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EVALUATION AND COMPARISION OF REGULATORY PROCESS AND COMMUNICATIONS RECEIVED FROM VARIOUS REGULATORY AUTHORITIES DURING PRE AND POST REGISTRATION OF BISOPROLOL FUMARATE TABLETS

G.Vidya, V. Prabhakaran, M. Alagusundaram* and P. Jayachandra Reddy

Department of Pharmaceutics and Drug Regulatory Affairs, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati– 517501, Andhra Pradesh, India.

ABSTRACT

Drug regulation has developed over the past 50 years in response to crises in relation to pharmaceutical products. Current drug regulation was the comprehensive multi-country study undertaken by the World Health Organization (WHO). In order to register a NDA & ANDA molecules globally, a pharmaceutical company develops a dossier that describes the pharmaceutical quality, safety and efficacy of the product for a specified indication. New dossiers are generally assessed by following regulatory authorities; their decisions should be an adequate basis that depends upon the given data in a dossier for a molecule, usually the same for every country, although the proposed indication may vary. Based on the following parameters, Increase % growth in demand for the molecule year on year, Number of companies are already lunched, Price comparison with competitors, Marketing strategy we have selected a drug Bisoprolol Fumarate Tablet. This drug was filed in Kenya, Tanzania, Uganda, Malaysia, Bahrain, Kuwait, Oman, Qatar, Mexico, Peru, and Venezuela. After studying the regulatory requirements to register a pharmaceutical product for human use and after analysing the communications received from respective regulatory authorities filing strategy has been developed to improve the quality of the submission file which helps to reduce the number of deficiencies received from each regulatory authority. It also helps to reduce the product registration lead time which allows commercial team to launch the product at the earliest.

Keywords: WHO, NDA, ANDA, Quality, Safety, Efficacy, Filling strategy, Communications, Product registration.

INTRODUCTION

As the pharmaceutical industries throughout the world are moving ahead towards becoming more and more competitive, these are realizing that the real battle of survival lies in executing the work by understanding the guidelines related to various activities carried out to give an assurance that the process is under regulation.

Drug regulation has developed over the past 50 years in response to crises in relation to pharmaceutical products. The initial regulatory standards were primarily related to ensuring the pharmaceutical quality of medicinal products and subsequent developments in the early 1960s led to the development of standards for testing efficacy and safety of new medicines as well. Despite the existence of standards for drug regulation now for at least 50 years, there are still many problems with the safety and quality of medicines, in both developing and developed countries [1].

Current drug regulation was the comprehensive multi-country study undertaken by the World Health Organization (WHO). The key issues identified in that study were that effective drug registration depends on appropriate legislation with adequate administrative structures, to ensure that the scientific assessment of new products (generic or innovator) can be undertaken in a rigorous and efficient fashion. Political support and financial and other resources are critical.

Corresponding Author:- **M. Alagusundaram** Email : alagusundaram77@gmail.com

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore it is necessary to have knowledge about regulatory requirement for MAA of each country [1].

The new drug approval process consists of two stages (phases)

- The first phase is for clinical trials and
- Second phase is for marketing authorization of drug.

Firstly, non-clinical studies of drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of respected country. In next step, clinical trials are carried out in four phases. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is carried out by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug found to be safe and effective with desired effect as compare to adverse effect.

PLAN OF WORK

- Identify the countries based on the commercial needs
- Understanding the regulatory requirements of each region
- For example: Asian, Europe, Africa, Latam……etc.
- Developing the filling strategy country wise/region wise.
- Comparative study of regulatory requirements country wise/region wise
- Preparation of comparison status by analyzing the communications received from regulatory authority.

REVIEW OF LITERATURE

The present work was done by reviewing the country guidelines, Dossiers submitted to the countries, Ministry of health websites, related published journals, Research books and other provided resources**.**

GENERAL DESCRIPTION OF REGISTRATION PROCESSES

Drug regulation generally covers the following areas:

• Pre-marketing assessment and evaluation of the quality, safety and efficacy of a medicine, including compliance of manufacturing sites and processes with Good Manufacturing Practice (GMP) standards.

• Assessment and inspection of all components of the pharmaceutical supply chain. Maintenance of a register of available products, and post-marketing surveillance activities, including random sampling of registered medicines for quality control And pharmacovigilance.

• Promotion, advertising and provision of medicines information [1].

KEY PLAYERS IN DRUG REGISTRATION

Drug regulation is interplay between law and sciences, as well as between regulators and the pharmaceutical manufacturers, with input and influences from patients and medical/health professions. In addition, a drug regulatory authority (DRA) interrelates with many other authorities active in the health sector, such as the Ministry of Health another health protection agency. In certain cases effective cooperation with other law enforcement agencies, such as customs and police, is necessary. Depending on the structure of the health sector, this may include interaction and/or control over medical practitioners, pharmacists and drug sellers, as well as interactions with agencies responsible for quarantine and control of imports and exports. DRAs also need to interact with politicians; apart from anything else, politicians need tube persuaded of the importance of effective regulation in order to ensure that it is paid for at an appropriate level. Regulation is not cheap but its costs usually outweigh the potential waste on ineffective and dangerous drugs. In general terms, effective drug regulation requires effective legislation and administration, as well as a mechanism for control of the market and enforcement of penalties for breaches of legislation that applies equally to both the public and private sector [2].

PROCESS OF DRUG REGISTRATION

In order to license/register a new chemical entity (NCE), a pharmaceutical company develops a dossier that describes the pharmaceutical quality, safety and efficacy of the product for a specified indication. An 'ideal' registration process would include:

• Evaluation and assessment of the pharmaceutical quality data, including:

- Assessing that the manufacturer(s) of all components, including that of the active pharmaceutical ingredient and the finished product, are certified as meeting the international standards for GMP that are appropriate for the component, with Mapping the registration process and describing a normative framework inspection of manufacturer(s)
- Laboratory testing the product against the proposed specifications for content and impurities, stability data, and packaging.
- Evaluation of the labeling to ensure that it complies with specified standards.

• Evaluation of animal (preclinical) toxicology studies in relation to acute and chronic toxicity, genetic toxicity, teratogenicity, carcinogenicity and others, including whether the studies have been carried out to international standards and whether the data and interpretation of the results are valid.

• Evaluation of human clinical trials (either placebo or active comparator randomized controlled clinical trials) that have been carried out to define the dose, frequency and duration of treatment that is effective and safe, including assessing that the design and conduct of the trials meets international requirements, that the data are valid and have been interpreted correctly
• Evaluation of the product information document (called the Summary of Product Characteristics), including the proposed indication and claims against the available data, and based on this information, the patient information leaflet/package insert. The scientific skills that are required to carry out such a registration process are highly specialized, and generally require experts in at least the following disciplines.

Pharmaceutical chemistry, toxicology, statistics, and a clinical scientist in the relevant clinical field. Dossiers for NCEs typically consist of hundreds of volumes of data. The time taken to review and evaluate such dossiers is a common measure of the performance of a DRA, which unfortunately puts pressure on small authorities to keep up with international standards set by agencies such as the US Food and Drug Administration (FDA) and the EMEA [3].

• Most small authorities do not have the expertise to assess the NCE dossiers (particularly in relation to the animal studies)
• Even when the expertise is available, it is usually in short supply and would before usefully employed in assessing generic products or problem products in the local market
• NCE dossiers are generally assessed by at least both the US and European authorities; their decisions should be an adequate basis for other countries, given that the data in a dossier for an NCE are usually the same for every country, although the proposed indication may vary.

REQUIREMENTS FOR PRODUCT REGISTRATION

Administrative Requirements

Manufacturing License

Any company who wishes to manufacture, import and/or wholesale any registered products needs to have Manufacturer's License, Import License and/or Wholesaler's License.

Good Manufacturing Practice (GMP) Certificate

Compliance to Good Manufacturing Practice (GMP) is prerequisite to application of a manufacturing license, as well as product registration/ cosmetic notification. GMP is a standard which shall be followed by the manufacturers to ensure that the products manufactured are safe, efficacious and of quality.

Upon complete application, a GMP certificate will be issued. If a manufacturer who wishes to build a new manufacturing premise, the manufacturer may submit a proposed premise layout plan to the Centre for Compliance and Licensing authority.

Certificate of Pharmaceutical Product (CPP)

A CPP which follows the format recommended by WHO shall be issued to locally manufactured products that are to be exported. Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days [4].

GENERAL REQUIREMENTS

Full Evaluation

- In accordance to ASEAN ACTD/ ACTR or ICH guidelines [5]
  - Part I - Administrative data and product information
  - Part II - Data to support product quality (Quality Document)
  - Part III - Data to support product safety (Nonclinical Document)
  - Part IV - Data to support product safety and efficacy (Clinical Document)
- In accordance to CTD/ICH guidelines [5]
  - Module 1. Administrative Information and Prescribing Information
  - Module 2. Common Technical Document Summaries
  - Module 3. Quality
  - Module 4. Nonclinical Study Reports
  - Module 5. Clinical Study Reports

Abridged Evaluation

Additional Information on Requirement
Bioavailability (BA) Study
Bioequivalent (BE) Study

AMENDMENTS IN REGULATORY PROCESS

Variation

Variation refers to change of particulars of a registered product. Throughout the life cycle of a registered product, changes to improve the product's efficacy, quality and safety are likely to occur. Therefore, applicant shall inform the Authority pertaining to any changes or amendment made to particulars of a registered product via variation applications [6].
a) For pharmaceutical products, there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N).
b) For health supplement and natural product, there are two (2) types of variation, which are Variation Type I and Variation Type II.

POST-REGISTRATION PROCESS

Registration status of a product shall be valid for 1-5 years depends upon the country guidelines or such

period as specified in the registration certificate (unless the registration is suspended or cancelled by the Authority).

Upon approval for product registration by the Authority, applicants shall fulfill all commitments and conditions imposed during approval of the product registration and shall be responsible for the maintenance of the product in terms of quality, safety and efficacy throughout the validity period of registration. Failure to do so may result in rejection of application for renewal of product registration.

The Authority shall be notified of any changes to the product's efficacy, quality and safety, Application for renewal of product registration of a product shall be done within six (6) months prior to the expiry of the validity period of a product registration. After the expiry date, status of product registration shall change to status of expired and application for renewal of the product registration can't be submitted [6].

DISCUSSION

Product Selection

- Product selection is done by product management team, if required business management team involved in selection of country.
- Regulatory has no role in the product Vs country matrix.
- Following are the few parameters which will be consider to identify the selecting the country for any particular molecule.
  - Increase % growth in demand for the molecule year on year
  - Number of companies are already lunched
  - Price comparison with competitors
  - Marketing strategy
- Based upon the above parameters we have selected a drug "BISOPROLOL FUMARATE TABLETS"

DRUG PROFILE

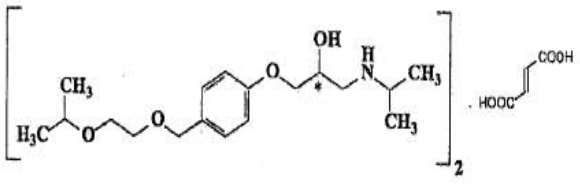
Name: Bisoprolol Fumarate Tablets

Chemical Name: (RS)-1-[4-[[2-(1-methylethoxy) ethoxy] methyl] phenoxy]-3-[(1- methyl ethyl) amino] propan-2-ol fumarate [7].

IUPAC Name

[2-hydroxy-3-(4-{[2-(propan-2-yloxy)ethoxy]methyl}phenoxy)propyl](propan-2-yl)amine

Structure



Mechanism of Action

Bisoprolol selectively blocks catecholamine stimulation of β1-adrenergic receptors in the heart and vascular smooth muscle

Indication

For management of heart failure, angina pectoris, and mild to moderate hypertension and for secondary prevention of myocardial infarction (MI).

COUNRTY SELECTION

The country selection is done by based on the filing strategy of Bisoprolol Fumarate tablets.

OVER VIEW

AFRICAN REGION

The African pharmaceuticals market has been growing at a fast pace. The continent has a population close to a billion. The pharmaceutical market in Africa is set to grow between $8bn and $10bn a year, with pharmaceutical spending in Africa expected to increase to about $30bn by 2016. Africa's healthcare market is growing at an annual rate of 10.6%. Industry growth is attributed to the extensive surge of middle-class spending on diseases, and rapid urbanization. The industry has been growing fast despite the infrastructural shortcomings in many of the African countries [7]. Filing strategy and regulatory requirements of the African countries are listed below in table2.

ASEAN REGION

ASEAN covers a land area of 4.46 million km², which is 3% of the total land area of Earth, and has a population of approximately 600 million people, which is 8.8% of the world's population.

The ASEAN pharmaceutical market has experienced strong growth and a rise in the regional standard of living which have made it a region of interest for companies looking to explore new business opportunities. The ASEAN Pharmaceutical market represents huge potential for companies looking to expand operations. Notably, there is strong interest in R&D for generics in this region, which are expected to grow from 8.3% of the total market in 2010 to 12.8% by 2015, when they will be worth USD 12.3bn. Within the next decade, Asia is expected to overtake Europe in pharmaceutical sales, driven by growth in key emerging markets Eightyfive percent of the world's population lives in the emerging markets, and during the past 5 years, all real economic growth has come from these markets. Some observations help to explain why many large pharmaceutical companies have increased their presence in emerging markets in recent year [7]. Filing strategy and regulatory requirements of the African countries are listed below in table 3.

MIDDLE EAST REAGION

- Middle East and North Africa, MENA region, spans 18 countries - from Morocco to Iran
- MENA pharmaceutical market began to develop in 1970's
- More than 140 pharmaceutical factories operating across the region today
- Local production dominated by generic manufacturers
- Strong dependence on imported finished products, raw materials and packaging
- Licensing by domestic producers has helped to accelerate the adoption of good manufacturing practices across the region
- The Middle East and the North Africa (MENA) region constitutes just 2% of global pharmaceutical sales. A rapid increase in population has stoked drug demand especially for higher-yield pharmaceutical products attracting the attention of multinational Pharma companies [8].
- The region now competes with Asia and Latin American countries in terms of the projected growth in its local pharmaceutical industries. Of the 22 odd countries in the region, Turkey, Israel, Saudi Arabia, Egypt and Iran stand out as the largest markets in terms of projected growth potential and value representing a host of opportunities.
- With the growth in populations across the MENA region, the demand for drugs increased to an estimated US$8.5 billion in 2012 compared to US$7.7 billion in 2011. Around 80% of the pharmaceuticals consumed in the Middle East are imported from foreign countries.
- Filing strategy and regulatory requirements of the African countries are listed below in table 3.

LATAM REGION

The LATAM pharmaceuticals market has grown steadily in the past 15 years. It has also been dominated by multinational companies based in Europe and the US that have spread to these emerging economies mainly to expand their businesses or to find untreated patients for clinical trials. This trend has also influenced the evolving growth of the local drug regulations in the LATAM region: with the rapid introduction of high-technology medicines into import, export and distribution networks, it has become critical for each HA to guarantee that the medicines allowed to reach local patients are in compliance with specific standards of quality, safety and efficacy. With varying levels of sophistication, resources and overall expertise, each LATAM has strengthened its health legislation. The region offers a wealth of opportunity for both the pharmaceutical industry and local patients but the variation in the drug registration processes causes time-consuming and costly obstacles for companies. Based on more than ten years of experience registering drug products in LATAM [9].

Latin America's Growing Parma Industry:

Latin America has been a long sought after, though difficult to penetrate pharmaceutical market. With the market size of Latin America at $66 billion as of May 2012, many companies have developed strategies to enable access to a portion of this growing market. Part of these strategic discussions center around how to address different regulations between countries in the region and the various components required to register a product from country to country. Adaptation and Growth - For years, pharmaceutical companies have turned to emerging markets as low cost manufacturing destinations, utilizing lower wages and, frequently, less stringent environmental, health and safety regulations. As emerging markets capture a greater share of the global pharmaceutical market, these countries are altering and adapting their regulations to compete with the quality expectations of highly regulated markets like the EU and U.S., while addressing their own sourcing needs. Led in large part by substantial growth in Brazil and Mexico, countries in Latin America are firmly establishing their place in the market [9].

Latin America health and pharmaceutical market overview

With its population reaching 6 million people in 2011 (WHO 2012)—Argentina Brazil and Mexico accounting for 60% of the population—Latin America is a fast growing region with equally fast growing economies. Brazil, Mexico, Argentina and Colombia are considered as the "top 4" Latin American economies and pharmaceutical powers. As a pharmaceutical market overview, Latin American sales in 2011 were at USD 62.9 billion, registering a 8.9% growth in 2012, which is particularly significant if considered within the wider picture of a global market value of USD 995 billion dollars in 2011 [10].In 2009, the national expenditure average in Latin America represented 85 of the region's GDP, equivalent to a per capital annual expenditure of USD 671 USD divided partly into public expenditure and partly into private out-of-pocket expenditure and payments made through insurance schemes. Latin America is also experiencing a transition in major health risk trends, going from infectious diseases to more traditionally westernized health risk trends such as hypertension, obesity, cancer, ischemic heart diseases and diabetes. This significant change in demographics, disease patterns, economics and market size are creating new challenges for domestic and international pharmaceutical companies operating in the country. Companies are facing other considerations such as emerging science, new products and services, shifting demographics, evolving regulations and transformed business models which consequently trigger increased stakeholder expectations in the region. Filing strategy and regulatory requirements of the African countries are listed below in table 4.

Table 1. Filed Country List

S.No	Name of the country	Name of MoH	Country website
Africa			
1	Kenya	Pharmacy and poisons Board	http://www.pharmacyboardkenya.org/
2	Uganda	NDA: National Drug Authority	http://www.nda.or.ug/
3	Tanzania	TFDA: Tanzania and Food and drug Administration	http://www.tfda.or.tz/
Asia			
4	Malaysia	National Pharmaceutical Control Bureau, Drug Control Authority (Registration Certificate Issuing Authority), Ministry of Health (MoH)	http://portal.bpfk.gov.mg/index.cfm http://www.pharmacy.gov.my/index.cfm
Middle East Asia			
5	Bahrain	The Pharmacy & Drug control directorate (MoH)	No web site identified.
6	Qatar	Pharmacy & Drug Control Department, Supreme Council of Health (SCH).	http://www.nha.org.qa/moh/under construction
7	Oman	Department of Drug Control, Ministry of Health (MoH)	http://www.moh.gov.om/nv menu.php fnm=pharma/regulation htm
8	Kuwait	Drug & Food Control, Ministry of Health (MoH)	No web site identified
Latam			
9	Mexico	COFEPRIS	http://www.cofepris.gob.mx/
10	Peru	Ministerio de salud DIGEMID - Minsa. Direccion General de Medicamentos Insumos y Drogas	http://www.digemid.minsa.gob.pe/
11	Venezuela	Instituto Nacional de Higiene "Rafael Rangel"	http://www.inhrr.gov.ve/

NA* = Not Available

Table 2. Filing Strategy of Regulatory Requirements Of African Countries				
Filing Strategy of Regulatory Requirements of African Countries,[11,12,13]				
	Requirements	Kenya	Tanzania	Uganda
	MOH	PPB: Pharmacy and poisons board	TFDA: Tanzania and food and drug administration	NDA: National drug authority
	Dossier Format	CTD	CTD-Country specific	CTD
Plant	cGMP Inspection	Required	Required	Required
	Fee			
	Validity period	3	5	3
	Admin documents	Mf.lic,GMP(Notarized), CPP(Notarized)	Mf.lic,GMP,FSC, CPP	Mf.lic(Notarized),FSC, CPP(Notarized)
	Artworks	English/ Anglofrench	English/ Anglofrench	English/ Anglofrench
	Sample requirements	8packs	6packs	5packs
	Stability data	30/65(6Months)	30/65(6Months)	30/65(6Months)
Product	Registration fee	USD 1000.00	USD 750.00	USD 1250.00
	Registration lead time	12-18 Months	6 - 9 M(Fast track), 9-18M(Normal)	12-18 Months
	Registration validity	1(Every year retention fee should be submitted)	5	1(Every year retention fee should be submitted)
	Renewal fee	-	-	-
	Renewal validity	-	5	-
	Retention fee	USD 300.00	USD 100.00	USD 300.00
	NA*= Not Available			

Table 3. Filing Strategy of Regulatory Requirements of Asian & Mena Countries

Filing Strategy Of Regulatory Requirements of Asian & Mena Countries, [14,15,16}

	Requirements	Malaysia	Bahrain	Kuwait	Oman	Qatar
Plant	MOH	National Pharmaceutical Control Bureau	The Pharmacy & Drug control directorate (MoH)	Drug & Food Control, Ministry of Health (MoH)	Department of Drug Control, Ministry of Health (MoH)	Pharmacy & Drug Control Department, Supreme Council of Health (SCH).
	Dossier Format	ACTD	CTD	CTD	CTD	CTD
	cGMP Inspection	PIC/S Certificate(Plant accreditation required)	Required	Required	Required	Required
	Fee	NA	NA	NA	NA	NA
	Validity period	NA	NA	NA	4 years	NA
	Administrative documents	Mfg.lic (Notarized)., FSC(Notarized), COPP(Original)	COPP (Legalized)	COPP (Legalized)	GMP(Legalized)	Copp(Legalized)
	Artworks	English/Official native language	English	English	English	English
	Sample requirements	No samples required		5 Packs	3 packs	6 packs
	Stability data	30°C/75%RH(12Months)	30°C/75%RH (12Months)	30°C/75%RH (12Months)	30°C/75%RH (12Months)	30°C/75%RH (12Months)
Product	Registration fee	2200 Malaysian ringgits, two or more API-4000MR	NA	NA	NA	No Product registration fee
	Registration lead time	210 working days	NA	6 months	6 to 9 months	3 -6 months.
	Registration validity	5 years	5 years	3 years	5 years.	Life Time.
	Renewal fee	333USD	NA	NA	NA	NA
	Renewal validity	5	NA	NA	NA	NA
	Retention fee	NA	NA	NA	NA	NA

Table 4. Filing Strategy Of Regulatory Requirements Of Latam Countries

Filing Strategy of Regulatory Requirements of Latam Countries, [17,18,19]

	Requirements	Mexico	Venezula	Peru
	MOH	COFEPRIS	Instituto Nacional de Higiene "Rafael Rangel"	Ministerio de salud DIGEMID - Minsa. Direccion General de Medicamentos Insumos y Drogas
	Dossier Format	CTD-Country specific	CTD-Country specific	CTD-Country specific
Plant	cGMP Inspection	Required	Not required	Not required
	Fee	NA	NA	NA
	Validity period	NA	NA	NA
	Administrative documents	Mf.lic, gmp, fsc,(L) copp(L),Country specific	Mf.lic, GMP(Notary), FSC(Legalized),CPP(Legalized)	Mf.lic, GMP(Notary), FSC(Legalized), CPP(Legalized)
	Artworks	English/spanish	English/Spanish	English/spanish
	Sample requirements	required for bio and dissolution	2-5 packs	NA
	Stability data	25/60	30/75	30/75
	Registration fee	62,270 Mexican pesos, 160,000 pesos (Fastrack)	175 USD	125 USD
Product	Registration lead time	12-18 months	12-18 months	12 months
	Registration validity	5 years	7 years	5 years
	Renewal fee	NA	NA	NA
	Renewal validity	NA	NA	NA
	Retention fee	NA	NA	NA
	Requirements	Peru	Venezuela	Mexico

NA* = Not Available

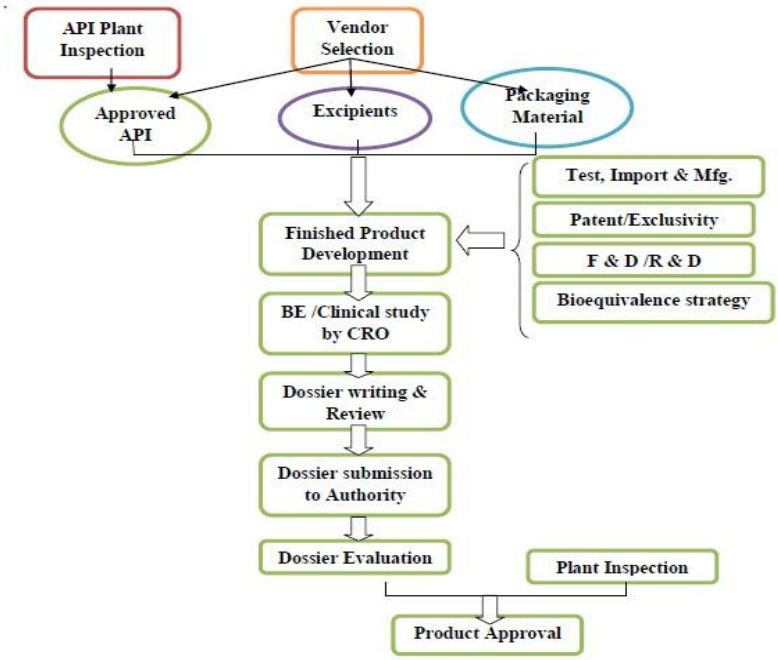
1

Table 5. Communication status of filing countries

Region	**Latam**	
Country	**Mexico**	**Venezuela**
Query Description	Please justify differences in addresses between bisoprolol tablets of different strengths.	Please find the evaluation feedback from Venezuela on the new dossiers.
	Please send CoA, raw data sheets and chromatograms of next batches for API. CoAs of API/Batch Processing Records/CoAs of FP/ Stability Study	Please send us the specification of packing material duly stamped and signed for Bisoprolol Fumarate tablets.
	Please send specifications of Finished Product	Please send that COPP of venezulae
	Please send Long Term Stability Studies of initial and final stage (minimum at 18th months)	Please inform us the commercial presentation to be registered in Venezuela (boxes X tablets???????)Including free samples.
	Please send a Stability Protocol considering Identification by HPLC & DSC and Assay by HPLC & Titration for both Accelerated and Long Term Stability Study, respectively.	Please note that there is a difference in batch number for 1 batch in documents stability protocol & conclusion please send the corrected protocol.
	Please send Chromatograms corresponding to Linearity, Precision (System Precision and Method Precision), Ruggedness, Accuracy (Recovery), Stability of Sample Solution and Robustness.	Please note that the stability results at 30+/-2c include data until 12 months .results.
	Please send Good Manufacturing Practices from the drug product's manufacturer	COA of finished product: Please send individual result of dissolution test
	Brief description and flow chart of manufacturing process indicating critical steps and in-process controls	
	Please send stability data, Raw data sheets of Bisoprolol Fumarate Tablets.	
Region	**Middle East**	
Country	**Oman**	**Quatar**
Query description	Please provide the primary & 2° standards & placebo of Bisoprolol Fumarate Tablets	Please provide the registration status in GCC countries
	Please provide the covering letter, invoice of the Bisoprolol Fumarate Tablets	Please find attached LOA of Bisoprolol.
	Please provide the fresh working standards and letter of access for your respective products for submission at the earliest.	Can please update the dossiers submission plan for our records.
	Please provide Updated long term stability study for batches	Please provide the fresh/valid WS
Region	**Asian**	
Country	**Malaysia**	
Query description	Please provide the process validation protocol	
	Please submit the COA with current specifications for evaluation	
	Please provide entire BE studies Please kindly state the full address of the manufacturer, and Pharmaceutical equivalence data Please kindly submit the certificate of analysis (CoA) for the reference product Pharmacokinetic parameter	

	Statistical analysis report
	Please clarify on the code ‘x’ and ‘2’ debossed on the tablet.
	Please send FP specification, STP and COA’s
	Please provide stability data (24M) of Bisoprolol Tablets.
	Please provide the justification for uniformity of content.
	Please provide the latest Certificate of Analysis (COA) of finished product.
	Please provide complete data on real time stability studies (24 months) for two batches of this product conducted by ASEAN Guideline on Stability Study Of Drug Product for the Zone IVB is at 30A ° 2/RH75% Â ± ca ± 5.
	Please send Comparative Dissolution Profile (test vs. reference product), in media pH 6.8

Fig 1. Regulatory approval process



CONCLUSION

Based on the IMS data and market survey by project management team & business potential survey by business development team identified following countries to register

Bisoprolol Fumarate Tablet

Kenya, Tanzania, Uganda, Malaysia, Bahrain, Oman, Kuwait, Qatar, Mexico, Venezuela, Peru. After studying the regulatory requirements to register a pharmaceutical product for human use and after analyzing the communications received from respective regulatory authorities, the above countries are classified as regulated and semi- regulated countries.

Regulated countries	Semi- regulated countries
Malaysia	Peru
Mexico	Venezuela
Kenya	Bahrain
Uganda	Oman
Tanzania	Kuwait
	Qatar

Based on the experience gained from this product registration above said countries regulatory filing strategy has been developed to improve the quality of the submission file which helps to reduce the number of deficiencies received from each regulatory authority.

It also helps to reduce the product registration lead time which allows commercial team to launch the product at the earliest.

Table 6. Filing strategy has been represented as comparative table for easy understanding									
Strategic documents	**Kenya**	**Tanzania**	**Uganda**	**Malaysia**	**Bahrain**	**Kuwait**	**Oman**	**Quatar**	**Mexico**
Dossier Format	CTD	CTD-Country specific	CTD	ACTD	CTD	CTD	CTD	CTD	Country specific
cGMP Inspection	Required	Required	Required	PIC/S Certificate (Plant accreditation required)	Required	Required	Required	Required	API-Required, FP-Required (pics) acceptable
Administrative documents	Mf.lic,GMP (Notarized), CPP (Notarized)	Mf. lic, GMP, FSC, CPP	Mf.lic (Notarized), FSC, CPP (Notarized)	Mfg. lic (Notarized)., FSC (Notarized), COPP(Original)	COPP (Legalized)	-	GMP(Legalized)	Copp (Legalized)	Mf.lic, GMP (Notary), FSC (Legalized), CPP (Legalized)
Artworks	English/ Anglofrench	English/ Anglofrench	English/ Anglofrench	English/Official native language	English	English	English	English	English/ spanish
Sample requirements	8packs	6packs	5packs	No samples required		5 Packs	3 packs	6 packs	required for bio and dissolution
Stability data	30/65 (6Months)	30/65 (6Months)	30/65 (6Months)	30°C/75 %RH (12Months)	30°C/ 75%RH (12Months)	30°C/ 75%RH (12Months)	30°C/ 75%RH (12M)	30°C/75%RH (12Months)	25°C /60%RH
Registration fee	USD 1000.00	USD 750.00	USD 1250.00	2200 Malaysian ringgits, two or more API-4000MR				No Product registration fee	62,270 Mexican pesos, 160,000 pesos (Fastrack)
Registration lead time	12-18 Months	6 - 9 M (Fast track), 9-18M(Normal)	12-18 Months	210 working days		6 months	6 to 9 months	3 -6 months.	12-18 months

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