharmaceutical. These new changes can implement only when authority receives the application. After that industry can distribute the drug in market officially. Submission should be done according to 21CFR 314.70 (c)(6).

  - **Supplement- Changes Being Effected in 30 days:** these types of changes have moderate to significant impact on the quality, safety and effectiveness of pharmaceutical product.

These changes are required to submit the application to the agency after implementing the change and 30 days before the distribution of improved change.

Submission should be done according to 21 CFR 314.70 (c)(3).

If the applicant submit the CBE-30 application to the agency, and after reviewing the application agency can ask to submit the prior approval supplement as per need. Then applicant has to stop the distribution of drug. This is according to the 21 CFR 314.70 (c)(5)(i).

In the CBE-30 application safety, quality & effectiveness related information is submitted as per requirement. If the agency thinks the provided information is not sufficient to justify the safety, quality and effectiveness of the pharmaceutical, FDA may ask the applicant to provide more justifying information and up to then the distribution of product is delayed. This information is given in 21 CFR 314.70 (c)(5)(ii).

If FDA is not satisfied with the CBE or CBE-30 change after reviewing the application, then FDA may disapprove the change and can stop the manufacturing of improved product according to the 21 CFR 314.70 (c)(7).

- **Major changes:**

  "A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product."

  These deliberate changes are less dangerous and most likely to have significant influence on the pharmaceutical's quality & safety as the implemented change have unfavourable effect on pharmaceutical's identity, strength, purity or potency. Hence these changes need authority assessment and approval before implementing the change. The application is called prior approval supplement. And submission should be done according to 21 CFR 314.70 (b).

  In certain conditions like rare disease conditions or shortage of drugs applicant may apply for expedited review of the application. These applications should be

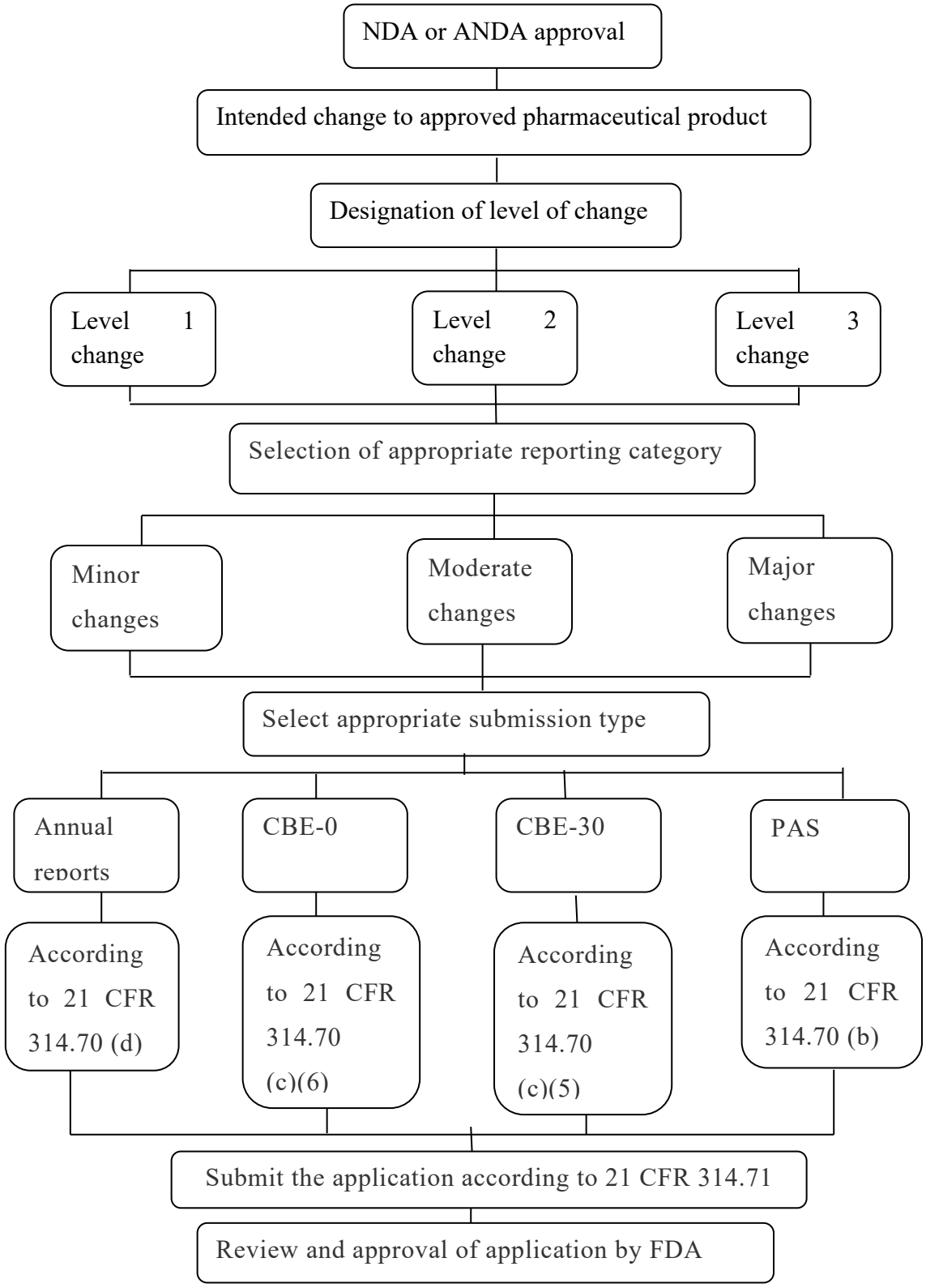
inarguably marked as 'Prior Approval Supplement- Expedited Review Requested'. The guidance regarding this provision is provided in 21 CFR 314.70 (b)(4). (Food and Drug Administration, 2004)

Designation of change	Reporting category	Type of suitable application	Regulation	Description of change
Level 1	Minor change	Annual report	21 CFR 314.70 (d)	Have less or negligible influence on pharmaceutical's quality, safety and effectiveness.
Level 2	Moderate change	CBE-0	21 CFR 314.70 (c)(6)	Have less to moderate influence on pharmaceutical's quality, safety and effectiveness.
		CBE-30	21 CFR 314.70 (c)(5)	Have moderate to significant influence on pharmaceutical's quality, safety and effectiveness.
Level 3	Major change	Prior approval	21 CFR 314.70	Have significant

		supplement	(b)	influence on pharmaceutical's quality, safety and effectiveness.

(Table no. 1: Post approval changes of USFDA)

- Documents required to submit the application for post approval changes:
  - Form 356 h
  - A covering letter that includes:
    - The type of submission
    - A list of the change(s) and a rationale for the change(s)
    - Cross-referenced information
  - Completed documents or forms based on requirements, such as a medicine submission application form, signed and dated.
  - GMP information:
    - GMP License
    - Inspection history
  - A side-by-side comparison showing the differences between the previous approved change and deliberate proposed new change
  - Product labelling information.



(Fig. (2): Submission process of post approval changes in USFDA)

Periodic Adverse Drug Experience Report

Every drug has to go through all clinical phases to get the FDA's approval. The FDA grants the approval on the basis of submitted data of phase-I, II and III clinical trials. Phase-IV clinical trial is post marketing surveillance. This study is on field study hence for the data marketing of the drug product is necessary. But at the time of submission of the application of drug, it is mandatory to conduct the post marketing surveillance. The commitment should be given by the applicant to the authority.

FDA has published the guidance document to provide guidance for the industry on periodic safety update reports. According to ICH E2C (R2), it is called Periodic Benefit-Risk Evaluation Report (PBRER) or Periodic Safety Update Report (PSUR) where USFDA calls them Periodic Adverse Drug Experience Report (PADER) or Periodic Adverse Experience Report (PAER). This is requirement of post marketing surveillance to monitor the post marketing adverse events. The requirements need to fulfil while submitting the application as described in subpart 314.80(c)(2) of 21 CFR and subpart 600.80(c)(2) of 21 CFR.

The applicant must report each post marketing event according to the regulatory requirement. The PADER should be submitted at quarterly intervals over the first three years from the pharmaceutical product approval date. After that annually over the subsequent years of the pharmaceutical product with respect to maintain the lifecycle. The quarterly reports should be submitted by the industry within last 30 days of closer of the quarter period. Same ways, annual reports should be submitted within 60 days of closer of the anniversary date of approved pharmaceutical.

Elements must contain in the each PADER:

1. Description of the information:
    - Detailed introduction of report, summary of information reported
    - Information regarding adverse events reported in 15 days alert

- Summary of actions taken after the last PADER submitted to authority i.e FDA.

2. ICSRs describing serious, non-serious and unexpected events reporting
    - Each ICSR which is indicating serious, non-serious and unexpected adverse reactions in first 15 days alert.
3. Scientific literature
    - If the first 15 days report is based on the information available in different scientific literatures should be published as article and not be considered as report.
4. Post-marketing surveillance studies
    - This should include the information collected during the post marketing surveillance study.
    - And submitted in the form of PADERs.
5. Electronic submission of report
    - The PADER reports are submitted electronically as per eCTD requirements and through eCTD software.
6. Multiple reports under single report submitted
    - The reports observed during the clinical trials study should not include in the PADERs.
    - The report is for specific drug having multiple approved applications for the drug, and then the PADER should be submitted for first application of drug product.
7. Confidentiality of patient
    - The PADER should not disclose the identity of patient i.e name and address of patient in the reports.
    - For the identification of patient, each patient should assign with the identification code to maintain the privacy of the patient.
8. Recordkeeping of each report
    - The applicant should maintain all generated data and information regarding the adverse events during the post marketing surveillance

should be maintained for approximately 10 years from the approval date of application.

9. Withdrawal of approval
    - If the applicant fails to achieve the desirable safety measures necessary to take after the post marketing study, or if the FDA authority thinks that changes are not sufficient for the safety of public health and FDA is not satisfied then FDA can withdraw the approval granted for the product. And FDA may cease the distribution in the market of drug.
      (*CFR - Code of Federal Regulations Title 21 314.81*, n.d.)

General format of PADER report:

PADER: Periodic Adverse Drug Experience Report

Content	Information
Name of company	XYZ laboratories limited
Trade name of drug	XXXX
Chemical name of drug	YYYY
Application type	PADER
Submission Number	111111
Submission code	ABC-222
Therapeutic classification of drug	Antibiotic
Date of submission	02/09/2018

- **Module 1:**
  - Cover letter:

    Cover letter should cover the introductory summary of the application describing the purpose of the application with proper reference addressing to the FDA authority.
  - Form 356 h:

    This is the form which should be filled for PADER reporting purpose.
  - Package insert:

    It should contain the updated version of package insert based on the information obtained from post marketing study reported in PADER.

- **Module 5:**
  - 5.3.1 Clinical study reports
  - PADER
  - Introduction:

Content	Information
Name of company	XYZ laboratories limited
Trade name of drug	XXXX
Chemical name of drug	YYYY
Application type	PADER
Submission Number	111111
Submission code	ABC-222
Therapeutic classification of drug	Antibiotic
Date of submission	02/09/2018

- **Section 1:**

  Case report narrative summary and analysis.

  This section contains total 6 study finding tables:

Table no.	Information contain
Table 1	List of 15 days alert reports
Table 2	Number of adverse experiences by body system, seriousness, labelling and geography.

Table 3	List of no. of patients and 15 days or no 15 days reports by classification of seriousness and labelling for initial and follow up cases in reports
Table 4	Listing of dose and overdose cases
Table 5	Listing of lack of efficacy cases
Table 6	Listing of non-most suspect drug report

- **Section 2:**

  The narrative discussion of necessary actions taken during the surveillance

- **Section 3:**

  Index line listing of Non 15 day reports

Table no.	**Information contain**
Table 7	List of non 15 day reports

- **Section 4:**

  Non-15 day report

The PADER report is submitted in eCTD format.

Annual reports of FDA authority

Annual reports should be submitted to USFDA each year within the 60 days prior to the anniversary date of the application granted of the pharmaceutical product. Applicant should submit 2 copies of the annual report to the agency for reviewing the application.

Each annual report should be accompanied with the cover letter, form 356h (application to market a new or abbreviated new drug or biologic for human use) and form 2252 (transmittal of annual reports for drugs and biologics for human use). Also should include all activities regarding changes in the approved product done in the whole year.

- **Elements of annual report:**
  - **Summary:** it should include a brief summary of all new activities regarding changes in the approved product done in the whole year.
    It should give description of each change.

  - **Distribution of data:** information of the distribution in the market of drug.
    Information regarding no of dosage forms distributed in each approved market.
    This information is accompanied with National Drug Code (NDC).

  - **Labelling:** labels should keep updated as per information and activities.
    According to information professional labels, package inserts and patient information leaflets should be updated.

  - **Chemistry, manufacturing, and controls changes:** any CMC change submitted previously in the particular year in PAS application to the agency, the summary of that changes and significant changes should be included in the annual reports.

- **Status reports of post-marketing study commitments**: As per FDA requirement, applicant should give commitment to conduct the post marketing surveillance to study the safety profile of drug. This study reported as PADER. And annual report should include the summary of PADER submitted in that year. (CFR, n.d.)

ANNUAL REPORT YEAR 2018-2019

Name of company	**Alkem laboratories limited**
Trade name of drug	XXXX
Chemical name of drug	YYYY
Application type	Annual report
ANDA no.	201889
ANDA sequence	0029
Therapeutic classification of drug	Antibiotic
Date of submission	02/09/2018

- **Cover letter:**

  Cover letter should cover the introductory summary of the application describing the purpose of the application with proper reference addressing to the FDA authority.

  It is submitted to Office of Generic Drugs, Centre for Drug Evaluation and Research.

- **Form 356 h:** Application to market a new or abbreviated new drug or biologic for human use.
  This is the form which should be submitted for annual reporting purpose.

- **Form 2252:** transmittal of annual reports for drugs and biologics for human use.
  This is the form which should be submitted for annual reporting purpose.

- **Package insert:**
  It should contain the updated version of package insert need to be submitted with every annual report.
  It is submitted in M1-14.2.2.

- **MODULE 1:**
- 1.13.1: Nonclinical laboratories study
  - Not applicable

- 1.13.2: Clinical laboratories study
  - Not applicable

- 1.13.4: Labelling
  - Report the changes in the labelling.
  - Printed copy of label should be attached.

- 1.13.5: CMC changes
  This includes,
  1) List of approved chemistry, manufacture and control information: drug substance
  2) List of approved chemistry, manufacture and control information: drug product.
  3) List of specifications and analytical methods: Drug substance

4) List of specifications and analytical methods: Drug product.

Attachment-I

Drug substance	**Submission**		**Approval date**	**Summary of changes in year 2018-2019**
	Type	**Date**		
Manufacturer	Original	12/07/2017	12/07/2018	No change
Methods of manufacturing	Original	12/07/2017	12/07/2018	No change
Container closure system	Original	12/07/2017	12/07/2018	No change
Stability protocol	Original	12/07/2017	12/07/2018	No change
Specifications and analytical methods.	Original	12/07/2017	12/07/2018	No change

Attachment-2

Drug product	**Submission**		**Approval date**	**Summary of changes in year 2018-2019**
	Type	**Date**		
Composition	Original	12/07/2017	12/07/2018	No change
Manufacture	Original	12/07/2017	12/07/2018	No change
Method of manufacture &	Original	14/09/2017	24/12/2017	Minor annual reportable

packing BMR BPR	 Original Original			change in 1.13.7
Specifications & analytical methods Excipients Container & closure system	Original Original Original	14/09/2017	24/12/2017	Minor annual reportable changes in 1.13.7
Expiration reporting period of 24 months	Original	14/09/2017	24/12/2017	Minor annual reportable changes in 1.13.7
Stability protocol	Original	14/09/2017	24/12/2017	Minor annual reportable changes in 1.13.7

- Revised drug products specifications are provided in section 3.2.P.5.1
- Revised drug product standard testing procedures are provided in section 3.2.P.5.2
- Revised excipients specifications are provided in section 3.2.P.4.1
- Revised excipients analytical procedures are provided in section 3.2.P.4.2
- Revised container closure specifications are provided in section3.2.P.7
- Revised BMR & BPR are provided in section 3.2.P.3.3

Attachment-III

Test	Specification	Change	Reference
Description	White coloured, flat from both sides, uncoated tablet	No change	In –house
Identification a) by HPLC b) by IR	Comparison of retention time in chromatograph of test and standard solution	No change	USP
Water content	Not more than 7.5%	No change	USP
Dissolution	Not less than 85% of labelled amount	No change	USP
Assay	90% to 120%	No change	USP
Residual solvents	In ppm(not more than criteria)	No change	In-house
Microbial limit tests A) total aerobic microbial count b) total microbial count c) micro-organisms	 NMT 1000 cfu/g NMT 100 cfu/g Absent	No change	USP

Attachment-IV

Test	Specification	Change in method	Approval date
Description	White coloured, flat from both sides, uncoated tablet	No change	12/07/2017
Identification	Comparison of retention	No change	12/07/2017

a) by HPLC b) by IR	time in chromatograph of test and standard solution		
Water content	Not more than 7.5%	No change	24/12/2017
Dissolution	Not less than 85% of labelled amount	No change	24/12/2017
Assay	90% to 120%	No change	24/12/2017
Residual solvents	In ppm(not more than criteria)	No change	24/12/2017
Microbial limit tests A) total aerobic microbial count b) total microbial count c) micro-organisms	 NMT 1000 cfu/g NMT 100 cfu/g Absent	No change	24/12/2017

- 1.13.7: Summary of significant new information

  Summary table of all changes has been done to the approved drug product in year 2018-2019.

  Summary table of activities done in year 2018-2019.

ANDA sequence generated	Change done to approved product
0023	Marketing status report Reason- as per FDA reauthorisation
0024	Marketing status report Reason- as per FDA reauthorisation
0025	PADER Reason- 1st quarterly periodic adverse drug experience report
0026	PADER

	Reason- 2nd quarterly periodic adverse drug experience report
0027	PADER Reason- 3rd quarterly periodic adverse drug experience report

- 1.13.11: Distribution data
  Exact no. of dosage units along with specific strength distributed in reporting period i.e year 2018-2019.

- 1.13.12: Status Reports of Post-marketing Study Commitments
  - Not applicable

- 1.13.13- Status of other post-marketing studies
  The long term stability data is given in this module.

- 1.13.14: Log of outstanding regulatory business
  Summary of changes were made through supplements during reporting period i.e year 2018-2019.
  - ANDA sequence 0023
  - ANDA sequence 0024
  - ANDA sequence 0025
  - ANDA sequence 0026
  - ANDA sequence 0027

MODULE 3:

- 3.2.P: Drug product
- 3.2.P.3: Manufacture

  - Control of critical steps
  - Includes specifications and STP
  - Manufacturing process and controls
  - Includes updated BMR & BPR

- 3.2.P.4: control of excipients
- 3.2.P.4.2:
  - Analytical procedures and STP of changed excipients
  - Specifications of changed excipients

- 3.2.P.5: Control of drug product
  - 3.2.P.5.1: specification of drug product of all strengths
  - 3.2.P.5.2: STPs of drug product of all strengths.

- 3.2.P.7: Container closure system
  This includes packaging material specifications.
- 3.2.P.8: Stability data

CHAPTER 7

SAHPRA Post Approval Compliance

SAHPRA

AMENDMENTS

Post approval changes in South Africa generally mentioned as amendments.

There are total four types of amendments mentioned in the guidance SAHPRA.

- **Type A:** "Amendment that do not require prior approval and that may be implemented without prior notification"
- **Type B:** "Amendments that require notification only"
- **Type C:** "Amendments that require prior approval"
- **Type D:** "Amendments that are considered new application"

- **Type A-**

  Amendments intended to change the approved product having less adverse impact on quality of product and don't require notification to the agency.
  These amendments should be registered in product review and should be available whenever ask at time of inspection.
  All 'Type A amendments' should be reported in the part 1Ac of MRF1/ Module 1.2.1 of CTD format.
  Amendment schedule and amendment history should be submitted in the product review at the time of submission along with the recent amendments have done specifically to the approved product.

- **Type B-**

  Amendments intended to change the approved product having less to moderate adverse impact on quality of product and require prior notification submitted to the SAHPRA health authority.

Having moderate impact on quality and performance of product, it is necessary to notify the authority. In case of type B amendments, SAHPRA authority should receive the application 30 days primal to actual implementation.

The cover letter works as notification in type B amendments and it is mandatory that application should have clear label indicating 'Type B Amendment.'

- **Type C-**

  Amendments intended to change the approved product having significant adverse influence on quality of formulated pharmaceutical and require prior approval of SAHPRA health authority.

  Type C amendment require prior approval hence the application submitted to SAHPR authority must contain appropriate test data and document to justify the proposed change.

  SAHPRA will review the application and written approval is send to applicant by authority. And after that only applicant can implement the change.

- **Type D-**

  Amendments intended to change the approved product having major significant adverse impact on quality of product and need to submit a new application to SAHPRA health authority.

  Cases where new application is required:

  - API changes from previous to different new one.
  - Addition or deletion of API from the product having multi-component pharmaceutical.
  - Change in the quantity per unit dose of API
  - Change in the route of administration.

- Amendment Schedule require for submission should completed with following documents:
  - Cover Letter

- MRF3 and MRF 3B forms
- All data and facts connected to amendment application
- Specific coding of change to be proposed
- MRF1Ac from with option of history of all amendments or 1.2.1 section of module of CTD.
- If the specific change to the specific section of module then all data and their updation should be maintained.
- The updation of previously approved dossier but not recently contemporized in last 5 years with current data and facts.
- SAPC certificate copy as per administrative requirements
- Medicine registration certificate required to submit wherever required as per demand or necessity
- Manufacturing site current inspection report
- Copy of manufacturing license
- Copy of GMP certificate and the manufacturing plants not residing in SA should provide WHO GMP certificate.
- If any new processes are implemented then new protocol of that process validation along with actual validation report
- Stability data, protocol and commitment with relating data in support of proposed change
- Dissolution data after implementation of proposed change as a proof of efficacy which is requirement of SAHPRA.

- Standard documentation of amendment applications**:**

  1. Letter of application with:
     - Purpose of the variation(s)
     - Internal SAHPRA Code as per General Information guideline to aid routing
     - Description, Classification and Code of the Variation(s) (e.g. Type II)

- If the variation or change is affecting the same part of the approved pharmaceutical, it should be cleared with appropriate data and facts and if possible could submit in the same part of CTD module.
- Where an amendment is accounted as 'unforeseen', a brief explanation/justification is required
- Where a variation is the implementation of wording requested by SAHPRA, reference to the associated agreement/assessment/decision should be attached to the letter of application

2. Application form
3. Proof of payment for the Variation application
4. The current approved PI and PIL
5. Annotated/revised proposed PI and PIL as well as the clean versions
6. Amendment/variation schedule
7. Admin and technical screening checklists. ("Medicines Control Council - Amendments," 1998)

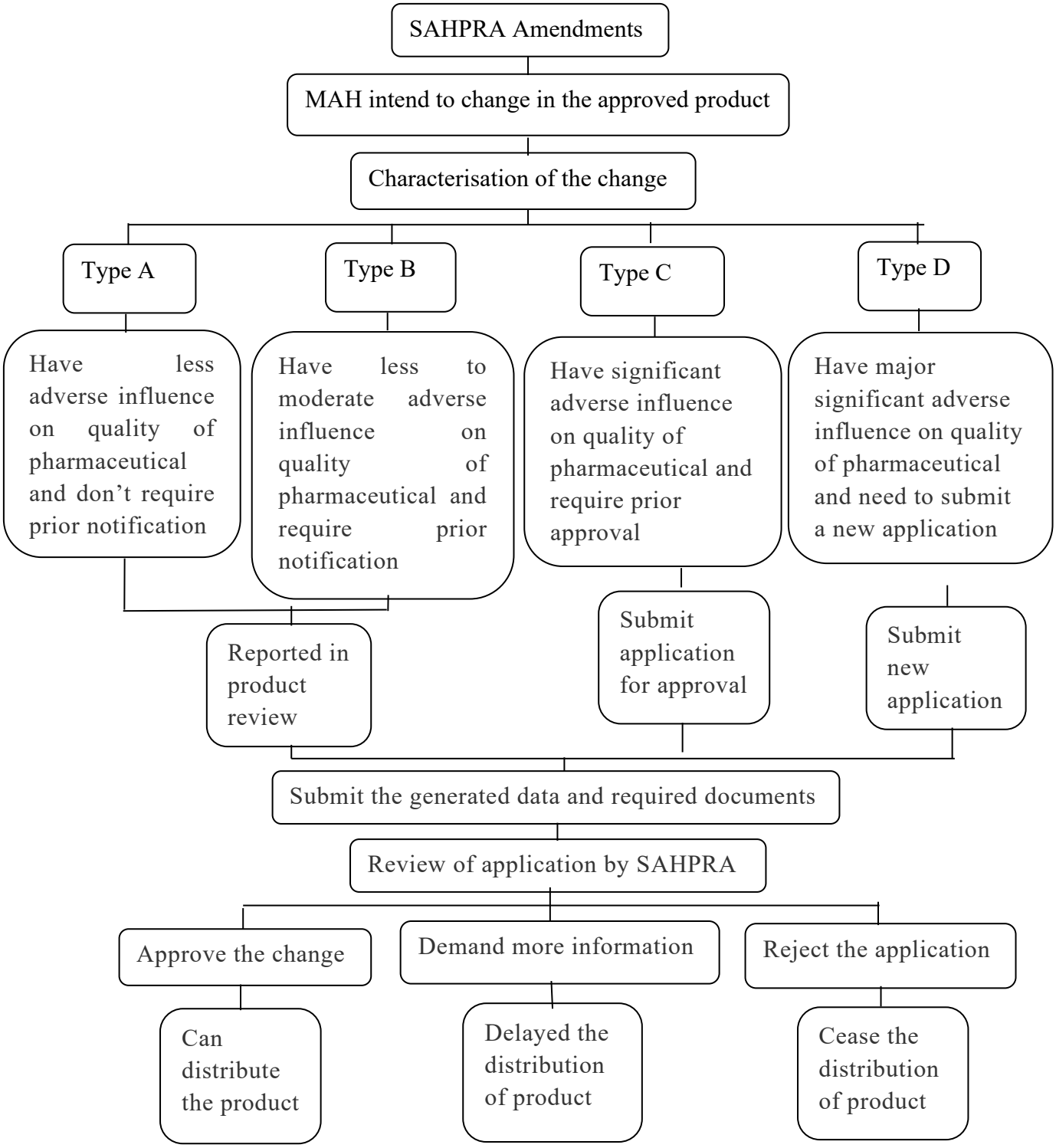


Fig. (2): amendment procedure of SAHPRA

Submission of Type C Amendment of drug "X" for SAHPRA

Proposed change:

This submission initiated as a result of addition of API source.

Type of amendment:

The change/addition of API source to a different company is described as type C amendment according to Amendment Guideline of SAHPRA.

Name of company	**Alkem laboratories limited**
Trade name of drug	XXXX
Chemical name of drug	YYYY
Present manufacture of API	XYZ mfg
Additional manufacture of API	ABC mfg
Application type	Type C amendment
Proposed change	This submission initiated as a result of addition of API source.
Therapeutic classification of drug	Antibiotic
Date of submission	02/09/2018

Required Data:

Sr. No.	Module	Name
Drug Substance		
1	3.2.S.1.1	Nomenclature
2	3.2.S.1.2	Structure
3	3.2.S.1.3	General Properties
4	3.2.S.2.1	Manufacturers
5	3.2.S.2.2	Description of Manufacturing Process and Process Controls
6	3.2.S.3.1	Elucidation of structures
7	3.2.S.3.2	Impurities
8	3.2.S.4.1	Specifications
9	3.2.S.4.2	Analytical Procedures
10	3.2.S.4.3	Validation of analytical procedures
11	3.2.S.4.4	Batch Analysis
12	3.2.S.4.5	Justification of Specifications
13	3.2.S.5	Reference standards
14	3.2.S.6	Container Closure System
15	3.2.S.7.1	Stability summary and conclusions
16	3.2.S.7.2	Stability commitment
17	3.2.S.7.3	Stability data
Drug product		
18	3.2.P.8.1	Stability summary and conclusions
19	3.2.P.8.2	Stability commitment
20	3.2.P.8.3	Stability data
Regional information		
21	3.2.R.1.8.1	
22	3.2.R.4.1	Comparative API manufacturers study report

23	3.2.R.4.2	Comparative Results Report

3.2.R.4.1 Comparative API Manufacturers Study Report

Full name and address of current & proposed API vendors

Current API vendor	**Proposed additional API vendor**
XYZ Limited 1482-1486, Trasad Road, Dholka, District- Ahmedabad, Pin Code – 382225 INDIA	ABC Limited Site 1 - 20th K.M. Hosur Road, Electronics City Bangalore - 560100, India Site 2 - Plot no 2, Road no 21, J.N. Pharma city, Thadi Village, IDA Paravada, Visakhapatnam, Andhra Pradesh – 531019, India.

Route of Synthesis comparison

XYZ Limited (Approved)	ABC Limited (Proposed)
Description of the synthesis process used for the synthesis of API by XYZ Limited along with all solvents used.	Description of the synthesis process used for the synthesis of API by ABC Limited along with all solvents used.

Route of Synthesis comparison

XYZ Limited (Approved)	ABC Limited (Proposed)	Remark
Chemical reaction presentation	Chemical reaction presentation	Both the suppliers are using the same key starting material and key raw material. The chemical reaction used is esterification process by both the suppliers. Changes are related to solvents used.

Comparison of the Impurity Profiling and Residual Solvents

XYZ Limited (Approved)			**ABC Limited (proposed)**		
IMPURITIES (W/W): ORGANIC IMPURITIES					
Impurity name	**Limit**	**Origin**	**Impurity name**	**Limit**	**Origin**
A	Not more than 0.5%	Starting Material	A	Not more than 0.5%	Process Related & Degradation Product
B	Not more than 0.2%	Process	B	Not more than 0.2%	Process related
C	Not more than 0.1%	Process	C	Not more than 0.1%	Degradation Product
D	Not more than 0.1%	Process	D	Not more than 0.1%	Degradation Product
E	Not more than 0.1%	Process	E	Not more than 0.1%	Process related
F	Not more than 0.1%	Process	F	Not more than 0.1%	Degradation Product
G	Not more than 0.1%	Process	G	Not more than 0.1%	Process related
			H	Not more than 0.1%	Process related

XYZ Limited (Approved)			ABC Limited (proposed)		
RESIDUAL SOLVENTS					
Impurity Name	Limit	ICH Limit	Impurity Name	Limit	ICH Limit
Isobutyl acetate	Not more than 2000 ppm	5000 ppm	Xylene	Not more than 300 ppm	2170 ppm
Xylene	Not more than 300 ppm	2170 ppm	Acetone	Not more than 1000 ppm	5000 ppm
Cyclohexane	Not more than 1000 ppm	3880 ppm	Toluene	Not more than 300 ppm	890 ppm
Acetone	Not more than 1000 ppm	5000 ppm			
Acetonitrile	Not more than 400 ppm	410 ppm			
Toluene	Not more than 300 ppm	890 ppm			

Tabulated Comparison of Old (XYZ API) and New Specification (ABC API)

Sr. No.	Test	XYZ API Specification	ABC API Specification	Remark
1	Description	White or almost white crystalline powder	White or almost white crystalline Powder	No change
2	Solubility	Practically insoluble in water , freely soluble in acetone , sparingly soluble in anhydrous ethanol	Practically insoluble in water , freely soluble in acetone , sparingly soluble in anhydrous ethanol	No change
3	Identification			
	By IR	The IR spectrum of the preparation of test sample should exhibit maxima only at same wavelengths as that of a similar preparation of 'X' working standard/reference standard	The IR spectrum of the preparation of test sample should exhibit maxima only at same wavelengths as that of a similar preparation of 'X' working standard/reference standard	No change
	By HPLC	The retention time of major peak of the sample solution corresponds to that of the standard solution, as obtained in the	The retention time of major peak of the sample solution corresponds to that of the standard solution, as obtained in the	No change

		assay	assay	
4	Melting Range	Between 94°C and 98°C	Between 94°C and 98°C	No change
5	Loss on drying at 60°C	Not more than 0.5%	Not more than 0.5%	No change
6	Heavy Metals	Not more than 0.002%	Not more than 0.002%	No change
7	Related substance (by HPLC) a. related compound A b. related compound B c. Any single unspecified impurity d. Total impurity	 Not more than 0.5% Not more than 0.2% Not more than 0.1% Not more than 0.7%	 Not more than 0.5% Not more than 0.2% Not more than 0.1% Not more than 0.7%	As per current USP specification
8	Residue on Ignition (w/w)	Not more than 0.1 %	Not more than 0.1 %	No change
9	Assay by HPLC (on dried basis)	Not less than 98.0% and not more than 102.0%	Not less than 98.0% and not more than 102.0%	No change
10	Residual solvents (By GC) Isobutyl acetate Xylene Cyclohexane Acetone Acetonitrile Toluene Ethyl acetate	 Not more than 2000 ppm Not more than 300 ppm Not more than 1000 ppm Not more than 1000 ppm Not more than 400 ppm Not more than 300 ppm Not Applicable	 Not Applicable Not more than 200 ppm Not Applicable Not Applicable Not Applicable Not more than 200 ppm Not more than 1500 ppm	Change in residual solvents in-line with Drug substance manufacturer and

				complies ICH Q3C
11	Particle size distribution (By Malvern analyser)	d (0.9): Not More Than 25 microns	d (0.9): Not More Than 25 microns	No change
12	Microbial Limits A) Microbial Enumeration Tests: Total Aerobic Microbial count Total Yeast and Mould count B) Test for specified Microorganism: Staphylococcus aureus Pseudomonas aeruginosa Escherichia coli Salmonella	 Not more than 100 cfu/g Not more than 10 cfu/g Absent in 1 g Absent in 1 g Absent in 1 g Absent in 10 g	 Not more than 100 cfu/g Not more than 10 cfu/g Absent in 1 g Absent in 1 g Absent in 1 g Absent in 10 g	No change

3.2.R.4.2 **Comparative Results Report**

Equivalency between API with approved and proposed manufacturer: Batch analysis data (in tabular format):

This section includes the tests, specifications and results of one batch of approved API vendor and proposed API vendor.

If the results are not same, they should be within the limits.

Certificate of Analysis:

API COA from both API manufacturer (XYZ Limited and ABC Limited) attached in this section along with COA of finished product manufacturer for both the vendors.

***In-vitro* Dissolution Data**

As per USP monograph of the 'X' Tablets, USP 500 mg for dissolution the comparative *in-vitro* dissolution data on 'X' Tablets, USP 500 mg of Alkem Laboratories Limited manufactured using an additional source of supplier for API 'X', USP (source: ABC Limited) and 'X' Tablets, USP 500 mg of Alkem Laboratories Limited manufactured using an existing source of supplier for API 'X', USP (Source: XYZ Limited).

The details of batches used for the determination of in-vitro dissolution profile are presented below for reference:

'X' Tablets, USP 500 mg

(Existing source for API: XYZ Limited)

Sr. No	**Description of Drug Product**	**Batch No.**	**Mfg. Date**
1.	'X' Tablets, USP 500 mg	123456	May 2010

'X' Tablets, USP 500 mg

(Additional source for API: ABC Ltd)

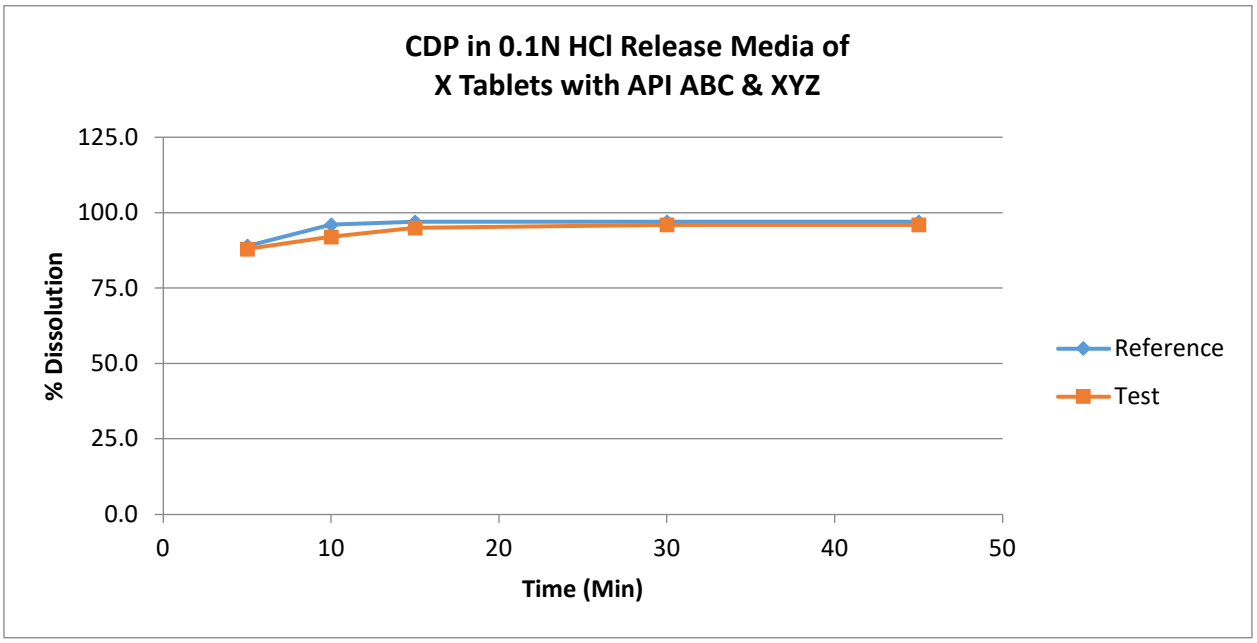
Sr. No	**Description of Drug Product**	**Batch No.**	**Mfg. Date**
1.	'X' Tablets, USP 500 mg	987654	June 2018

Dissolution data of both 'X' Tablets USP 500 mg was generated by the same laboratory using the same equipment and methodology.

Tabulated Data:

Dissolution media	0.1 N HCl	
Product Name	**'X' Tablets, USP 500 mg** (Existing source for API: XYZ Limited)	**'X' Tablets, USP 500 mg** (Additional source for API: ABC Ltd)
Batch No.	123456	987654
Time points	Cumulative drug release(%)	
5	89	88
10	96	92
15	97	95
30	97	96
45	97	96
F 2 value		81.30

Graphical representation of dissolution study:



Periodic Safety Update Report

PSUR reports are necessary regulatory document which is responsibility of pharmacovigilance department which evaluate the risk-benefit ratio of the pharmaceutical product of post marketing safety surveillance. MAH are necessary to submit these report at defined intervals to the regulatory authority.

SAHPRA has requirement of the QPPV for the PSUR reports. MAH should designate a qualified person for the position of QPPV.

The QPPV also should have other relevant skills and expertise to manage the activities related to pharmacovigilance department.

Timeline to submit the PSUR:

- Upon request of SAHPRA health authority, MAH must submit the PSUR within period of 30 working days.
- Applicant must declare the period for summary report of 12 months.
- If any changes in 12 months summary report, applicant should communicate change to the authority. (*POST-MARKETING REPORTING OF ADVERSE DRUG*, 2020)

Product review

SAHPRA has implemented many new guidelines and provisions to be stringent regulatory authority to enhance the safety and care towards public health. The major implementation is eCTD adaptation. Hence now SAHPRA starts providing lifetime approvals. Hence the renewals of dossier are replaced with annual reporting i.e product review.

CHAPTER 8

SFDA Post Approval Compliance

Saudi Food and Drug Authority

Variations

Post approval changes are the major and important element of post approval compliance.

Each regulatory authority has different regulations regarding submission of post approval changes.

In SFDA it is called as variations.

According to SFDA, variations are classified into two major categories:

1) **Minor changes:**

   The changes have less or negligible impact on product's quality, safety and efficacy. Minor changes are mainly divided into two sub-categories.

   a) **Type IA:**

      These changes have less or nominal impact on product's quality, safety and efficacy.

      These types of variations generally do not require agency's prior approval to implement the change. But regulatory agency should be notified about the change by the MAH of 60 days period after the implementation of the proposed change.

      Type IA changes are known as "Do and Tell procedures"

      SFDA authority has developed variations guidelines describing conditions for each change. If type IA changes don't follow the conditions mentioned in the guideline, the variation proposed change will be rejected by the authority. And authority may ask to MAH to stop the implementation of proposed change.

b) Type IB:

These changes have nominal to moderate impact on product's quality, safety and efficacy.

These changes generally do not require formal prior approval by the SFDA authority but MAH should notify the SFDA authority about proposed change before implementing the same. After notifying to the SFDA, MAH should wait for 120 working days. If MAH won't receive any response within waiting period, then MAH can consider it as acceptance of authority and can implement the change.

Type IB changes known as "Tell, Wait and Do procedure"

The changes which are not fall into the conditions of type IA are categorised into type IB.

2) Major changes:

Type II:

These changes have significant impact on product's quality, safety and efficacy. As these changes have major significant impact on product's performance, the proper scrutiny of proposed change should be done. MAH must require a formal prior approval to implement the proposed change.

There is no exact specific timeline for SFDA to review the application.

MAH receives the written approval by the authority after which MAH can implement the change. (*The GCC Guideline for Variation Requirement*, 1979)

Sr no.	Reporting category	Procedure	Timeline	Description of change
1	Minor changes			
	Type IA	"Do and Tell procedure"	Notify agency within 60 working days after implementation	have less or nominal impact on product's

				quality, safety and efficacy
	Type IB	"Tell, Wait and Do procedure"	120 days waiting period before implementation	have nominal to moderate impact on product's quality, safety and efficacy
2.	Major changes	-	Not specified	have significant impact on product's quality, safety and efficacy

(Table no. 2: variations of SFDA)

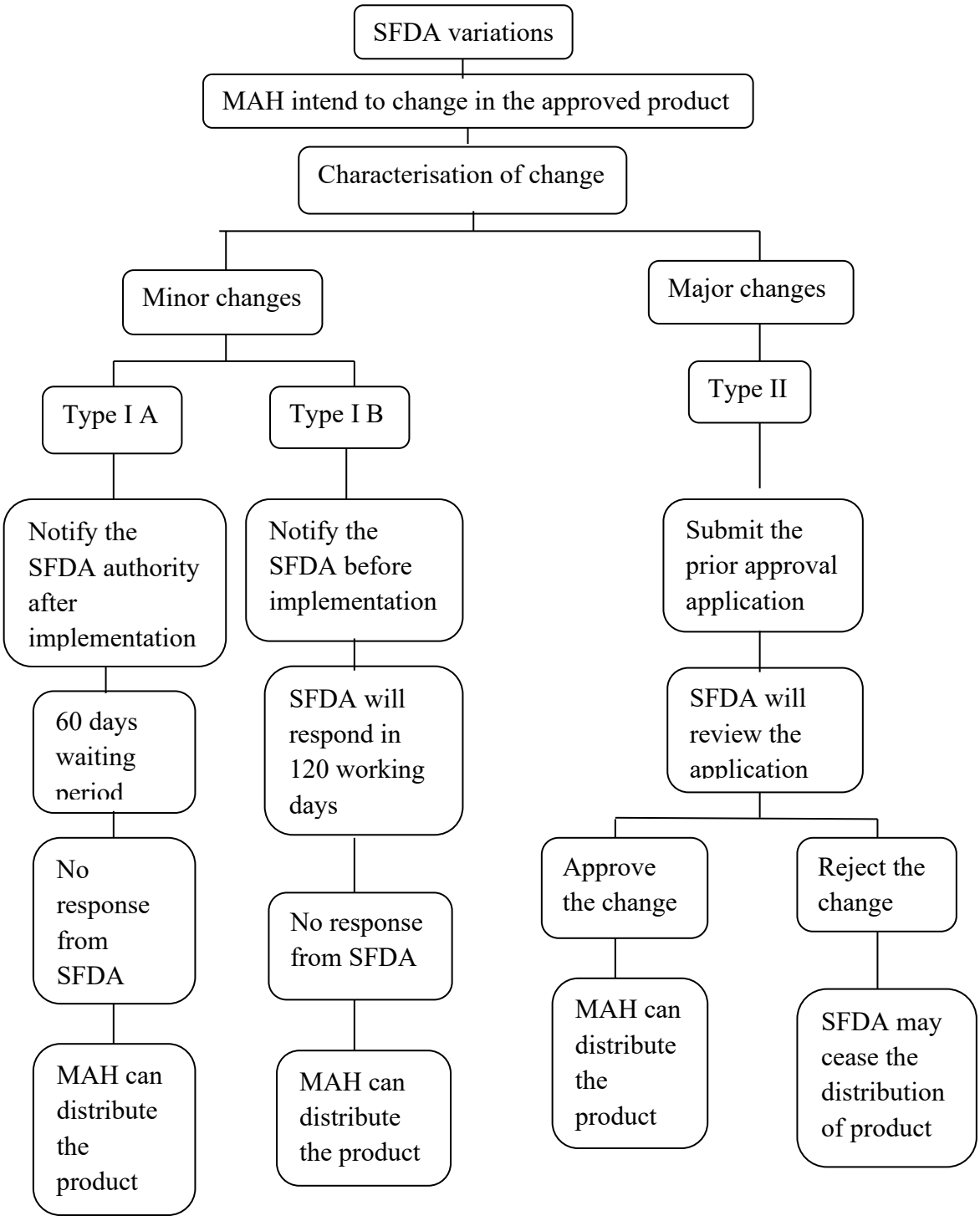


Fig. (4): variation process in SFDA

Periodic Safety Update Report

PSUR reports are necessary regulatory document which is responsibility of pharmacovigilance department which evaluate the risk-benefit ratio of the pharmaceutical product of post marketing safety surveillance. MAH are necessary to submit these report at defined intervals to the regulatory authority.

SFDA has requirement of the QPPV for the PSUR reports. MAH should designate a qualified person for the position of QPPV.

- Qualification criteria for QPPV:
    - QPPV should have sufficient technical and practical knowledge required to perform activities related to pharmacovigilance.
    - QPPV should be qualified with at least a bachelor degree of pharmacy or medicine. And should have basic training of biostatics. And he should properly license or certified by regulatory health authority of SFDA.
    - The QPPV also should have other relevant skills and expertise to manage the activities related to pharmacovigilance department.

MAH is expected to submit the PSUR as per the requirement of SFDA with respect to the submission of drug product:

- Timeline to submit PSUR:
    - Once the MAH receive the approval for the pharmaceutical, MAH should submit the PSUR report at interval of 6 months even if the product is not distributed in market.
    - When the marketing of product starts, MAH should submit 6 months interval over the initial 2nd year, once in a year over the subsequent 2 years and thereafter at interval of 3 years. (*Guideline on Good Pharmacovigilance Practices (GVP)*, 2015)

Renewal of Marketing Authorisation

The renewals of marketing authorisations are the important element of the post approval compliance. The marketing authorisation of pharmaceutical is valid for 5 years by SFDA. To maintain the authorisation status of product marketing authorisation should be renewed after every 5 years.

The renewal of marketing authorisation should be submitted 6 months prior of the expiry date of marketing authorisation application.

According to SFDA renewal requirements MAH have to submit Module 1 and Module 3. (*SFDA: Regulations & Guidelines*, n.d.)

Following documents need to submit at the time of renewal submission:

Module 1	**Administrative information**
1.0	Cover letter
1.1	Table of content
1.2	Application form
1.3	Product information
1.3.1	Summary of product characteristics
1.3.2	Labelling
1.3.3	Patient information leaflet
1.3.4	Artwork
1.3.5	Sample
1.7	Certificate and documents
1.7.2	Certificate of pharmaceutical product or free sale certificate
1.7.7	Certificate of suitability
1.8	Pricing
1.8.1	Price list

Module 3	**Quality**
3.2.S	Drug substance
3.2.S.2.1	Manufacturer
3.2.S.4.1	Specifications
3.2.P	Drug product
3.2.P.1	Description and composition of the drug product
3.2.P.5.1	Specifications
3.2.P.8	Stability

CHAPTER 9

MOHAP Post Approval Compliance

United Arab Emirates

Ministry of Health and Prevention

Minor variations

Post approval changes are the major and important element of post approval compliance.

Each regulatory authority has different regulations regarding submission of post approval changes.

In MOHAP, it is called as variations.

MOHAP has guideline for minor changes. The changes other than minor changes which are not described in the guideline must consider as a major change and submit as separate application.

Minor variations are categorised mainly into 2 types as follows:

- **Type IA:**
  These changes have very nominal or negligible impact on product's quality and performance. Hence these changes should notify the MOHAP drug registration authority.
  These changes are known as "Tell and Do" changes. These changes should submit on MOHAP customer service section.
  For these types of changes, stamped receipt of the application by the MOHAP authority is equivalent to the approval letter.
  The Variation certificate i.e 'notification of disposition of request for variances' will not be provided by the MOHAP, just like for other type of changes.

- **Type IB:**

  These changes have very nominal to moderate impact on product's quality and performance. These types of changes must submit the application of change to the MOHAP drug registration department officially.

  These are "Tell, Wait and Do changes". MAH must wait for 10 working days after submitting the application to MOHAP.

  Within 10 days, MOHAP authority reviews the application and issue a variation certificate i.e 'notification of disposition of request for variances'. After receiving the variation certificate, MAH can implement the proposed change.

  The type IA changes which require pricing or repricing decisions are evaluated under type IB category.

  At the time of issuance of variation certificate, MOHAP authority communicates regarding the pricing of change to the MAH.

- **Type II A:**

  These changes have very moderate impact on product's quality and performance. These types of changes must submit the application of change to the MOHAP QCL department officially.

  These are "Tell, Wait and Do changes". MAH must wait for 90 working days after submitting the application to MOHAP.

  For these types of changes, stamped receipt of the application by the MOHAP authority after the waiting period is equivalent to the approval letter.

  The Variation certificate i.e 'notification of disposition of request for variances' will not be provided by the MOHAP.

- **Type II B:**

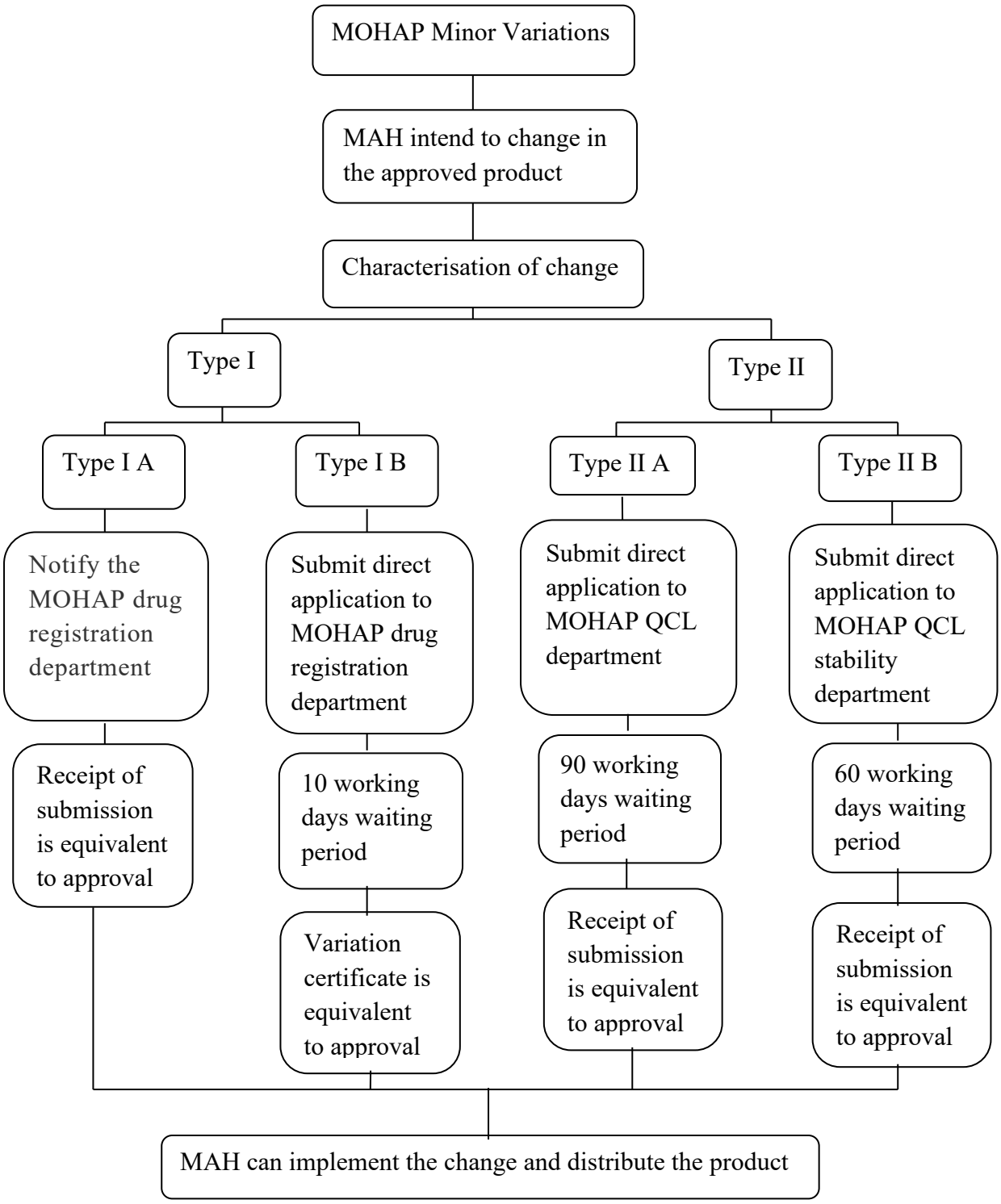
  These changes have very moderate to significant impact on product's quality and performance. These types of changes must submit the application of change to the MOHAP QCL stability department officially.

These are "Tell, Wait and Do changes". MAH must wait for 60 working days after submitting the application to MOHAP.

For these types of changes, stamped receipt of the application by the MOHAP authority after the waiting period is equivalent to the approval letter.

The variation certificate i.e 'notification of disposition of request for variances' will not be provided by the MOHAP. (*Minor Variation for Registered Pharmaceutical Product in UAE*, n.d.)

Type of change	**Submitting department**	**Procedure**	**Timeline**	**Certificate**
Type I A	MOHAP drug registration department	Tell and Do	Not exactly	No variation certificate
Type I B	MOHAP drug registration department	Tell, Wait and Do	10 working days	variation certificate
Type II A	MOHAP QCL department	Tell, Wait and Do	90 working days	No variation certificate
Type II B	MOHAP QCL stability department	Tell, Wait and Do	60 working days	No variation certificate



(Fig .(5) : Minor variation submission process of MOHAP)

Periodic Safety Update Report

PSUR reports are necessary regulatory document which is responsibility of pharmacovigilance department which evaluate the risk-benefit ratio of the pharmaceutical product of post marketing safety surveillance. MAH are necessary to submit these report at defined intervals to the regulatory authority.MOHAP has requirement of the QPPV for the PSUR reports. MAH should designate a qualified person for the position of QPPV.

- Qualification criteria for QPPV:
    - QPPV should have sufficient technical and practical knowledge required to perform activities related to pharmacovigilance.
    - QPPV should be qualified with at least a bachelor degree of pharmacy or medicine. And should have basic training of biostatics. And he should properly license or certified by regulatory health authority of SFDA.
    - The QPPV also should have other relevant skills and expertise to manage activities related to pharmacovigilance department.

For the registration of the QPPV following required document should be submitted by MAH to the authority:

- Appointment letter from the company for QPPV designation
- Pharmacovigilance training certificate
- Pharmacovigilance experience certificate
- Company's register product list
- Company's ADR reports
- PV officer SOP program

- Timeline for the submission of PSUR report:
    - Up to initial 12 months at the interval of 70 calendar days starting from lock point of data i.e day 0.

- After 12 months at the interval of 90 calendar days starting from lock point of data i.e day 0.(*UAE MOH Guidelines in Good Vigilance Practice (GVP) For Marketing Authorization Holders / Pharmaceutical Manufacturers In UAE*, 2018)

MOHAP Renewal Provision

Renewals are the one of the element of post approval compliance to maintain the dossier registration in the market.

MOHAP registration approval is valid for 5 years from the date of approval of dossier.

To maintain the registration of product in market MAH must renew the dossier every 5 years.

- Important note of renewal submission:
- The renewal application must be in CTD format following the CTD module structure.
    - Module 1: one soft copy required
    - Module 3: two soft copies are required.
- Old application should submit with current stability data and updated quality data.
- Copy of receipt of notification or application of minor variation from the date of approval or from last renewal period.

Checklist Module 1:

1.0	Payment receipts
1.1	Covering letter
1.2	Comprehensive Table of content
1.3	Declaration for renewal of registration of a pharmaceutical conventional product /Scanned or a Copy is accepted
1.4	Product information
1.4.1	Summary of Product Characteristics (SmPC)
1.4.3	Patient Information Leaflet (PIL)
1.4.3.1	Arabic leaflet

1.4.3.2	English leaflet
1.4.4	Artworks (outer label, inner label and leaflet) as a hard copy and JPEG format soft copy
1.7	Pharmacovigilance
1.7.1	Pharmacovigilance System (soft copy)
1.7.2	Risk Management Plan (soft copy)
1.8	Certificates and Letters
1.8.1	A copy of latest CPP signed and stamped by the Competent Authority in COO
1.8.5	Alcohol-content declaration
1.8.6	Pork - free declaration
1.8.7	TSE/BSE free certificate
1.8.8	API certificate of suitability or US-FDA approval of the DMF
1.8.9	Copy of valid GMP certificate for the API source
1.8.10	API Acknowledgment letter
1.8.13	Copy of the manufacturing site(s) registration certificate(s)
1.8.14	Composition certificate with active ingredient(s), inactive ingredient(s) Quantities per unit dose and functions
1.8.17	Registration and Marketing status in other countries (Worldwide registration list)
1.11	Module 1 (1 soft copies)
2.0.	Module 3 (2 soft copies)

CHAPTER 10

Comparative Representation of Post Approval Changes

Comparative Representation of Post Approval Changes

- **Manufacturing site change:**

- Change in manufacturing site of finished products:

Element	USFDA	SAHPRA	SFDA	MOHAP
Type of change	Level 3	Not specified	IB	IB
Condition	Change to a different sit but equipments, procedures environmental conditions remain same.	-	Change to a different site where batch control measures and testing is same as previous.	Change to a different address but same building for whole manufacturing process.
Requirements and documents	-new site address -updated batch records -compliance with release requirements -long term and accelerated stability data of three batches.	-	-GMP certificate issued in last 3 years -relevant documents must include comparison of “present” & “proposed” changes.	-justification for change -mfg license -updated CoPP -application form -artwork including changes.

Application type	CBE-0	-	Tell, wait & do	Tell, wait & do

(Table No. (4). Comparison of manufacturing site changes)

- **Change in manufacturing process**:
- Change in equipment:

Element	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Level 1	Type B	Type I B	Type II B
Conditions	Change to different equipment but operating principles are same.	Different equipment or process of machines but operating principles is same.	Minor change in mfg process of solid dosage form IR.	Minor change in mfg process of solid dosage form IR.
Requirements and documents	-notification of change to FDA -comply with the release requirements. -updated BPR -long term stability study on at least one batch.	-updated mfg procedure -site master file -dissolution study -long term stability study of 1st production	-present and proposed comparison of mfg process. -dissolution study of new batch. -comparison of dissolution study of last	-present and proposed comparison of mfg process. -dissolution study of new batch. -comparison of dissolution study of last

		batch up to 12 months.	process and new process. -copy of approved specifications. -stability study on at least 2 pilot batches. -application form.	process and new process. -copy of approved specifications. -stability study on at least 2 pilot batches. -application form.
Application type	Annual report	Covering letter equivalent to notification.	Tell, wait & do	Tell, wait & do

(Table No.(5). Comparison of change in equipment)

- **Composition change:**
- Change in excipients:

Elements	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Level 2	Type B	Type I B	Type II A
Conditions	Change in technical grade of excipients	Replacement of single IPI with new equivalent excipients.	Replacement of single excipient with new equivalent excipients.	Replacement of single excipient with new equivalent excipients.
Requirements	-case A	- updated	-shelf life	-application

and documents	dissolution study. -comparison of dissolution study of previous and new batches. -long term and accelerated stability study on at least 1 batch each. -bioequivalence study if dissolution studies are not satisfied.	formulation -IPI specifications and control procedures. - Comparison of "present" & "proposed" IPI specifications. -dissolution study -long term stability study up to 12 months and accelerated study up to 3 months of one production batch.	specifications -stability study and commitment -TSE certificate -comparison of "present" & "proposed" change specifications -dissolution study on at least two pilot batches and comparison of dissolution study -justification for not submitting BE study.	form -stability study -TSE certificate -FPP specifications - dissolution study on at least two pilot batches and comparison of dissolution study - comparison of "present" & "proposed" change specifications -updated BMR
Application type	PAS	Covering letter is equivalent to notification.	Tell, wait & do.	Tell, wait & do.

(Table No.(6). Comparison of change in excipients)

- **Specifications:**
- Change in limits of acceptance criteria:

Elements	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Major change	Type C	Type II	Type II A
Conditions	Relaxing the specifications' acceptance limits	Less stringent requirement of specifications	Widening of the specifications limit	Widening of the specifications limit
Requirements and documents	-final product specifications -stability study -relevant documents	-excipients control procedures and final specifications -FPP control procedures and specifications -stability study	new specification list -comparison of "present" and "proposed" specifications -stability data	-new specification list -comparison of "present" and "proposed" specifications -application form -justification of change
Application type	Prior approval supplement	Require prior approval	Require prior approval	Tell, wait & do

(Table No.(7). Comparison of change in specifications)

- **Scale-up changes:**
- Change in batch size:

Elements	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Level 2	Type C	Type IB	Type II B
Conditions	Batch size changes more than 10 fold factors maintaining design and operating principles of equipment as it is.	-increase in batch size more than 10 folds maintaining same formulation, control procedures, design & operating principles of equipment	increase in batch size more than 10 folds as compared to latest approved batch size of the product	Change in batch size of finished product.
Requirements and documents	-updated batch records -revised BMR - 3 months accelerated and 12 month long term study on one batch -meet release specifications -Dissolution study	-updated mfg process -stability study with batch wise information -3 months long term and accelerated stability data minimum required -'proof of efficacy' must	-comparative table of "present" & "proposed" data of batch analysis - comparative table of "present" & "proposed" FPP specifications. -validation protocol for	-application form -process validation protocol along with generated data -"present" & "proposed" BMR -"present" & "proposed" FPP

		be given	new batches - stability study and stability commitment	specifications -6 months long term and accelerated stability data -comparative dissolution profile
Application type	CBE-30	Prior approval	Tell, wait & do	Tell, wait & do

(Table No.(8). Comparison of scale-up changes)

- **Container closure system:**
- Change in material of immediate packaging:

Elements	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Minor change	Type B	Type IB	Type II B
Condition	Change in components of CCS as long as new packaging provides better or equivalent protection.	Change in components of immediate packaging which is providing better protection as of previous.	Quality or quantity change in the composition of immediate packaging material	Quality or quantity change in the composition of immediate packaging material

Requirements and documents	-relevant data must be submitted e.g BPR -stability study --"present" & "proposed" specifications of packaging material	-packaging material control procedures & specifications -updated BPR -package insert information. -stability study	-relevant data must be submitted e.g BPR -proof of new composition is not harmful & not affecting the properties. -stability study -"present" & "proposed" specifications of packaging material	-notification letter -relevant data showing material compliance with compendia. -proof of new composition is not harmful & not affecting the properties. -"present" & "proposed" specifications of packaging material
Application type	Annual report	Tell, wait & do.	Tell, wait & do.	Tell, wait & do

(Table No.(9). Comparison of change in material of immediate packaging)

- **Shelf-life:**
- Extension of shelf-life:

Elements	**USFDA**	**SAHPRA**	**SFDA**	**MOHAP**
Type of change	Major change	Type C	Type II	Type II B

Condition	Extension of shelf life period on the basis of approved stability protocol	Extension of shelf life of Final product	Extension of shelf-life as packaged for sale	Extension of shelf-life as packaged for sale
Requirements and documents	-stability study according to protocol -FPP specifications	-stability data covering the extension period -relevant batch	-real time stability testing -stability testing according to recently approved protocol -finished product specifications	- real time stability testing on 3 production batches -application form - stability testing according to recently approved protocol -finished product specifications
Application type	Prior approval supplement	Prior approval	Prior approval	Tell, wait & do

(Table No.(10). Comparison of change in shelf life)

Comparative View of Post Approval Compliance

Element	United States	South Africa	Saudi Arabia	United Arab Emirates
Regulatory authority	Food and Drug Administration	South African Health Product Regulatory Authority	Saudi Food & Drug Authority	Ministry of Health And Prevention
Post approval changes	Post approval changes	Amendments	Variations	Minor variations
Reporting category	Level-1 Level-2 Level-3	-	-	-
Codification of change type	-	Exist for different changes	-	-
Type of changes	Minor-Annual reports, Moderate-CBE 30 & CBE 0, Major-PAS	Type A Type B Type C Type D	Minor- type I A, type I B Major- type II	Minor change- Type I A, Type I B, Type II A, Type II B.
Submission	eCTD	eCTD	eCTD	eCTD
Grouping of variation	Have provision	Don't have provision	Don't have provision	Don't have provision
Validity of	Lifetime	Lifetime	Valid up to 5	Valid up to 5

registration	approvals	approvals	years from the date of approval	years from the date of approval
Maintenance of dossier	Annual report- shall submit every year within the previous time span of 60 days of date of annual anniversary.	Annual report i.e product review- provision is there but not in practice yet	Renewal of dossier- within the previous time span of 6 months of date on which the marketing authorisation is going to expired.	Renewal of dossier- after every 5 years
Post marketing surveillance	PADER- quarterly for 1st three years and then annually for next years.	PSUR- 12 months specific period and submit within 30 days upon request.	PSUR- Initial 2 years- 6 months interval Subsequent 2 years-once in year Next subsequent years- 3 years interval	PSUR- Within 70 calendar days in initial 12 months, within 90 days after 12 months

CHAPTER 11

Conclusion

Conclusion

The study gives insight of whole regulatory view of post approval compliance of US, South Africa, Saudi Arabia and United Arab Emirates. The study gives the idea of regulatory framework of post approval compliance activities and its regulatory importance. It covers the post approval compliance activities like post approval changes, annual reports, renewals of dossier and post marketing safety surveillance and their comparative view. Study also describes the comparison of types of post approval change, its submission type, regulatory and documents requirement. The post compliance activities are important to maintain the dossier lifecycle. Also study helps to design the post approval change management and build a control strategy. The study findings are useful to give the comparative overview of these semi regulated countries with the regulated USFDA authority.

After studying the requirements of US, South Africa, Saudi Arabia and United Arab Emirates, it is very evident that the quality requirements of all regulatory authorities are similar demanding the same or relevant data as maintain the quality of pharmaceutical and safety of public health is the prime aim of all authorities. Hence it is very easy to cope up with any quality changes with these comparisons of regulations.

Also post approval change management and protocol are the most highlighted parts of the lifecycle and every industry should practice these along with new technical control strategies. This study gives the ease of comparative view of rules and regulations and overview of post approval compliance.

This thesis also include the industry reports for the better understanding of process and documents and tried to give the oversight of practical or field work.

CHAPTER 12

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