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INDIAN PHARMACEUTICAL INDUSTRY, ITS CHALLENGES WHILE EXPORTATION OF PHARMACEUTICALS RELATING TO EUROPE

Stella Parusha*

India.

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***Corresponding Author**
Stella Parusha
India.

ABSTRACT

The global pharmaceutical market size is estimated to reach USD 1.4 trillion and the Indian pharmaceutical market size is estimated as USD 55 billion by the year 2020. The Indian pharmaceutical sector is expected to grow with faster compound annual growth rate (CAGR) compared to global growth rate during the period 2015- 2020. The world market will be dominated by countries like USA, EU and Japan and the contribution of merging countries is expected to be more in coming years. The future of the world pharmaceutical sector will be dominated by medicines for non communicable diseases and original branded medicines. The Indian pharmaceutical sector evolved in different phases from pre independence era to postTrade-Related Aspects of Intellectual Property Rights (TRIPS). Presently, Indian pharmaceutical sector is dominated by the generics drugs and more drugs are sold in anti-infective category. The Indian pharmaceutical industry is having opportunities in the domestic market with growing demand for quality health care. More opportunities are seen in the area of Contract Research and Manufacturing Services (CRAMS) by Mergers and Acquisitions (M&A) and Biogenic market. The government of India has taken measures to boost pharmaceutical sector, even though, the pharmaceutical sector is facing challenges in patent rights and methods used for fixing ceiling price for drugs. More challenges are expected due to immature clinical trial regulations and ethical aspects.

KEYWORDS: Indian pharmaceutical sector, Drug price, Patent rights, Generic drugs.

1. INTRODUCTION

About indian pharmaceutical industry

The pharmaceutical industry of India is currently at the top of the chart amongst all of the

India's science-based industries. It has a wide range capability in the complex field of drug manufacture and technology. A highly organized sector, the Indian Pharmaceuticals market is expected to expand at aCAGR of 23.9% to reach US$55 Billion by 2020. In terms of quality, technology and the vast range of medicines that are manufactured, it ranks high amongst all the third world countries. Almost all types of medicines are now made in the Indian pharmaceutical industry e.g. Headache pills to sophisticated antibiotics and complex cardiac medicines.

The Indian pharmaceutical sector is highly fragmented with more than 20,000 registered units. It has expanded drastically in the last two decades. The Pharmaceutical and Chemical industry in India is extremely fragmented market with severe price competition and government price control. The Pharmaceutical industry in India meets around 70% of the country's demand for Bulk drugs, intermediates, Chemicals, Pharmaceutical formulations like Tablets, Capsules, Liquid Orals and Injectables. Approximately there are about 8000 Small Scale Units and 250 large scale units, which forms the core of the Pharmaceutical industry in India.[1]

Evolution of pharmaceutical sector in india

In 1930, the first pharmaceutical company called Bengal Chemicals and Pharmaceuticals Works, was started. Till today, Bengal Chemicals and Pharmaceutical Works is one of the five government-owned drug manufacturers. The history of Indian Pharmaceutical market in 1970's was almost non-existent. Today, India has gained immense importance and carved a niche for itself in Pharmaceutical domain. In fact, it has emerged as a big mark for the Pharmaceutical industry. Formulations, Bulk Drugs, Generics, Novel Drug Delivery Systems, new Chemical Entities, or Biotechnology etc. Indian companies are dominating in the market place which was traditionally manned by MNC.[2]

The evolution of Indian Pharmaceutical sector was divided into five phases.They are

Phase 1: Early Years: (Before 1970) In this phase market share domination by foreign companies was taken place and relative absence of organized Indian companies.

Phase 2: Government Phase: (1970-1980) In this phase, Indian patent act was started in the year 1970. Drug prices were capped. Local companies begin tomake an impact.

Phase 3: Development Phase: (1980-1990) In this phase, process development, export initiatives and Production infrastructure creation weretaken place.

Phase 4: Growth Phase: (1990- 2000) In this phase, there is a rapid expansion of domestic

market and international market development. Research orientation was taken place.

Phase 5: Innovation and Research: (2000-2010) In this phase, new IP law and discovery research taken place.

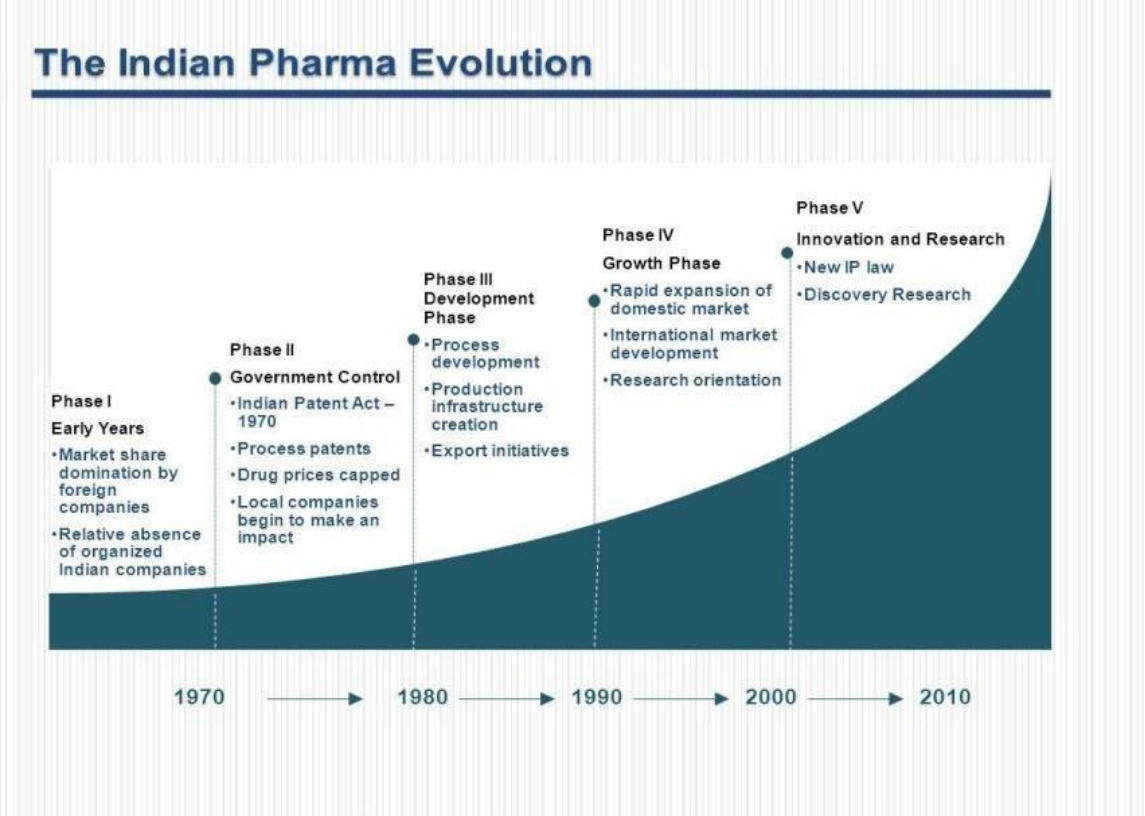


Figure 1

Pharmaceutical companies in india[2]

India claims a position of its own in the global pharmaceutical industry, as its pharmaceutical market stands the third largest when considered the volume of production and stands thirteenth in the value of the industry. The top Indian pharma companies include Sun Pharma, Lupin, Aurobindo Pharma, Cipla, Dr.Reddy's Labs etc. India being the largest producer of generic medicines exports 20% of the global generic medicines exports, no wonder generic medicines constitute 70% of the pharmaceutical market share in India. While OTC (Over the Counter) and patented medicines accounts for 21% and 9% of the market share respectively. Here is the list of the top 10 pharmaceutical companies in India 2017 as per Revenue.

Top 10 pharmaceutical companies in india during theyear 2016

Table 1

Company name	Revenue(Crore inr)
Dr.Reddy's Laboratories	15470.82
Lupin Pharmaceuticals	13701.60
Cipla Pharmaceuticals	11735.18
Cadila Pharmaceuticals	6436.52
Aurbindho Pharmaceuticals	8608.55
Torrent Pharmaceuticals	5280.00
Glenmark Pharmaceuticals	5817.39
Sun Pharmaceuticals	7127.95
Divis Laboratories	3713.96
Piramal Enterprises	3477.53

Structure of pharma industry in india

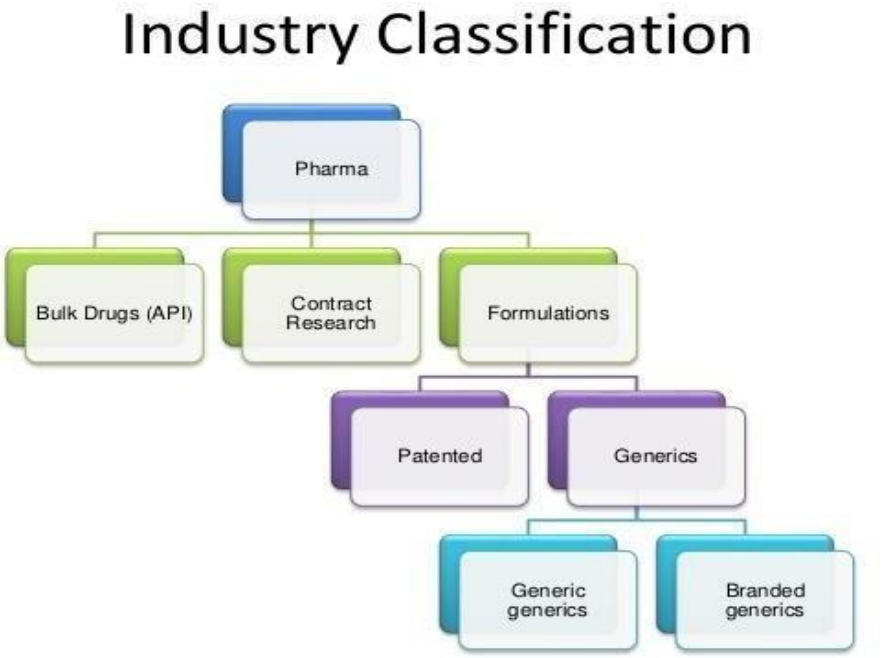


Figure 2

Porter's five force analysis

It is a framework for industry analysis and business strategy development formed by ***Micheal. E. Porter.*** It determines the competitive intensity. It also determines the ultimate profit potential of the industry.

The potential of these forces differs from industry to industry. These forces jointly determine the profitability of industry because they shape the prices which can be charged, the costs which can be borne, and the investment required to compete in the industry. Before making strategic decisions, the managers should use the five forces framework to determine the

competitive structure of industry.

Risk of entry by potential competitors: Potential competitors refer to the firms which are not currently competing in the industry but have the potential to do so if given a choice. Entry of new players increases the industry capacity, begins a competition for market share and lowers the current costs. The threat of entry by potential competitors is partially a function of extent of barriers to entry.

Rivalry among current competitors: Rivalry refers to the competitive struggle for market share between firms in an industry. Extreme rivalry among established firms poses a strong threat to profitability.

Bargaining power of buyers: Buyers refer to the customers who finally consume the product or the firms who distribute the industry's product to the final consumers. Bargaining power of buyers refer to the potential of buyers to bargain down the prices charged by the firms in the industry or to increase the firms cost in the industry by demanding better quality and service of product. They purchase in large quantities. They have full information about the product and the market. They emphasize upon quality products.

Figure 3

Bargaining power of suppliers: Suppliers refer to the firms that provide inputs to the industry. Bargaining power of the suppliers refer to the potential of the suppliers to increase the prices of inputs (labour, raw materials, services, etc.) or the costs of industry in other ways. Strong suppliers can extract profits out of an industry by increasing costs of firms in the industry. Suppliers products have a few substitutes. Strong suppliers' products are unique. They have high switching cost. Their product is an important input to buyer's product.

Buyers are not significant to strong suppliers. In this way, they are regarded as a threat.

Threat of substitute products: Substitute products refer to the products having ability of satisfying customers needs effectively. Substitutes pose a ceiling (upper limit) on the potential returns of an industry by putting a setting a limit on the price that firms can charge for their product in an industry. Lesserthe number of close substitutes a product has, greater is the opportunity for the firms in industry to raise their product prices and earn greater profits (other things being equal).

Porter ignored, however, a sixth significant factor- complementaries. This term refers to the reliance that develops between the companies whose products work is in combination with each other. Strong complementors might have a strong positive effect on the industry. Also, the five forces model overlooks the role of innovation as well as the significance of individual firm differences. It presents a stagnant view of competition.[3]

Swot analysis

Strengths

- Low cost of skilled manpower
- Access to large pool of highly trained scientists
- Strong marketing and distribution network
- Proven track record in design of high technology manufacturing devices
- Low cost of innovation, manufacturing and operations

Weakness

- Stringent pricing regulations
- Poor transport and medical infrastructure
- Lack of data protection
- Very competitive environment
- Poor health insurance coverage
- Production of low quality drugs tarnishes image of industry abroad
- Low investment in innovative R&D

Oppurtunities

- Increase in per capita income
- Global demand for Generics rising

- Increasing population with more sedentary lifestyle
- Increasing health insurance sector
- Significant investment from MNC'S
- Medical tourism; Cheap, diverse clinical trials
- Global out sourcing hub due to low cost of medicines

Threats

- Other low cost countries affecting demand
- Government regulations changing
- Expanding of Drugs Price Control Order
- Lack of investment in infrastructure
- Wage inflation
- R&D restricted by lack of animal testing

Pharmaceutical industry in india

Current scenario

The Indian pharmaceuticals market is the 3rd terms of volume and 13th largest in terms of value, as per a report by Equity Master. India is the largest providerof generic drugs globally with the Indian generics accounting for 20 per cent ofglobal exports in terms of volume. Of late, consolidation has become an important characteristic of the Indian pharmaceutical market as the industry is highly fragmented.

India enjoys an important position in the global pharmaceuticals sector. The country also has a large pool of scientists and engineers who have the potentialto steer the industry ahead to an even higher level. Presently over 80 per cent of the antiretroviral drugs used globally to combat AIDS (Acquired Immuno Deficiency Syndrome) are supplied by Indian pharmaceutical firms.[4]

Market size

The Indian pharma industry, which is expected to grow over 15% per annum between 2015 and 2020, will outperform the global pharma industry, which is set to grow at an annual rate of 5% between the same period. The market is expected to grow to US$ 55 billion by 2020, thereby emerging as the sixth largest pharmaceutical market globally by absolute size. Branded generics dominate the pharmaceuticals market, constituting nearly 80% of the

market share (in terms of revenues). The sector is expected to generate 58,000 additional job opportunities by the year 2025. India's pharmaceutical exports stood at US$ 16.4 billion in 2016-17 and are expected to grow by 30% overthe next three years to reach US$ 20 billion by 2020, according to the Pharmaceuticals Export Promotion Council of India (PHARMEXCIL).

Indian companies received 55 Abbreviated New Drug Application (ANDA) approvals and 16 tentative approvals from the US Food and Drug Administration (USFDA) in Q1 of 2017. The USFDA approvals are expected to cross 700 ANDA in 2017, thereby recording a year-on-year growth of 17%.The country accounts for around 30%(by volume) and about 10% (value) in the US$ 70-80 billion US generics market.

India's biotechnology industry comprising bio-pharmaceuticals, bio-services, bio-agriculture, bio- industry and bioinformatics is expected grow at an average growth rate of around 30% a year and reach US$ 100 billion by 2025.[4]

Investments

The Union Cabinet has given its nod for the amendment of the existing Foreign Direct Investment (FDI) policy in the pharmaceutical sector in order to allow FDI up to 100% under the automatic route for manufacturing of medical devices subject to certain conditions.

The drugs and pharmaceuticals sector attracted cumulative FDI inflows worth US$ 14.71 billion between April 2000 and March 2017, according to data released by the Department of Industrial Policy and Promotion (DIPP).[4]

Regulatory environment in india

The Pharmaceutical Industry is characterized by maintenance of high quality standards as it concerns the lives of people. Regulatory bodies impose regulations to ensure that drugs meet the safety and quality standards. Regulatory bodies not only ensure that pharmaceutical companies meet the setquality standards, but also ensure that the pharmaceutical companies do not charge unreasonable prices from consumers.[5]

Global regulatory authorities

The stringency of regulatory procedures varies across countries. On the basis of established regulations and patent laws, the global pharmaceutical industry can be broadly classified into regulated and emerging markets.

Regulated markets include the USA, EU, Canada, Australia, New Zealand and Japan that have established systems of patent laws and sophisticated regulatory systems for controlling drug quality. On the other hand, emerging markets include countries such as China, India, South Africa, malaysia and Brazil which have less stringent systems of patent laws and less sophisticated regulatory systems for drug quality control.

However, there is no single harmonized protocol for drug approval across countries. Countries have their own regulatory authorities and drug approval mechanisms.

List of regulatory authorities across key countries

Table 2

Country	Regulatory Authority	Abbreviation
Regulated markets		
United States	US Food & Drug Administration	USFDA
Europe	The European Medicines Agency	EMA
Canada	Health Canada	HC
Australia	Therapeutic Goods and Administration	TGA
Emerging markets		
South Africa	Medicines Control Council of South Africa	MCC
Malaysia	National Pharmaceutical Regulatory Agency	NPRA
Brazil	National Health Surveillance Agency	ANVISA
United Kingdom	UK Medicines and Healthcare Products Regulatory Agencies	MHRA

Indian pharmaceutical exports

Indian pharma companies are capitalizing on export opportunities in regulated and semi-regulated markets.

In FY16, India exported pharmaceutical products worth USD16.89 billion, with the number expected to reach USD40 billion by 2020. Department of Pharmaceuticals targets to export USD18.02 billion worth of pharmaceuticals in 2016. Indian drugs are exported to more than 200 countries in the world. The country's generic drugs account for 20% of global generic drug exports (in terms of volumes) In terms of value, exports of pharmaceutical products increased at a CAGR of 14% during FY12–15. During 2015-2016 (April- Dec), pharmaceutical products imports into India stood at USD3.7 billion.

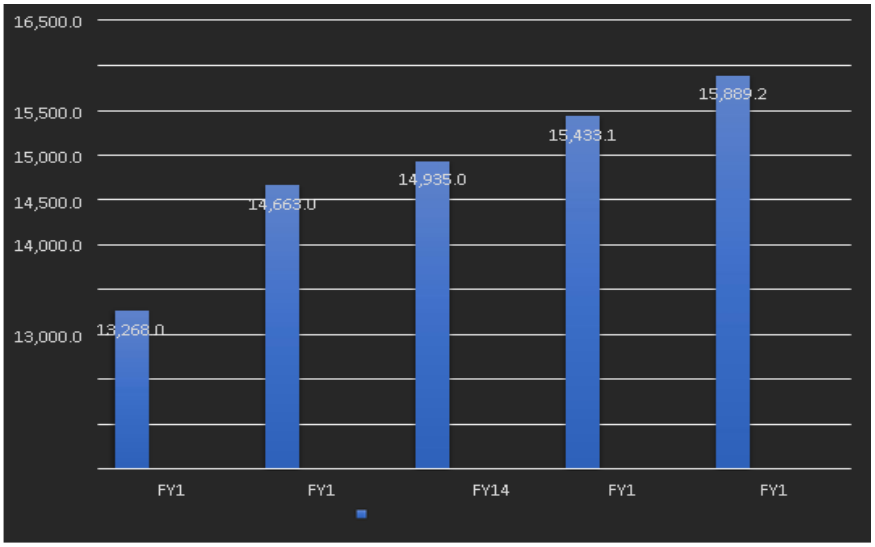
India is expected to rank amongst the top three pharmaceutical markets in terms of incremental growth by 2020.

The Indian pharmaceutical industry is the largest supplier of cost effective generic medicines to the developed world. With the widest range of medicinesavailable for exports and with the availability of the largest number of approved pharmaceutical manufacturing facilities, India is all set to become the leader of pharmaceutical exports to the world.[6]

Statistical analysis

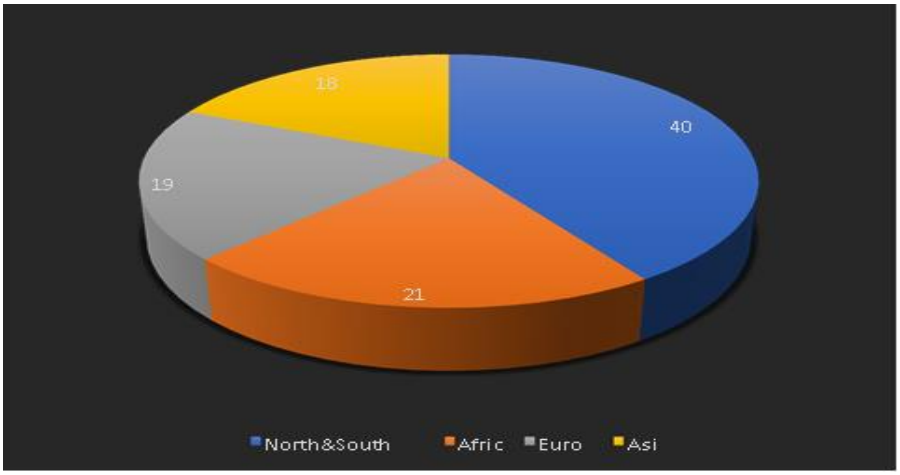
Table 3

Year	Exports US($)(Million)
FY2012	13,268.0
FY2013	14,663.0
FY2014	14,935.0
FY2015	15,433.1
FY2016	16,889.2



Graph 1

Indian pharma exports to various countries during fy16



Graph 2

USA and Europe are the dominant markets in global Pharmaceutical industry. During the year 2016, US is having the highest Pharmaceutical exports from India. All new / generic drug products must be approved by the respective regulatory agency governing the respective market before a particular product can be introduced into the market. By law, all new drugs must first be shown to be safe and effective before they can be approved by the respective regulatory agency for marketing. The regulatory agency is responsible for the safety regulation of food and drug products in their respective country.US is thesingle market having single regulatory authority and it is easy procedure whereas Europe is having multiple number of regulatory authorities and it is complex procedure for the approval of Drug products. Therefore, the Drug approval process in Europe is explained in a detailed manner when the pharmaceutical products are exported from India. In order to understand marketing authorization procedure first we have to know about the India and EU relation in terms of trade.[7]

India -EU Relation

India-EU relations date to the early 1960s, India being amongst the first countries to establish diplomatic relations with the European Economic Community. A cooperation agreement signed in 1994 took the bilateral relationship beyond trade and economic cooperation. At the 5th India- EU Summit at The Hague in 2004, the relationship was upgraded to 'Strategic Partnership'. The two sides adopted a Joint Action Plan in 2005 (which wasreviewed in 2008) that provided for strengthening dialogue and consultation mechanisms in the political and economic spheres, enhancing trade and investment, and bringing peoples and culture together.

The first India-EU Summit took place in Lisbon in June 2000 and marked a watershed in the evolution of the relationship. 14th summit was organized in the year 2017 at New Delhi.

India received around $83 billion of foreign direct investment from Europe between 2000 and 2017, constituting approximately 24 percent of total FDI inflows into the country.

The EU is India's number one trading partner (13.5% of India's overall trade with the world in 2015-2016). EU investment stocks in India amount to € 51.2 Billion in 2015, increasing from €44.2 Billion in 2014.

Pharmaceutical exports and imports to europe

Each country is endowed with some specific resources. Once countries start exporting whatever they are rich in, as well as importing goods they lack, their economies begin developing. Importing and exporting goods is not only important for businesses; it is important for individual consumers, too. It is not just the core of any large, successful business; it also helps national economies grow and expand. If you're striving to make your business the leader in its industry, or you are thinking of lowering production costs, importing is certainly worth considering. Otherwise, if your local market is too small for your business and you're searching for new opportunities to expand – exporting may be your key to success.

Benefits of exporting

1) Increasing in sales potential.
2) Increasing Profits
3) Providing high quality of medicines

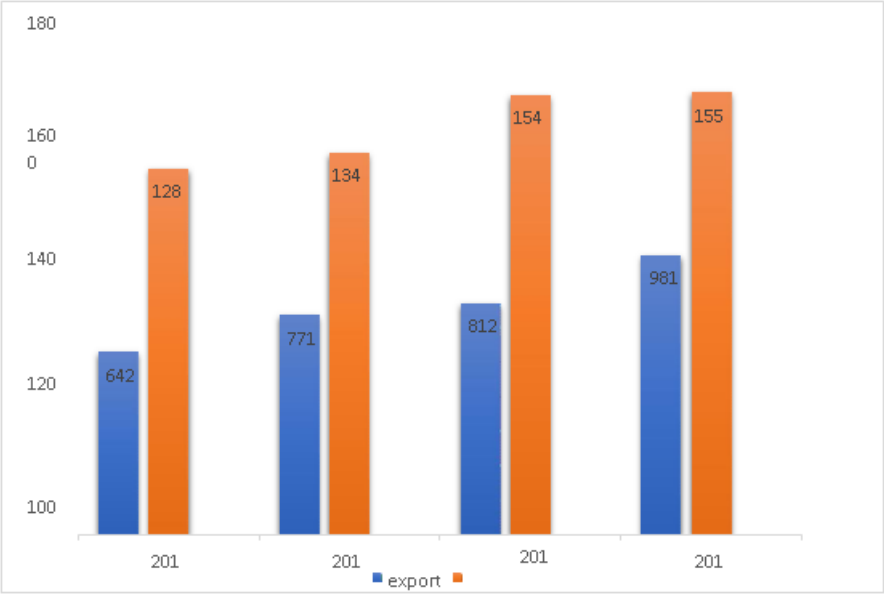
Benefits of importing

1) Introducing New Products to the market
2) Reducing costs
3) Becoming a leader in the industry
4) Providing high quality of Medicines

Statistical Analysis of Pharmaceutical Exports and Imports from India to Europe[8]

Table

Year	Exports(€)	Imports(€)
2013	642	1,287
2014	771	1,342
2015	812	1.544
2016	981	1,552



Graph 3

Central Drugs Standard Control Organization(CDSCO)

The Central Drugs Standard Control Organization (CDSCO) is the CentralDrug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act. CDSCO has six zonal offices, four sub-zonal offices, 13 port offices and seven Laboratories under its control.[9]

Major functions

- ✓ Regulatory control over the import of drugs, approval of new drugs and clinical trials, meetings of Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB), approval of certain licenses as Central License Approving Authority is exercised by the CDSCO.
- ✓ The Central Drugs Standard Control Organization (CDSCO) is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the European Medicines agency of the European Union, the PMDA of Japan, the Food and Drug Administration of the United States and the Medicines and Healthcare products

1. Purchase order

a. Order from the foreign buyer either in the name of manufacturer or in the name of trader mentioning list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size duly signed by the competent authority with specific destination point of the importing country. In case of purchase order in the name

of trader further a letter from the trader in the name of manufacturer is required to be submitted along with the application.

b. It should be signed by the competent authority/person with a valid purchase order no. and recent date not more than 6 months prior to the application madeby the firm.

2. Manufacturing license

License issued by the State Licensing Authority should be enclosed along with each application for the required location to manufacture the drug forexport purpose.

3. Performa invoice

a. A copy of Performa invoice from the importing country should accompany with application for import of unapproved Active Pharmaceutical Ingredients, used in the drug formulation.

b. A copy of Performa invoice duly signed by the competent authority should be addressed to the manufacturer mentioning the required quantity of the bulkdrug.

4. Registration certificate

a. For the export of drugs which are banned in India by Central government, which coming under list of drugs prohibited for manufacture and sale through gazette notifications under section 26a of drugs & cosmetics act 1940 by the ministry of health and family welfare.

b. A copy of registration certificate from the specific importing country along with composition and strength of the drug should accompany with the application

c. Registration certificate should be provided in the name of manufacturer.

India's accrediations to europe as on december, 2016[10]

Table 5

Authorit Y	Name of regulatory agency	Number
Europe	Number of CEPs received (as of December, 2016)	1458
	Number of companies with CEPs	220
	Number of molecules for which CEPs have been filed with EDQM	382
	Number of sites with EU GMP compliance as onDecember, 2016	666
	UK MHRA, Market authorizations as on March, 2015	1559
	Number of CEPs with Irish Medicines Board	300
	Number of companies registered in Irish Medicines Board	19
	Number of Authorizations with Sweden MPA	209
	Number of companies having MA's with Sweden MPA	14

Overview

The main purpose of this dissertation is to explain the challenges faced by Indian Pharmaceutical Industry and the regulatory requirements related to the European Regulatory system for Medicines. USA and Europe are the dominant markets in global Pharmaceutical industry. During the year 2016, US is having the highest Pharmaceutical exports from India. India is currently the fastest growing economy in the world and a strategic partner for the EU representing the large sizable and dynamic market. The EU and India are committed to further increase their bilateral trade and investment through the Free Trade Agreement negotiations that were launched in 2007.

From the obtained information i.e, statistical data of pharmaceutical exports and imports to Europe and India's Accrediations to Europe, we came to know that there is a continuous growth of pharmaceuticals in India. Also increasing new oppurtunities to expand the market size of India by exporting the pharmaceuticals of high quality (either API or Drug Products) to Europe. For smooth export of Pharmaceuticals we need to understand the complete marketing authorization procedures in Europe. So, we have to study about the European Regulatory system for Medicines to ensure that patients in the EU have access to high-quality, effective and safe medicines.

2. LITERATURE REVIEW

Dr. A. Selvaraj et al.,[11] submitted an article "Indian Pharmaceutical industry: A vision with its strengths and weakness. The future of Indian Pharmaceutical sector looks extremely positive. Several Indian Pharmaceutical companies have acquired companies in the US and Europe. Today, India produces some of the cheapest drugs in the world, especially because experts indicate that infrastructure costs are 40% lower and fixed cost is estimated to be 12%-20% less than in the US and Europe. Consequently, India can produce Bulk drugs that costs 60% less than in the west and can open a production plant in India40% cheaper than in developed countries. Some of the weakness are low level of investment in R&D, low margins, lack of experience in drug discovery, Corruption.

Sarda Rohit. R et al.,[12] published an article "The Indian Pharmaceutical industry, evolution of regulatory system and present scenario." Indian Pharmaceutical industry evolved in true sense only after independence. Government provided the impetus to growth with the establishment of few public sector units. Healthcare facilities in India are still below standard as compared to most developed nations. Indian government is stringent on price control of

pharmaceuticals and this becomes a major hurdle for global players to enter in India but Indian patent act and new drug policy has bought a new dimension to Indian pharmaceutical industry.

Arjun Gupta et al.,[13] published an article on "Indian Pharmaceutical industry: A diagnostic overview." In this the author stated that the pharmaceutical industry is a knowledge driven industry and is heavily dependent on research and development for new products and growth. Any economy cannot self-sustain, it needs to look out in the world for the other option thus analyzing the pattern for export and import is necessary. The pharmaceutical industry develops, produces, and markets drugs or pharmaceuticals licensed for use as medications.

U. Nitin Kashyap et al.,[14] submitted an article on "comparision of Drug Approval Process in Unites States and Europe". The Drug approvals in the United States & Europe are the most demanding in the world. The primary purpose of the rules governing medicinal products in US & Europe is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

Akhilesh. P et al.,[15] submitted an article on " DMF Filing in US, Europe and Japan". Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API). The DMF filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP status of any human drug product. The DMF consists of open part (non- confidential) and closed part (confidential).

V. Senthil et al.,[16] published an article on "Regulatory Process for Import and Export of Drugs in India". The process of Import & Export of Drugs in any country including India is a lengthy process involving the various reviewing and registration processes; as a result lot of inputs are required to achieve the core objective of supply of medicine to the public. The D & C rules (1945) prescribe various procedures for getting a drug approved to be imported/exported for human-veterinary use in the country. The rules are very clear prescribing the procedure to be adopted in this regard however; it is a tedious task to follow

the procedures systematically and to meet the requirements. Latest amendments are given by the CDSCO according to the current Laws and Trading strategies for the approval for Import/Export in India. “Approval Process for Import and Export of Drugs in India” gives an outlook on the entire process of getting a Drug Imported/Exported in India. The procedure and requirements vary considerably dependingon the status of the Drug Applied.

Jawahar et al.,[17] submitted an article on “Procedures and applications for marketing authorization of medicinal products in Europe”. Regulatory requirement for the approval of the medicinal drug in European Union was found to be more rigid. EU has different types of procedure and different types of applications which will specify the product and time frame required for the approval of the drug which helps in tracking of life of the respective product. The retaining of the current marketing authorization systems, DCP togetherwith scope of CP provide a great flexibility of the choice between different marketing authorizations and also allowed to go for the national application of medicinal product. To harmonies and fasten the process of medicinal product evaluation, the European Union adopted the eCTD format for the submission.

Nupur Sunil Bhargava et al.,[18] published an article “ Registration Process of API inUS and Europe along with comparision of USDMF and EUDMF”. Active Pharmaceutical Ingredients are not only the heart and brain of drug products, but are also crucial to the regulatory filing success of drug applications. From the current scenario of the regulatory requirements, it is important to keep in mind that FDA is scrutinizing DMFs more closely than ever before. With the considerable increase in the number of DMF submissions and FDA’s interest in keeping track of such filings electronically and FDA more stringently insists on uniformity in DMF submissions in accordance with its current administrative guidelines. Thus, more than ever before, it is important to consult FDA’s current DMF guidance when preparing DMF submissions and to adhere to FDA’s requirements for various types of DMF filings. Moreover, to maintain the active status of a DMF and ensure that it is not retired by FDA making it unavailable for review, it is important to regularly comply with FDA’s Annual Report requirement. At the end, the Drug Master File is a critical document used to support a drug application. Deficiencies in the Drug Master File can result in the delay of approval of drug applications. It is important that the DMF be filed in a timely manner and that the standards used to compete it are of the same quality as the actual drug application

Alamelu. R et al.,[19] published an article "Pharma Export: comforts and confronts in India" in Asian Journal of Pharmaceutical and Clinical Research. In this study he mentioned about the comforts and confronts faced by pharma companies in India. As the Indian pharma market is perceived to achieve US$ 100 billion by 2025 determined by spending habit of consumer on health issues, infra facilities and deep roots of health insurance awareness, this predicted growth in domestic sales would also depend on the need arised from consumer side which decides the portfolio of products in curing chronic diseases such as cardiovascular, anti-diabetes, anti-depressants, and anti-cancers thatare on the augment state.

3. AIM AND OBJECTIVE

Aim

To demonstrate About the Indian Pharmaceutical industry, its challenges while exportation of pharmaceuticals relating to European regulatory system and marketing authorization procedures in Europe.

Objectives

The objective of this study was to know about the challenges facing by Indian Pharmaceutical industry relating to European regulatory system.

- To know about the Indian Pharmaceutical industry and its market size.
- To understand the complete European medicines regulatory system and marketing authorization procedures.
- What are the challenges while exportation of pharmaceuticals to Europe

METHODOLOGY

European regulatory system formedicines

Introduction

The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU member states plus Iceland, Liechtenstein and Norway), the European Commission and EMA. This network makes the EU regulatory system unique.

The diversity of experts involved in the regulation of medicines in the EU encourages the exchange of knowledge, ideas and best practices between scientists striving for the highest standards for medicines regulation.

By working closely together, member states reduce duplication, share the workload and ensure the efficient regulation of medicines across the EU.[20]

European Union:(EU)

The European Union is a unique economic and political union between 28 European countries that together cover much of the continent.

The EU was created in the aftermath of the Second World War.

The European Economic Community (EEC), created in 1958, and initially increasing economic cooperation between six countries: Belgium, Germany, France, Italy, Luxembourg and the Netherlands. Since then, a huge single market has been created and continues to develop towards its full potential.[21]

European Economic Area: (EEA)

Norway, Iceland and Liechtenstein form the EEA with 28 member states of European union. These countries have, through the EEA agreement, adopted complete community acquis on medicinal products and are consequently following community procedures. Where reference is made of member state of community this should be understood to include Norway, Iceland, Liechtenstein thus EU consists of 31 countries. The only exception from this is that legally binding acts from the community (e.g.: Commission decision) do not directly confer rights and obligations but firstly they have to be translated into legally binding acts in Norway, Iceland, Liechtenstein. According to decision N° 74/1999 of the EEA joint committee, when decisions on approval of medicinal products are taken by the community, Norway, Iceland, Liechtenstein will take corresponding decisions on the basis of relevant acts. The marketing authorizations granted by Norway, Iceland and Liechtenstein are eligible for Mutual Recognition Procedure (MRP) in the same way as the marketing authorizations granted by other member states.

European Medcines Agency: (EMA)

The European Medicines Agency (EMA) is a Decentralized Agency of the European Union (EU), located in London. It began operating in 1995. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

It was founded in the year 1995. EMA worked across the EU and globally protect public and animal health. It mainly ensures the efficacy and safety of human and veterinary medicines. In

first two decades EMA recommends 975 human medicines and 188 veterinary medicines. Today, seven EMA scientific committees and more than 30 working parties provides scientific experts for the regulation of medicines.[21]

Role of EMA

The main aim of EMA is to show the scientific excellence in the evaluation and supervision of medicines for the benefit of public and animal health.

- Facilitate development and access to medicines
- Evaluate applications for marketing authorizations
- Monitor the safety of medicines across their life cycle
- Provide information to HCP'S and patients.

EMA can't do the following

- Evaluate the initial marketing authorization application of all medicines in EU
- Evaluate applications for the authorization of clinical trails
- Evaluate medical devices, food supplement, cosmetics.
- Carryout research (or) develop medicines
- Take decisions on the price
- Control the advertising of medicines
- Have information on pharmaceutical patents
- Develop treatment guidelines
- Provide medical devices
- Issue marketing authorizations.

Members of EMA

It is mainly governed by an independent management board.

a) Management board

The management Board is the European Medicines Agency's integral governance body. It consists of 35 members.

The board sets the agency's budget, approves the annual work programme responsible for ensuring that the agency work effectively and co -operates successfully with partner organizations.

The management board consists of the following members

- 1 representative of each of the 28 EU member states
- 2 representative of the European Commission
- 2 representative of the European Parliament
- 2 representative of Patient's organizations
- 1 representative of Doctor's organizations
- 1 representative of the Veterinarian's organizations

In addition to the above members, it also has one observer each from Iceland, Liechtenstein and Norway. Board members are appointed for 3 years term, which may be renewed

b) Executive director

Executive Director is the legal representative of the agency. Responsible for all operational matters, staffing issues and drawing up the annual work programme.

c) Agency staff

The Agency's staff support the Executive director in carrying out his responsibilities, including administrative and procedural aspects of EU law related to evaluation and safety monitoring of medicines in the EU.

d) Scientific committees

EMA has 7 scientific committees that evaluate medicines along their life cycle from early stages of development, through marketing authorization to safety monitoring once they are on the market. They are:

1) Committee for medicinal products for human use (CHMP)
2) Pharmacovigilance Risk Assessment Committee (PRAC)
3) Committee for Medicinal Products for Veterinary Use (CVMP)
4) Committee for Orphan Medicinal Products (COMP)
5) Committee on Herbal Medicinal Products
6) Committee for advanced Therapies (CAT)
7) Paediatric Committee (PC)

Benefits

Pool resources and co-ordinate work to regulate medicines efficiently and effectively.Reduces the administrative burden through centralized authorization procedure.

Exchange of information on important issues like safety of medicines.

European Commission: (EC)

A) Introduction

The European Commission plays an important role in the regulation of medicines in the EU. On the basis of scientific assessments carried out by EMA, it grants or refuses, changes or suspends marketing authorizations for medicines that have been submitted via the centralized procedure. It can also take EU-wide action when a safety issue has been identified for a nationally authorized product and when harmonized regulatory measures in all MSs are considered necessary following assessment by EMA's PRAC.[21]

The European Commission can also take action concerning other aspects of medicine regulation:

i) **Right of initiative** – it can propose new or amended legislation for the pharmaceutical sector;
ii) **Implementation** – it can adopt implementing measures as well as oversee the correct application of EU law on pharmaceuticals;
iii) **Global outreach** – it ensures appropriate collaboration with relevant international partners and promotes the EU regulatory system globally.

B) Establishment

It was established in the year 1958 in Brussels (Belgium). It consists a team of commissioners; one from each EU country.

C) History

It is the principal executive body of EU. At the beginning, each community had its own executive body. High authority for the European coal and steel community (1951) and a commission for each of the two communities set up by the treaty of Rome in 1957, the EEC and Euratom. These were merged into a single EC on 8 'April, 1965 by the merger Treaty.

D) Role of EC

Promotes the general interest of the EU by proposing and enforcing legislation as well as by implementing policies and the EU budget.

E) Composition

Political leadership is provided by a team of 28 Commissioners (one from each EU country)

led by the Commission President, who decides who is responsible for which policy area.
The College of Commissioners, includes the President of the Commission, his seven Vice-Presidents, including the First Vice-President, and the High-Representative of the Union for Foreign Policy and Security Policy and 20 Commissioners in charge of portfolios.

Heads of Medicines Agency: (HMA)

A) Introduction

The Heads of Medicines Agency (HMA) is a network of the heads of the National Competent Authorities (NCA) whose organizations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area.

The HMA co-operates with the European Medicines Agency (EMA) and the European Commission in the operation of the European medicines regulatory network and it is a unique model for cooperation and work sharing on statutory as well as voluntary regulatory activities.[22]

B) History

It was established in 1995 with a first full meeting took place in Amsterdam in February, 1996. Initially the agency is only responsible for the regulation of medicines for human use.

In February 1998, a parallel group bringing together the Heads of Agencies responsible for medicines for veterinary use.

In 2000, two groups started organizing joint meetings.

Since 2004, these activities have been integrated under the umbrella of HMA.

C) Main activities

- Addresses key strategic issues for the network, such as the exchange of information, IT developments and sharing of best practices.
- Focuses on the development, co-ordination and consistency of the European medicines regulatory system.
- Ensures the most effective and efficient use of resources across the network. Thisincludes developing and overseeing arrangements for work-sharing.
- Co-ordinates the mutual recognition (MRP) and decentralized procedure (DCP).

D) Membership

It comprises of about 46 NCA'S responsible for the regulation of human/veterinary medicines.46 NCA'S represents the 28 EU member states and 3 additional EEA members.

- ✓ 15 have responsibility for human medicines.
- ✓ 14 are purely responsible for veterinary medicines
- ✓ 17 are joint veterinary and human agencies
- ✓ Some of them have responsibility for pricing and reimbursement of human medicines.
- ✓ 22 have joint responsibility of medicines and medical devices. All are accountable under the National Governments.

Co-ordination Group for Mutual Recognition and DecentralisedProcedures for Human: (CMDh)

A) Introduction

The CMDh started its activities in November, 2005 replacing the informal Mutual Recognition Facilitation Group (MRFG), which was in operation over 10 years to co-ordinate and facilitate the operation of MRP.

It was setup in directive 2004/27/EC for the examination of any question relating to marketing authorization of a medicinal product in two or more member states in accordance with MRP/DCP. The task of CMDh was substantially extended in 2012 by directive 2010/84/EC, amending directive 2001/83/EC as regards Pharmacovigilance(PV).[21]

B) Specific tasks laid down in the legislation

1) Aim to solve disagreements on the grounds of a potential serious risk to public healthbetween member states involved in MRP/DCP.
2) Examination of questions related to Pharmacovigilance.
3) Examination of questions related to variations.
4) Laying down the yearly list of medicinal products for which harmonized summary ofproduct characteristics should be drawn up.

***C)* To fulfil the above tasks CMDh establishes working parties/working groups**

- Process improvement working party
- Joint CMD/CHMP/CVMP/EDQM working group on ASMF procedures.
- Joint CMD/EMA working party on variation regulation
- Joint CMDh/EMA working party on paediatric regulation

- Working party on PV procedures work sharing
- Joint CMDh/GCP inspectors working party
- Communication Tracking System(CTS) working group

The CMDh ids composed of one representative per member state and Norway, Iceland and Liechtenstein, appointed for arenewable period of three years. The European Commission participates on a regular basis as an observer. Observer status can be granted in line with the CMDh rules of procedure to other institutions.

The chairperson of the coordination group is elected by and from amongst its members for a period of three years, renewable once. The Vice-chairperson shall be appointed from among the members of the coordination group by the Member State which has the presidency of the Council of the European Union for the duration of the term of the presidency. The coordination group meets normally once a month at the EMA.

National Competent Authorities: (NCA's)

Table 6

Austria (AT)	Austrian medicines and medical devices agency
Belgium (BE)	Federal agency for medicines and health products
Bulgaria(BG)	Bulgarian drug agency
Croatia(HR)	Croatian agency for medicinal products and medical devices
Czech Republic(CZ)	State institute for drug control
Denmark(DK)	Danish medicines agency
Estonia(EE)	State agency of medicines
Finland(FI)	Finnish medicines agency
France(FR)	The French national agency for medicines and health products safety
Germany(DE)	Federal institute for drugs and medical devices
Greece(EL)	National organization for medicines
Hungary(HU)	National institute of pharmacy and nutrition
Iceland(IS)	National institute of pharmacy and nutrition
Italy(IT)	Italian medicines agency
Ireland(IE)	Health products regulatory authority
Latvia(LY)	State agency of medicines of Latvia
Liechtenstein(LI)	Office of health /Medicines control agency
Lithuania(LT)	States medicines control agency
LuxemBorg(LU)	Ministry of health
Malta(MT)	Medicines authority
Netherlands(NL)	Medicines evaluation board
Norway(NO)	Norwergian medicines agency
Poland(PL)	Chief pharmaceutical inspectorate
Portugal(PT)	National authority of medicines and health products

Romania(RO)	National agency for medicines and medical devices
Slovakia(SK)	State institute for drug control
Slovenia(SI)	Javna agencija republike slovenje za zdravilla in medicinske pripomocke
Spain(ES)	Spanish agency of medicines and medical devices
Sweden(SE)	Medical products agency
United Kingdom(UK)	Medicines and healthcare products regulatory agency

Api filing requirements

There are two different procedures in EU.

I. European drug master file

In Europe, Drug Master File is known as Active Substance Master File (ASMF) or European DrugMaster File (EDMF).[23]

Active Substance Master File (ASMF) or European Drug Master File (EDMF)

Active substance Master File (ASMF) is only applicable to Active Substance (new or pharmacopoeial). Active Substance Master File is also known as "European Drug Master File (EDMF)". Active Substance Master File (ASMF) is to allow valuable confidential intellectual property or know-how of the manufacturer of the Active Pharmaceutical Ingredient (API) to be protected, while at the same time allowing the Applicant or Marketing Authorization (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance.

Content of the active substance master file

The Scientific information in the ASMF is divided into two separate parts:

i. The Applicant's Part (AP) or Open Part and
ii. The Restricted Part (RP) or Closed Part.

The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF holder regards as confidential. It is emphasized that the AP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the ASMF holder. The RP may contain the remaining information, such as detailed information on the individual steps ofthe manufacturing method (reaction conditions, temperature validation and evaluation data of critical steps) and the quality control during the manufacture of the active substance. The applicant's ("open") part of the ASMF should be included in section 3.2.S of the Quality documentation presented in the CTD-format. The active substance manufacturer's restricted

("closed") part of the ASMF should follow the structure of Module 3.2.S of the CTD. A separate Quality Overall Summary for the information included in the active substance manufacturer's restricted ("closed") part should also be provided, as part of the ASMF. When an ASMF is provided as part of a new application for which the Quality data are submitted in the EUCTD format, the complete ASMF (open and closed part and the Quality Overall Summary on the ASMF) must also be presented in the EU-CTD format.

Overview of ASMF Contents

Table 7

	CTD Format	Applicant'spart	RestrictedPart
3.2.S.1	General Information	×	
3.2.S.1.1	Nomenclature	×	
3.2.S.1.2	Structure	×	
3.2.S.1.3	General properties	×	
3.2.S.2	Manufacture	×	×
3.2.S.2.1	Manufacutre (s)	×	
3.2.S.2.2	Description of Manufacturing Process and Process controls	**(a)**	**(b)**
3.2.S.2.3	Control of Materials		×
3.2.S.24	Control of Critical steps and intermediates	**(c)**	**(d)**
3.2.S.2.5	Process validation and /or Evaluation		×
3.2.S.2.6	Manufacturing Process Development		×
3.2.S.3	Characterisation	×	
3.2.S.3.1	Elucidation of structure and othercharacterstics	×	
3.2.S.3.2	Impurities	×	**(e)**
3.2.S.4	Control of drug substances	×	
3.2.S.4.1	Specification	×	
3.2.S.4.2	Analytical Procedure	×	
3.2.S.4.3	Validation of Analytical Procedure	×	
3.2.S.4.4	Batch analysis	×	
3.2.S.4.5	Justification of Specification	×	**(f)**
3.2.S.5	Reference standards or materials	×	
3.2.S.6	Container closure system	×	
3.2.S.7	Stability	×	
3.2.S.7.1	Stability overall summary	×	
3.2.S.7.2	Post approval stability protocol and stabilitycommitment	×	
3.2.S.7.3	Stability data	×	

a) Flow chart and short description is regarded as sufficient, if detailed information is presented in the Restricted Part. However, full validation data on the sterilization process maybe requested in the Applicant's Part (in cases where there is no further sterilization

of the final product).

b) Detailed information.

c) As far as the information is also relevant for the Applicant/MA holder.

d) As far as the information is related to the detailed description of the manufacturing processand as far as this information is not relevant for the Applicant/MA holder.

e) In so far as the information is related to the detailed description of the manufacturing process and in so far as the ASMF holder sufficiently justifies that there is no need to control these impurities in the final active substance.

f) As far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

(< From active substance master file holder on headedpaper>)

Template letter of access

Address of Competent Authority/EMA] [Date]

Number of Active Substance Master File:< EU/ASMF/XXXXX or National ASMF reference number> Name of Active Substance:

Internal API Code (if applicable):

Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby authorizes the to refer to and review the above mentioned Active Substance Master File in support of the following Marketing Authorization Application(s) or Marketing Authorization Variation(s)6 submitted by [Name of Marketing Authorization Holder/Applicant] on [planned date of submission]: [Name of product7 and Marketing Authorization number (if known)]

[Name of Applicant or Marketing Authorization holder]

The aforementioned Active Substance Master File holder commits to ensure batch to batch consistency and to inform [Name of Marketing Authorization Holder/Applicant] and Competent Authority/EMA of any change in the Active Substance Master File.

The aforementioned Active Substance Master File holder hereby is informed of and accepts that the EEA National Competent Authorities, the EMA including all CHMP and CVMP Members and their experts, and the Certification of Substances Division of the European Directorate for the Quality of Medicines & Healthcare may share the assessment reports of the above mentioned Active Substance Master File amongst themselves.

Signature for the Active Substance Master Fileholder [Name and function]

[Signature]

(< From active substance master file holder on headed paper>)

Template Submission Letter and Administrative Details for documents relating to an ActiveSubstance Master File (ASMF)8

From:<ASMF Holder name>

<ASMF Holder address>

<ASMF Holder address>

<ASMF Holder <Post code>Town>

<ASMF Holder Country>

To: < Name and Address of Competent Authority>

<Date>

<Reference>

Subject: Submission of documents relating to an ASMF

For <Name of Active substance >- <EU/ASMF/XXXXX or national ASMF reference number>

Dear Sir or Madam:

This active substance master file is submitted in relation to the following product

Medicinal Product	<Name of the Medcinal product>
Allocated procedure number	<EMEA/H/C/Product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing application/Authorization Reference>
(Intended)Submission date of the marketing authorization (or) variation(if known)	<DD/MM/YYYY>

Yours faithfully,

<Signature of authorized contact person>

<Name, address and position in company>

Administrative details for documents relating to an Active Substance Master file (ASMF)[1]

This submission letter should be used for an Active Substance Master File to be assessed in conjunction with a marketing authorisation application or variation for medicinal product for

human/veterinary use, using either a national or mutual recognition or decentralised or centralised procedure.

This submission is also sent to:	**Rapporteur**
(as applicable)	Co-Rapporteur
	All CHMP/CVMP members, as appropriate
	RMS
	All CMS
	<National Competent Authority> only[2]
ASMF reference number	<EU/ASMF/XXXXX[3] or national ASMF Reference number[4]>
ASMF holder's version (as included in	Applicants part:
this submission)	Version [version number]/date (dd-mm-yyyy)
	Restricted part:
	Version [version number]/date (dd-mm-yyyy)
Active substance name	<INN, common name> (+ salt/water content when applicable)
Active Substance Manufacturer's internal API code (if applicable):	<API internal code>
Additional information (as applicable, e.g. different route of synthesis, grade)[5]	

1. It is mandatory to complete all information fields
2. For ASMFs used in national marketing authorisations only
3. EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA
4. The national ASMF reference numbers is allocated by the Competent Authority and shouldbe used for national Marketing Authorisations only or when EU/ASMF reference number isnot allocated
5. Applicable when an ASMF holder has more than one ASMF for the same active substance.
6. All companies involved in the manufacture of the active substance, including quality control in process testing sites, intermediate manufacturers, milling and sterilisation sites should belisted in separate boxes.
7. A Data Universal Numbering System (D-U-N-S) for all manufacturing sites should be provided,if registered. The D-U-N-S system was developed by Dun & Bradstreet (D&B) which assigns unique digit numeric identifier to a single business entity. It is used in this case to facilitatethe identification of manufacturing sites outside of EEA
8. Latitude (S or N) and Longitude (E or W) expressed in Degrees Minutes Seconds to 1 decimal place (Alternatively it can be expressed in Degrees to at least 5 decimal places or

Degrees Minutes to at least 3 decimal places). If not main entrance, specify site.

9. From 1 January 2010, the mandatory format in the Centralised Procedure for applicationsfor Human medicinal products in electronic submissions is eCTD only.
10. For ASMFs used in applications for Veterinary medicinal products only
11. For ASMFs used in applications for Veterinary medicinal products only
12. In the Centralised Procedure (applications for Human medicinal products) paper submissions can be accepted as a transitory measure only. ASMF Holders are strongly encouraged to move to eCTD when possible; paper submissions will not be accepted after submission of a first eCTD sequence.
13. see Annex 2
14. Only where the ASMF has not been submitted in (V)NeeS or eCTD format
15. For an ASMF provided in the CTD format for applications for Veterinary medicinal products

Submitted Documents	Letter of Access[13] A copy of the Expert's curriculum vitae QOS or detailed and critical summary, as appropriate Table of Changes (only for submission of an update to a currently authorised ASMF) A copy of the proposed ASMF holder's active substance specification (3.2.S.4.1 or part 2.C.1.1, as appropriate)[14] A copy of the ASMF Deficiency Letter sent by Competent Authority/EMA (only for submission of response documents) Correlation table15 for CTD:NtA formats
	paper submission and other electronic format[12]
Number of Volumes of PaperCopy	<Number>
Number of Media Units	<Number>

ASMF Holder	<ASMF Holder name> <Full ASMF Holder administrative address> <Country> Contact person: <name> Telephone: <telephone No.>e-mail:<e-mail>
Active Substance ManufacturerManufacturing site(s)[6]	<Active substance manufacturer name> <Manufacturing site address(es)> <Country> <D-U-N-S number[7]> <GPS (WGS 84) coordinates of the site[8]> Contact person: <name> Telephone: <telephone No.>e-mail:<e-mail>
Submission Format	Ectd[9] <sequence No.>

	[Related Sequence <Related sequence No.>] History of the sequences (Sequence Tracking Table) is attached (V)NeeS CTD[10]NtA[11]

(< From active substance master file holder on headed paper>)

Template withdrawal of access letter

[Address of CompetentAuthority/EMA] [Date]

Number of Active Substance Master File:

<EU/ASMF/XXXXX>[16] or <National ASMF Reference number[17]>

Name of Active Substance:

InternalActive API Substance Code

Master File holder:

(if [name and applicable):address]

The aforementioned Active Substance Master File holder hereby informs the <name of National Competent Authority> <EMA including all CHMP and CVMP Members and their experts> that they no longer wish the above Active Substance Master File to be used in support of the following Marketing Authorisation Application,[18] held by [Name of MarketingAuthorisation Holder/Applicant]:

Medicinal product	<Name of the medicinal product>[19]
Allocated procedure number (as applicable)	<EMEA/H/C/product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing Application/Authorisation Reference>

The aforementioned Active Substance Master File holder hereby confirms that they have previously informed [Name of Marketing Authorisation Holder/Applicant] of this decision in line with the terms of their supply agreement.

Active Substance manufactured in accordance with the above Active Substance Master File will no longer be supplied after [supply agreement termination date],[16] EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA[17] The national ASMF reference numbers is allocated by the Competent Authority and should be used for national Marketing Authorisations only or when EU/ASMF reference number is not available[18] Separate Letters of Withdrawal should be submitted for different Marketing Authorisation Holders /

Applicants[19] If a Marketing Authorisation has not been granted for the product and an invented name not agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorisation Holder name'

Replacement of the Active Substance Master File by Certificate of Suitability, [CEP no].
A copy of the Certificate of Suitability is attached to this letter Signature of the Active Substance Master File holder [Name and function][Signature]

II. Certificate of Suitability: (CEP)

CEP is applicable to Pharmacopoeial substances only (active substance or excipient). The manufacturer of a substance will be able to provide proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia by means of a certificate of suitability granted by the certification secretariat of the European Directorate for the Quality of Medicines (EDQM). To apply for a certificate a manufacturer will submit a detailed dossier which may contain confidential data.

The certificate of suitability certifies that by applying the relevant monographs of the European Pharmacopoeia, it is possible to check whether or not the quality of the substance is suitable for use in medicinal products. This procedure is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European Pharmacopoeia Commission.[24]

This guidance is given in Resolution AP-CSP (07) 1 Public Health Committee (CD-P-SP)(Partial agreement), Council of Europe. It was established in the year 1994. It is applicable for:

- Existing active substance described in Ph. Eur or Pharmacopoeia of member states
- Substances produced by fermentation as indirect gene products, which are metabolites of micro organisms, irrespective of whether or not the micro organisms have been modified by traditional procedures or r-DNA technology and products with risk of transmitting agents of animal spongiform encephalopathy(TSE).

The procedure will not applicable for direct gene product (proteins), products obtained from human tissues, vaccines and blood product and preparation.

Objective

The manufacturer of a substance will be able to provide proof that the quality of the substance issuitably controlled by the relevant monographs of the European Pharmacopoeia by means of a certificate of suitability granted by the certification secretariat of the European Directorate for theQuality of Medicines (EDQM).

Scope

The following procedure is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European Pharmacopoeia Commission:

- Organic or inorganic substances (active or excipients), manufactured or extracted.
- Substances produced by fermentation as indirect gene products, which are metabolites of microorganisms, irrespective of whether or not the microorganisms have been modified by traditional procedures or r-DNA technology (see the monograph Products of Fermentation).
- Products with risk of transmitting agents of animal spongiform encephalopathies (TSE).

CEP Procedure

The procedure for the certification of suitability will consist of the following steps:

A. Submission of the Dossier
B. Acknowledgement of Receipt
C. Designation of Assessors
D. Assessment
E. Notification of the Decision
F. Follow Up to Certification of Suitability

Documents required

- A copy of Dossier in English (preferably) or French according to the CTD format the relevant part of the Quality Overall Summary.
- A application form duly filled in together with samples of commercial batches and fees.

For Product bearing risk of TSE, Application cab be for special monograph or for general monograph and for which no special monograph is there. TSE – risk evaluation documents are to be supplied. Total time period for procedure is 21 months (min 6 months, max 6 years) with 2 or 3 request for additional info for the majority of the applications. A certificate of

Suitability is valid for 5 years and it is the responsibility of the holder of the certificate to ask for its renewal in due time, at the latest 6 months prior to expiry date. Late request lead to a gap between the expiry date of the certificate and the approval of the request for renewal, during which no valid certificate would be available. CEP, if renewed once, is valid for an unlimited provided if is kept up to date by the holder.

Fee structure

Table 8

Reference	Item	Fee(€) euros
New Application		
CEP 028	Simple chemical certificate	5000
CEP 027	Simple TSE or herbal certificate	3000
CEP 026	Double certificate (chemical + TSE) *	8000
CEP 025	Certificate for chemical purity and sterility	8000
CEP 024	Certificate for chemical purity and sterility+ TSE**	9000
***In the case of TSE supported by a CEP the fees are only 5000 € ** In the case of TSE supported by a CEP the fees are only 8000 €**		
Revisions for Certificates		
CEP 09	Notification	1000
CEP 05	Minor revision	1500
CEP 019	Grouped revision (affecting several dossiers)	2000
CEP 006	Transfer of holdership	1500
CEP 020	Major revision (may include minor changes and notifications)	2000
CEP 004	Renewal	1500
CEP 015	Evaluation of sterility data	3000
Technical Advice		
CEP 011	Technical advice	1000
Inspections		
CEP 016	Inspection requested by company and approved by EDQM	9000
CEP 023	Inspection or re-inspection decided by EDQM (4 days)	6500
CEP 002	Inspection or re-inspection decided by EDQM (3days)	5000
CEP 021	Inspection or re-inspection decided by EDQM (2 days)	3500
CEP 022	Inspection or re-inspection decided by EDQM (1 day)	2000
INS 003	Travel and subsistence expenses during an inspection in Asia	6000
INS 004	Travel and subsistence expenses during an inspection in Europe	800
INS 005	Travel and subsistence expenses during an inspection in else where	4500

CEP Advantages

It is valid for 5 years.

It is a Centralized approval of quality by EDQM. It eliminates the need of filingASMF/EDMF

in individual member states involved in MRP/DCP Procedures.

Marketing authorization procedures

Every country has its basic legislation concerning medicinal product for human use. The marketing authorization of the product is granted by the competent health authority. The marketing authorization of the respective drug is granted and renewed on the basis of the favourable risk- benefit balance which has to maintain throughout the entire life cycle of the medicinal product.[25] The life cycle of the medicinal product can be described as;

- Development, corresponding to the pre-submission phase.
- Marketing (includes Marketing routine production)
- Discontinuation of marketing, which may correspond to the expiration of the marketing authorization.

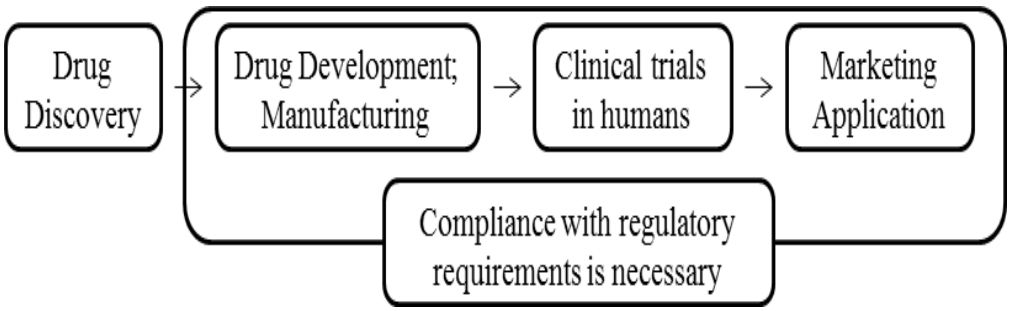


Figure 4

Application types

The legal requirements and the procedures for making an application for a marketing authorization are set out in Directive 2001/83/EC and in Regulation (EC) No 726/2004.[25] Basic Requirements :

- Continuous update of marketing authorization
- Standardized nomenclatures and quality standards
- Standard Terms
- Evaluation of the potential environmental risk

Types of applications for eu marketing authorization

Table 9

Class	Details	Legal type
Full dossier	Contain complete CTD modules	Article 8(3)
Generic	Pure generic application	Article 10(1)
Generic, additional data	Hybrid	Article 10(3)
Bio Similar	Generic biotech products	Article 10(4)

Bibliographic application, Well established use	Pre-clinical and Clinical data	Article 10(a)
Fixed combination products	Pre-clinical and clinicaldata Combination	Article 10(b)
Informed consent	Innovators generic product (Duplicatedossier)	Article 10(c)

Marketing authorization application format

A) EU-Common technical document

It is effective from 1st july, 2003. The CTD is an internationally agreed format preparation of well- structured applications to be submitted to regulatory authorities in the ICH region of Europe. The CTD gives no information on the content of a dossier, but provides for a harmonized format of presentation of the necessary data to support the application. It is organized into five modules:

1) Module 1: Region specific
2) Module 2: Summaries
3) Module 3: Quality
4) Module 4: Non-Clinical
5) Module 5: Clinical

B) e-CTD

From 1 October 2016 only eCTDs compliant with EU M1 v3.0 or EU M1 v3.0.1 and validation criteria v6.1 are accepted. From 1 April 2017 only eCTDs compliant with EU M1 v3.0.1 and validation criteria v6.1 are accepted. Where an e-CTD submitted, the paper CTD remains the formal submission and therefore both paper and electronic submissions must comply fully with the common technical document as regards presentation and content of the dossier. In case of e CTD submission, 2 copies of the eCTD should be provided to the EMEA. The latest version is of ICH M2 e-CTD.

Procedures and Applications for marketing authorisation of medicinal products

In general there are **4** types of marketing authorization for the drug product to enter into European Union drug market. They are as follows:

1) Centralized Procedure
2) National Procedure
3) Mutual Recognition Procedure
4) Decentralized Procedure

1) Centralized procedure

Regulation (EC) NO. 726/2004 of the European Commission and of the council of 31 March 2004 ("the Regulation") lays down a centralized Community procedure for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorization allowing direct access to the single market of the Community.

A marketing authorization granted under the centralized procedure is valid for the entire Community market, which means the medicinal product may be put on the market in all Member States.

New Active Substances – "mandatory scope":

Applications for medicinal products containing a new active substance2 must use the centralized procedure in accordance with Article 3(1) and point 3 of the Annex to the Regulation, when such substance has not been authorized in the Community before 20 November 2005 and for which the therapeutic indication is the treatment of:

- Acquired immune deficiency syndrome,
- Cancer,
- Neurodegenerative disorder,
- Diabetes

As of 20 May 2008, the centralized procedure will also become mandatory for medicinal products containing a new active substance for the treatment of auto-immune diseases and other immune dysfunctions and viral diseases

Other Medicinal Products- "Optional Scope":

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure.

In accordance with Article 3(2) of the Regulation, applications for the following categories of medicinal products may, at the request of the applicant, be accepted for consideration under the centralized procedure, when the applicant shows that:

a) A new active substance (or)
b) The medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization for the medicinal product is in the interests of patients at Community level.

- ❖ Multiple/duplicate or informed consent or generic applications from the same or a different marketing authorization holder for a medicinal product with an active substance(s) already authorized via the centralized procedure, have 'automatic' access to the centralized procedure.

- ❖ Generic applications of medicinal products authorized via the centralized procedure may be authorized via the centralized procedure. Alternatively, they may be authorized by the competent authorities of the Member States through a national, mutual recognition procedure or decentralized procedure provided that the conditions, laid down in Article 3(3) of the Regulation are met (e.g. same summary of product characteristics, same name in all the Member States.

Procedure for submission of marketing authorisation application

Pre-submission

At least seven months before submission, applicants should notify the EMA of their intention to submit an application and give a realistic estimate of the month of submission. In that notification applicants should include:

- A draft summary of product characteristics;
- A justification of the product's eligibility for evaluation under the centralized procedure (if not already requested at an earlier stage);
- In case of a product falling under the scope of Article 3(2), a concise summary document of preferably maximum 2 pages stating why the product should qualify forthe granting of a marketing authorization through the centralized procedure;
- An indication on the number of strengths / pharmaceutical forms / pack sizes (if already known);
- The proposed legal basis of the application according to Articles 8(3), 10, 10a, 10b or 10c of Directive 2001/83/EC;
- In case of 'generic' or 'bio-similar' applications, details of the proposed Reference medicinal product used throughout the quality, safety and efficacy development programme
- if appropriate, a statement on the appropriateness of the granting of a marketing authorization under exceptional circumstances (in accordance with Article 14(8) of the Regulation);
- if appropriate, a statement on the intention to request an accelerated assessment procedure

(in accordance with Article 14(9) of the Regulation);

- If appropriate, a statement on the intention to request a conditional marketing authorization (in accordance with Article 14(7) of the Regulation);
- Scientific advice received in the past in accordance with Article 57(1)(n) of the Regulation;
- A Statement as to whether orphan designation is granted / pending for the medicinal product;
- A proposed classification for the supply of the medicinal product;
- If appropriate, their intention to present a Active Substance Master File for active ingredient(s) prepared in accordance with the guideline on the European Active substance master file; if appropriate, their intention to present any existing Vaccine Antigen Master File (VAMF) or Plasma Master File (PMF) Certificates in the application;
- Proposed Invented Name(s);
- A reference to any request for a CHMP Opinion on compassionate use, which may have been or will be submitted or for which a CHMP Opinion has already been adopted (in accordance with Article 83(4) of the Regulation);
- Details of compliance with the requirements of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, if relevant;
- The details of proposed manufacturing and batch release arrangements of finished product and active substance manufacturing.
- Whether the quality dossier presents enhanced product and process understanding, and novel manufacturing or control approaches are employed, such as Design Space concepts and Process Analytical Technology (PAT);
- Any request for total or partial fee exemptions;
- An indication of any regulatory issues or difficulties already identified which may require clarification or detailed consideration.

When an applicant decides to apply to the EMA for the drug product authorization then at least seven months before the submission of application, the applicant should notify the EMA of their intention to submit an application. So, the applicant will have the opportunity to meet the EMA's product team in person in a Pre- Submission meeting where the procedural, regulatory and legal advice will be provided to the applicant.

The applicant's request for eligibility for evaluation via the Centralized Procedure, together

with a justification and other documents is presented to all CHMP [Committee for Medicinal Products for Human Use] members. Following discussion at CHMP, the EMA informs the applicant whether the product is eligible for evaluation via the Centralized Procedure. Amongst the members of CHMP a Rapporteur and a Co-Rapporteur will be appointed for the purpose of scientific evaluation and to prepare an Assessment Report for the CHMP on the application. This Assessment report will be submitted to the CHMP and EMA on DAY 80 where a peer review will be done by the members of CHMP for the validity of Scientific/Regulatory conclusions. A list of Questions raised by the CHMP along with the conclusions and review of scientific data will be sent to the applicant on DAY 120. At this point EMA stops the clock for giving time to applicant for responding to the data with proper responses. After receipt of the responses from the applicant, the CHMP adopts a timetable for the evaluation of the responses. The EMA ensures that the opinion of the CHMP is given in additional 90 days.

After the positive opinion of CHMP, the applicant provides the EMA with final translations of the necessary documents in all EU languages and the clock resumes from this point. A draft decision will be prepared within fifteen days by the commission on the application, and then the medicinal product will be assigned by a Community registration number which will be placed on product's package if the authorization is granted.

Finally, within 30 days the EMEA transmits the CHMP opinion and other required documents to the European Commission, and the Members of the Standing Committee and to Norway and Iceland. The applicant may go for the other procedures like Mutual Recognition Procedure (MRP) or the Decentralized Procedure (DCP) if the product does not fall within the mandatory scopes of the Centralized Procedure (CP).

Product team

An EMA 'Product Team' will be set up for each medicinal product intended to be submitted through the centralized procedure. The Product Team consists of a Product Team Leader (PTL) and Product Team Members (PTM) nominated by the EMA. The applicant will be notified of the appointed PTL. The Product Team is responsible for the handling of all procedural aspects of the application, both in the pre- and post-authorization stage.

Payment of fees

The fee shall be due on the date of the administrative validation of the application.

The EMA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 days of the date of the said notification. The invoice will be sent to the billing address indicated by the Applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment.

The EMEA should receive the full application fee in Euro in accordance with Council Regulation (EC) No 297/95 as amended, net of all bank charges.

If the application cannot be validated, the EMA will issue an invoice on the date of the notification of the administrative non-validation to the applicant for an administrative charge to cover administrative costs.

Standard time table for the evaluation of a centralizedapplication

Table 10

Day	Action
1	Start of the Procedure
80	Receipt of the Assessment Report(s) or critique from Rapporteur and Co-Rapporteur(s) by CHMP members and EMA. EMA sends Rapporteur and Co-Rapporteur Assessment Report /critique to the applicant making it clear that it only sets out their Preliminary conclusions and that it is sent for information only and does not yet present the position of the CHMP.
100	Rapporteur, Co- Rapporteur, other CHMP members and EMA receive comments from members of the CHMP (incl. peer reviewers).
115	Receipt of the draft list of questions (including the CHMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur, as discussed with peer reviewers, by CHMP members and EMA.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA. Clock Stop. At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).
121	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.
150	Joint response Assessment Report from Rapporteur and Co- Rapporteur received by CHMP members and the EMA. EMA sends joint Assessment Report to the applicant making it clear that it only sets out their preliminary conclusions and that
	it is sent for information only and does not yet represent the position of the CHMP. Where applicable, Inspection to be carried out, EMA/QRD sub-group meeting of English product information with participation of the applicant.
170	Deadline for comments from CHMP members to be sent to Rapporteur and Co-

	Rapporteur, EMA and other CHMP members.
180	CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and /or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Submission of final inspection report to EMA, Rapporteur and Co-Rapporteur by the inspections team (at the latest by Day 180).
181	Restart the clock and oral explanation (if needed).
181 to 210	Final draft of English summary product characteristics, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMA and other CHMP members.
By 210	Adoption of CHMP opinion + CHMP Assessment Report (and Timetable for the provision of product information translations).
215 at the latest	Applicant provides the EMA with summary of product characteristics, Annex II, labelling and package leaflet and Annex A in the 20 languages (All EU languages including Norwegian). EMEA circulates draft translations to member states for review.
232 at the latest	Applicant provides EMA with final translations of summary of product characteristics, Annex II, Labelling and package leaflet in the 20 languages, taking account comments received from member states by Day 229.
By 237	Transmission of opinion and Annexes in all EU languages to applicant, Commission, and members of the standing committee, and Norway and Iceland.
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock- up of outer and inner packaging for each pharmaceutical from.

2) National authorization procedure

The competent authorities of the Member States are responsible for granting marketing authorizations for medicinal products which are placed on their markets, except for medicinal products which are authorized under Regulation (EC) No 726/2004 Inorder to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State. The Experts of the Agency assess the quality, safety and risk of the medicine. If these issues are in order a national authorization is granted.

But this procedure is stringently limited from 1 January 1998 to the early phase of mutual recognition (granting of the marketing authorization by the Reference Member State) and to medicinal products which are not to be authorized in more than one Member State.

3) Mutual recognition procedure

The legal provisions covering the mutual recognition procedure for human medicinal products are contained in Directive 2001/83/EC.

Both MRP and CP aim at facilitating across to a single market by relying on the principle of mutual recognition. Thus with the exception those medicinal products which are subject to the

centralized procedure (see Chapter 4 of the Notice to Applicants), a marketing authorization or the assessment in one Member State (the so-called reference Member State) ought in principle to be recognized by the competent authorities of the other Member States (the so-called concerned Member States. The mutual recognition procedure must be used for applications for marketing authorization for medicinal products in more than one member state.

The mutual recognition procedure is divided into following steps

1) National validation by the reference Member State
2) Preparation or update of assessment report by reference Member State (90 days)
3) Validation by the concerned Member States
4) Approval by the concerned Member States (90 days)
5) Discussion at the coordination group level, if needed
6) National Marketing Authorization step

The objective of this procedure is to obtain marketing authorizations in one or several Member States, when the medicinal product has already been granted authorization by at least one country in the European Community. In this case, the applicant requests one or more CMS(s) to mutually recognize the authorization granted by the RMS. If the marketing authorization in the RMS is based on an old dossier format, it is an obligation to update the dossiers before starting the MRP. The marketing authorization holder should submit an application to the competent authorities of the RMS and each of the CMS(s). Within 90 days of receipt of a valid application by the RMS, the RMS provides the Assessment Report, or if necessary, updates any existing one and sends it together with other documents to the CMS(s) and to the applicant. The RMS launches the clock after receipt of the Assessment Report and validation of the application by each of the CMS(s). Within 90 days, the CMS(s) recognize the decision of the RMS. Thirty days after the close of the procedure, the competent authorities of the CMS(s) adopt a decision and grant marketing authorization. Therefore, at the end of the MRP with a positive agreement, a national marketing authorization will be issued in each of the CMS(s).

Before submission of the application to the concerned Member State(s)

In accordance with Article 28(4) of Directive 2001/83/EC, all Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet, submitted for mutual recognition.

Both the reference Member State and the applicant are expected to react in a flexible manner. The marketing authorization holder should ensure that:

i) The product will be regarded as a medicinal product in all concerned Member States andthat it will not be regarded, for example, as a cosmetic, a food supplement, a medical device ora biocide;

ii) The product is falling under the scope of the mutual recognition procedure;

iii) The application including the three Overall Summaries and Overviews on Module 3, 4 and5 is updated appropriately (i.e. in accordance with relevant legislation);

iv) Either the clinical indications sought have been previously authorized for a medicinal product containing the same active substance in the concerned Member State(s) (or) adequate clinical data is available to support the claimed indications in the summary of product characteristics, package leaflet and labelling; (or) it is an application according to Article 14 of Directive 2001/83/EC (registration procedure forthe homeopathic medicinal products)

v) In the case of generic applications the requirements of Article 10(1) of Directive 2001/83/EC have been met, i.e. that there is a medicinal product which is or has been authorized in a Member State for the following period:

- For more than 6 or 10 years (i.e. the period of protection of Directive 2001/83/EC before amendment by Directive 2004/27/EC) in case the application for authorization of the reference product had been submitted before Directive 2004/27/EC started to apply;
- For not less than 8 years in case the application for authorization of the Reference product had been submitted after the date of transposition of Directive 2004/27/EC;

vi) The dossiers in the reference Member State and concerned Member States are the same;

vii) Variations or renewals to the original authorization have been authorized by the reference Member State in advance of the initiation of the procedure; and The final text of the approved summary of product characteristics, and that of the package leaflet and labelling, for information, in the national language of the reference Member State should be available, with appropriate translations and taking into account relevant guidelines.

In order to ensure a smooth procedure for this recognition, Member States have agreed to use the following procedure intended for clarification and dialogue.

Before initiation of the mutual recognition procedure, the reference Member State is requested to achieve and agree on a summary of product characteristics, package leaflet and

labelling through discussion with the applicant, which would take into account all existing national summaries of product characteristics, package leaflets and labelling for the medicinal product and for medicinal products with the same active substance which have been approved in earlier mutual recognition procedure and decentralized procedures.

Flow chart for the mutual recognition procedure

Table 11

Approx.90 days before submission to CMS	**Applicant requests RMS to update Assessment Report (AR) and allocateprocedure number.**
Day 14	Applicant submits the dossier to CMS. RMS circulates the AR including SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure.
Day 50	CMSs sends their comments to the RMS and applicant.
Day 60	Applicant sends the response document to CMSs and RMS.
Until Day 68	RMS circulates their assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A break-out session can be organized between 73-80.
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMD secretariat of the EMEA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points of disagreement submitted by CMS(s) arereferred to CMD(h) by the RMS within 7 days after Day 90.
Day 150	For procedure referred to CMD(h): If consensus is reached at the level of CMD(h), the RMS closes the procedure. If consensus is not reached at the level of CMD(h), the RMS refers the matter to CHMP for Arbitration.
5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and Labelling toCMSs and RMS.
30 days after close of procedure	Granting of national marketing authorizations in the CMSs subject to submission of acceptable translations.

4) Decentralized procedure

The decentralized procedure is to be used in order to obtain marketing authorizations in several Member States where the medicinal product in question has not yet received a marketing authorization in any Member State at the time of application.

The legal provisions covering decentralized procedure for human medicinal products are contained in Directive 2001/83/EC. The new DCP came into effect in the EU in 2005.

The procedure to be followed will depend upon whether it is a Member State or the marketing authorization holder which initiates the decentralized procedure.

The decentralized procedure is divided into five steps. They are as follows

- Validation step
- Assessment step I
- Assessment step II
- Discussion at the coordination group level, if needed
- National Marketing Authorization step

The objective of this procedure is to obtain marketing authorizations in several Member States, when no marketing authorization has been granted in the European Community. The applicant should send an application to the competent authorities of each of the Member States, where there is intent to obtain a marketing authorization. The applicant may designate a country to act as the Reference Member State (RMS). Selection of the RMS depends on many considerations including workload, previous experience, interests, and acceptance of the dossier by the RMS. The RMS will start the procedure after the application is determined to be complete by both the RMS and all the CMS(s). The RMS forwards a preliminary Assessment Report (PrAR) on the dossier to the CMS(s) and the applicant within 70 days. The CMS(s) is asked to give comments on the proposed national prescription status and to inform the RMS. On day 105, the RMS will forward all comments to the applicant and stops the clock if necessary, until the applicant prepares a response document. The RMS prepares a Draft Assessment Report on day 120 and may close the procedure if a consensus has been reached between the CMS(s) and the RMS. Otherwise, the CMS(s) has 90 more days to approve the Draft Assessment Report, and other documents. Competent authorities of the RMS and the CMS(s) adopt a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents. At the end of the Decentralized Procedure with a positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS(s).

Before submitting the application to the reference and concerned Member State(s)

In accordance with Article 28(4) of Directive 2001/83/EC, all Member States concerned shall approve the assessment report, the summary of product characteristics, package leaflet and label submitted.

Both the reference Member State and the applicant are expected to react in a flexible manner. The marketing authorization holder should ensure that:

i) The product will be regarded as a medicinal product in all concerned Member States andthat it will not be regarded, for example, as a cosmetic, a food supplement, a medical device ora biocide;

ii) The product is falling under the scope of the Decentralized procedure;

iii) The application including the three Overall Summaries and Overviews on Module 3, 4 and5 is updated appropriately (i.e. in accordance with relevant legislation);

iv) Either the clinical indications sought have been previously authorized for a medicinal product containing the same active substance in the concerned Member State(s) (or) adequate clinical data is available to support the claimed indications in the summary of product characteristics, package leaflet and labelling; (or) it is an application according to Article 14 of Directive 2001/83/EC (registration procedure forthe homeopathic medicinal products)

v) In the case of generic applications the requirements of Article 10(1) of Directive 2001/83/EC have been met, i.e. that there is a medicinal product which is or has been authorized in a Member State for the following period:

- For more than 6 or 10 years (i.e. the period of protection of Directive 2001/83/EC before amendment by Directive 2004/27/EC) in case the application for authorization of the reference product had been submitted before Directive 2004/27/EC started to apply;
- For not less than 8 years in case the application for authorization of the Reference product had been submitted after the date of transposition of Directive 2004/27/EC;

vi) The dossiers in the reference Member State and concerned Member States are the same.

Flow chart for the decentralized procedure

Table 12

Pre-Procedural step	
Before Day 14	Applicant discussions with RMS RMS allocates procedure number. Creation in CommunicationTracking System (CTS).
Day 14	Submission of the dossier to the RMS and CMS Validation of the application.
Assessment step I	
Day 0	RMS starts the Procedure.
Day 70	RMS forwards the preliminary Assessment Report (PrAR), SPC,PL and labelling to the CMSs
Until Day 100	CMSs send their comments to the RMS.

Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops clock to allow applicant tosupplement the dossier and respond to the questions.
Clock-off Period	Applicant may send draft responses to the RMS and agrees the date with the RMS submission of the final response. Applicant sends the final response document to the RMS and CMS within a recommended period of 3 months, which could be extended if justified.
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure.
Day 106-120	RMS updates PrAR to prepare Draft Assessment Report (DAR) draft SPC, draft labelling and draft PIL to CMSs
Day 120	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Assessment Step II	
Day 120(Day0)	If consensus not reached RMS sends the DAR, draft SPC, draft labelling and draft PIL to CMSs.
Day 145(Day 25)	CMSs sends final comments to RMS
Day 150(Day 30)	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Until Day180(Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification and prepare a short report for discussion at Coordination Group.
Until Day 205 (Day 85)	Breakout group of involved member states reaches consensus on the matter.
Day 210(Day 90)	Closure of the procedure including CMSs approval of assessment report, SPC, labelling and PIL or referral to Co-Ordination Group. Proceed to national 30 days step for granting MA.
Day 210(at the latest)	If consensus was not reached at day 210, points of disagreement will be referred to the Co- Ordination Group for resolution.
Day 270(at the latest)	Final position adopted by Co-Ordination Group with Referral to CHMP/CVMP for arbitration in case of unresolved disagreement.
National Step	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, Labelling and PIL to CMS and RMS.
Day 135/150/180/240	Granting of national marketing authorization in RMS and CMSs if no referral to the Co-Ordination Group. (National Agencies will adopt the decision and will issue the marketing authorization subject to submission of acceptable translations).
Day 300	Granting of national marketing authorization in RMS and CMSs ifpositive conclusion by the Co-Ordination Group and no referral to the CHMP/CVMP. (National Agencies will adopt decision and will issue the marketing authorization subject to submission of acceptable translations).

Data exclusivity

Data Exclusivity is a form of product exclusivity for medicinal products in Europe and market exclusivity is a related form of additional protection. The rationale for granting data ad market exclusivity is to compensate the innovator company for the investment it has put into developing the new medicinal product and to generate the data required to obtain MA. Regulatory approval for medicinal products requires applicants to provide information about the efficacy and safety of their product to regulatory authorities.[25]

Innovator company enjoys a period of "data exclusivity" during which their pre-clinical and clinical trials data may not be referenced in the regulatory filings of another company (generic company) for the same drug substance.

For MAA made before November, 2005 onwards, the period of data exclusivity varies from EU member state to member state and is either 6 or 10 years.

For MAA made from November, 2005 onwards, the period of data exclusivity in Europe has been harmonized as 8 years from the date of authorization in Europe. There is an additional period of 2 years of market exclusivity. This is the period of time during which a generic company may not market an equivalent generic version of the originators pharmaceutical product (although their application for authorization may be processed during this period. Such that they are in a position to market their product on the expiry of additional 2 year period).

An extra year of protection for new indications

- Under 'Old rules' data exclusivity lasted either 6 or 10 years.
- 'New Rules' follows an **8+2+1**year approach.
- During the First 8 years from the grant of the innovator company's Marketing authorization and data exclusivity applies.
- After the 8 years have expired, a generic company can make use of the pre-clinical and clinical trial data of the originator in their regulatory applications but still cannot market their product.
- Additional 1 year may be obtained in a number of circumstances. Such as, where innovator company is granted a MA for a significant new indication for the relevant medicinal product. In such situation, the generic company can only market their product after 11years from the grant of the innovator company marketing authorization.

Renewal

In accordance with Article 24 of Directive 2001/83/EC the marketing authorization may be renewed after 5 years on the basis of a re-evaluation of the risk/benefit balance by the competent authority of the authorizing Member State. Once renewed, the marketing authorization shall be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

Variations

Variations are nothing but the modifications requested by the applicant after the grant of a marketing authorization. The submission of variation applications makes sure that the dossier and the Summary of Product Characteristics(SPC) are always kept up to date. During the life cycle of a medicinal product, the modifications are repeatedly made to the dossier, which may be simple changes, such as a change in the manufacturing method or a change in a manufacturer (Type 1 variations) and also can be quite complex, such as the application for a new indication, where new clinical and pre-clinical data has to be presented (Type 2 variations).[25]

Type IA VARIATIONS (NOTIFICATIONS: "DO AND TELL")

Type IA and Type IAIN

In case of Type IA variations notification shall be submitted within 12 months from the date of implementation and in case of Type IAIN variations notification shall be submitted immediately after implementation. This type of variations does not have serious impact on quality, safety and efficacy of product.

Type IB: ("TELL, WAIT and DO")

Type IB Variations are processed in an efficient and timely manner. The quality of the submission and supporting documentation is responsibility of Marketing Authorization Holder (MAH) This type of variations also does not have any potential effect on the quality, safety and efficacy of product. But, without proper supporting documentation the case may beconsidered as Type II Variation.

Type II Variations

These types of variations have significant impact on quality, safety and efficacy of product and require prior approval before implementation. The 60 and 90-day time frames for

evaluation of procedure are maximum time lines thus allowing flexibility for shorter procedures in particular situations. In such cases MAH should contact to the RMS as soon as possible for proposed procedure.

Extension of a Marketing Authorization

A line extension is a change to a marketing authorization that cannot be classified as a variation. Line extension applications are examined in accordance with the procedure for the granting of a new marketing authorization.[25]

Examples of a line extension are:

- ✓ Application for a product with a new strength
- ✓ Application for a product with a new pharmaceutical Form
- ✓ The dossier of the line extension can partially refer to the dossier of the initial product.

Challenges faced by indian pharmaceutical industry while exporting of pharmaceuticals to europe

India Pharmaceutical Companies are key players in the space of generic market of global pharmaceutical sector and India is one of the important players of Pharma emerging market. The nature and diversity of the Indian pharmaceutical market, health care objectives and legal system pose unique challenges for pharmaceuticals sector in India. The diversity of the challenges are very complex, hence, Indian pharmaceutical sector have to face these challenges with more courage to emerge as one of the leading players in the world pharmaceutical market and to achieve progress in the health care.

The European Union (EU) is a unique partnership in which member states have mutual authority in certain policy areas and harmonized laws on a wide range of economic and political issues. The EU consists of 28 member states and European economic Area (EEA) is formed of 28 member states plus Norway, Iceland, Liechtenstein.

EU members share a customs union; a single market in which goods, services, people, and capital move freely (known as the “four freedoms”); a common trade policy; a common agricultural policy; and a common currency (the euro), which is used by 19 member states (collectively referred to as the “eurozone”).

The most prominent challenges in European Union with respect to Pharmaceutical exports are briefly outlined below:

1) Regulatory directive differentiations

Europe has different regulatory and quality requirements compared with the remaining stringent regulatory authorities. For instance, all products manufactured outside of Europe must undergo EU import testing according to Article 51 of Directive 2001 / 83 / EC to ensure that they are compliant with the specifications outlined in the marketing authorization application (MAA).

All drug products must be released onto the market within Europe by the Qualified Person (QP) to confirm that the products are fit for the intended purpose and have been manufactured as per cGMP standards. These two requirements are unique to Europe and it is a challenge for all third countries, which are exporting Pharmaceuticals to Europe.

The objective of the guidance on Qualified Person (QP) declaration is to emphasise the importance of providing a valid declaration, to harmonise the format for the declaration so as to enhance the efficiency of the regulatory process.[26]

5. SUMMARY

- Marketing authorisations require a QP declaration to confirm that the active substancehas been manufactured in accordance with Good Manufacturing Practice (GMP) for medicinal products for human and veterinary use, Part II: Basic Requirements for Active Substances used as Starting Materials.
- A QP declaration is required from each registered EEA manufacturer and Importer Authorisation Holder (MIAH) that uses the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinarymedicinal product.
- When more than one MIAH is involved, rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP.

The basis of the qp declaration

Audit

The QP declaration should be based on on-site audit of the active substance manufacturers of human and veterinary medicinal products. The audit cannot be replaced by GMP certificates from a relevant competent authority.

Scope

- With respect to the application of GMP for products for human use, ICH Q119, states, "Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the Drug Substance.
- The GMP requirement for Active Substance starts from the introduction of a starting material at all the manufacturing sites, including intermediate sites.
- For chemically synthesised active substances, the details of the suppliers of designated starting materials may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer's quality system for starting materials.

Application of QP Declaration

The QP declaration applies to all human and veterinary medicinal products. A QP declaration is required to be submitted with all applications for new marketing authorisations, renewals and submissions of quality variations, concerning changes (addition or replacement) to the manufacturer of a starting material and / or to the registered manufacturer(s) of the active substance, finished product or batch importation/certification sites.

If site changes are introduced during the regulatory review procedure, then a new declaration will need to be provided.

Format of QP Declaration Template

The format of the QP declaration template is in five parts (Parts A to E).

PART A: Concerned active substance manufacturing sites

- ✓ The name and address of each manufacturing site to be registered that is involved in the manufacture of the active substance should be stated, beginning from the first use of the designated starting material including intermediate sites.
- ✓ For EDQM CEPs, the MIAH should confirm with the active substance manufacturer, the names and addresses of all sites involved, including any intermediate manufacturing sites in case these are not openly declared on the CEP.
- ✓ The site address should be provided in detail to ensure that the site is accurate, e.g. where appropriate building numbers should be included in the address.

- ✓ In the case of an intermediate, which is itself an active substance and is supported by either an independent ASMF or CEP, the sites of manufacture for this intermediate should also be registered in the marketing authorisation and be the subject of a QP declaration.

PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

- ✓ Declarations are required from the QP of each registered EEA MIAH (using the active substance as a starting material and / or QP batch certification). When more than one MIAH is involved, it may be acceptable to provide a single declaration signed by one QP.
- ✓ The relevant MIAHs for which the QP declaration is applicable should be listed.
- ✓ The registered MIAH site, number and manufacturing activity should be provided

PART C: Basis of the declaration

An on-site audit was conducted and confirmed by completing the section (i) tick box in the template.

When an on-site audit is not practical (e.g. atypical actives), then they are considered as out of scope of the declaration. In some cases, a suitable quality system is expected to be applied by the Active Substance and finished Product manufacturers.

Section (ii) sites audited, auditors and date of audit

- ✓ The audit of the active substance manufactured at the site(s) may be completed either by MIAH(s) or by a third party body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s).
- ✓ The site that has been audited and the date of audit should be stated.

Section (iii) supplementary information

- ✓ Section (iii) refers to supplementary information that may be attached to the QP declaration to support a risk-based approach by the manufacturer in establishing priorities for its own audit programme.
- ✓ For example, results of inspection report(s) or GMP certificate(s) issued by EEA, Mutual Recognition Agreement (MRA) partners or other recognised authority together with other supporting information may be submitted. According to Article 46b(2)(b) of Directive 2001/83/EC human medicines include the written confirmation of GMP compliance from the competent authority of the exporting third country.

PART D: QP declaration

The QP in signing the QP declaration is confirming that these statements are correct and are the basis by which the regulatory submission may be approved.

The statements relate to the following components

QP responsibility

The signatory confirms that he or she is the authorised QP with specific responsibility for GMP compliance of the active substance manufacture and that audit reports and all other documentation relating to the QP declaration will be made available for inspection by competent authorities, if requested.

GMP compliance

The signatory confirms that the manufacture of the active substance complies with GMP, that this is based on an audit and that the audit outcome confirms compliance with GMP.

Audit

The signatory confirms, in the case of third part audit(s), that each contract acceptor has been evaluated and technical agreements are in place. The signatory also confirms, in all cases, that theaudits were conducted by suitably qualified and trained staff.

Responsibilities in the case of multiple MIAH(s)

The signatory confirms that the declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B and that a documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.

Part E: Name and signature of QP responsible for this declaration

The declaration is signed and the relevant details of the QP are provided (name, status, and MIAH name and number). The QP details should be consistent with those named within the relevant regulatory submission application form and/or the Manufacturing Authorisation (if applicable).

The typical QP Declaration format (EMA /334808/2014) is enclosed

Challenges faced

85% of Human Medicines available in Europe are manufactured outside Europe i.e, third countries. India is one of the third country exporting Human Medicines to the Europe. Some of

the Indian Pharmaceutical industries are not able to fulfill the requirements of cGMP especially when there is redefinition of starting material to Intermediate. Once cGMP requirements met, then only QP will sign the Declaration.

21 May 2014 EMA/334808/2014

Compliance and Inspections Department

Qualified Person's declaration concerning GMP compliance of the active substance manufacture "The QP declaration template"

Reference number

Name of Active Substance:

Part A: Concerned active substance manufacturing sites

Name and Address of Active Substance Manufacturing Site[1,2]	**Manufacturing Operation /Activity[3]**

1. List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material, include intermediate manufacturing sites / part–processing sites.
2. State the site name and address in detail, including the building numbers (if applicable).
3. For example – Full or partial manufacture of the active substance, micronisation.

Part B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

This QP declaration is applicable to the following registered MIAH(s), that use the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product, where the active substance is registered as a starting material and is manufactured at the sites listed in Part A:

MIAH Site	MIAH Number	Manufacturing Activity

Part C: Basis of QP Declaration of GMP Compliance

Please tick section (i), complete the table in section (ii) and, if applicable, add the supplementarysupporting information to section (iii).

(i) On-site audit of the active substance manufacturer(s)

(ii) Audit(s) of the active substance manufactured at the site(s) listed in PART A has/have been completed either by the MIAH(s) listed below or by a third party auditing body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s) as listed:

MIAH Site (or contract giver)	Auditing body (contract acceptor)	Site audited	Date of audit[4]

4 Justification should be provided if the date of last audit exceeds 3 years:

(iii) Supplementary supportive information (optional)

Results of inspections or GMP certificate(s) issued by EEA, MRA partners or other recognisedauthority together with other supporting information are attached.

Part D: QP declaration of GMP compliance

Summary of supporting information provided

I declare that

QP Responsibility

- I am a QP with specific responsibility for GMP compliance of the active substance manufactured at the sites listed in Part A and I am authorised to make this declaration.
- The audit report(s) and all the other documentation relating to this declaration of GMP compliance of the active substance manufacturer(s) will be made available for inspection by the competent authorities, if requested.

GMP Compliance

- The manufacture of the named active substance at sites given in Part A is in accordance with the detailed guideline on good manufacturing practice for active substances used as starting materials as required by Article 46(f) of Directive 2001/83/EC and Article 50(f) of Directive 2001/82/EC.
- This is based upon an audit of the active substance manufacturer(s).
- The outcome of the audit confirms that the manufacturing complies with the principlesand guidelines of good manufacturing practice.

Audit

- In the case of third party audit(s), I have evaluated each of the named contract acceptor(s) given in Part C and that technical contractual arrangements are in place and that any measures taken by the contract giver(s) are documented e.g. signed undertakings by the auditor(s).
- In all cases, the audit(s) was/were conducted by properly qualified and trained staff, in accordance with approved procedures.

Responsibilities in the case of multiple MIAH(s)

- This declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B;
- A documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.

Part E: Name and Signature of QP responsible for this Declaration

This declaration is submitted by

Signatory **Print name** **Date** **Status (job title)**	**MIAH Site_** **MIAH number**

2) Marketing Authorisation Application(MAA) submission

The MAA submission strategy in Europe can present challenges in itself because of the different filing routes (Centralized and decentralized procedures, Mutual Recognition procedure and National Procedure), and the various options and constraints that must be considered depending on the type of product and therapeutic indication.

The primary purpose of rules governing medicinal products is to safe guard the public health. Prior to the marketing of a medicinal product in Europe, Marketing Authorization procedures have to be approved.

Marketing authorizations procedures

There are different marketing authorization procedures for medicinal product to enter into the European market. They are:

1) Centralized procedure

Centralized procedure is valid for the entire market, which means that the medicinal product may be kept in all member states. According to Annex to Regulation (EC) No. 726/2004, the medicinal products which fall under the "Mandatory scope" i.e, article 3(1) are authorized in this procedure. Once the marketing authorization is granted it is valid for all member states. The medicinal products which fall under **mandatory** scope are categorized based upon the Therapeutic indication treatment. They are:

- Acquired immune deficiency syndrome
- Cancer
- Neurodegenerative disorder
- Diabetes

It is **optional** for other medicines according to the article 3(2) of the regulation the medicinal products. Optional scope applies for the following categories of medicinal products are:

- Containing new active substances for indications other than those stated in themandatory

scope; medicinal products that have a significant therapeutic, scientific or technical innovation; whose authorisation would be in the interest of public or animal health at EU level. The EMA is responsible for the evaluation, supervision and pharmacovigilance of medicinal products. CHMP is responsible for preparing the opinion of the EMA on any question relating to the evaluation of medicinal products for human use. The evaluation time for CP is246 days from the clock start time.

Advantages of CP

- Medicines are authorized for all EU member countries at the same time.
- Single Evaluation by European experts which facilitates quicker approval.
- Product information available in all EU languages at the same time.

Disadvantages of CP

- It is not applicable for all types of medicinal products.
- Only new and innovative medicines can only approve by this procedure.

2) National procedure

In the national procedure only one member state is involved. The evaluation of the application was done by the same member state. The evaluation time for an application of a national procedure varies from country to country.

Advantage of NP

This procedure is used based on the market potential in a particular country.

Once the product is approved by national procedure the MRP can be filed in those countries where the market potential is there.

Disadvantages of NP

Limited market.

3) Mutual recognition procedure

The regulation for Mutual Recognition procedure is laid down in the directive 2001/83/EC. When the national authorizations are requested for the same medicinal product in more than one member state and if the marketing authorization holder has already received a marketing authorization in one member state then the applicant can submit an application in concerned member state using this procedure. The time taken for the completion of MRP is 150 days.

Advantages of MRP

- Applicant can avoid the need to go through different national procedures in each country.
- Applicant can choose the RMS that will conduct the evaluation of drug product.

Disadvantages of MRP

- It oftens suffers from the disagreements between member states and causing thedelays in the procedure.
- For solving the disputes, it may waste the time and money of the applicant.

4) Decentralized procedure

The regulation for Decentralized Procedure is laid down in the directive 2001/83/EC. The main purpose of this procedure was to acquire marketing authorization in several member states at a time without prior marketing authorization approval. The applicant can submits the application in all member states to obtain the marketing authorization at the same time. It chooses one of the member state as the reference member state. The time taken for the completion of this procedure was 300 days.

Advantages

- Applicant avoids the need to go through different National Procedures in each country.
- It avoids the some of the disputes between the member states by involving each of the member state.

Disadvantages

- Applicant have to request one of the member state to acts as the RMS.

The Marketing Authorization must contain the summary of the product characteristics according to the article 11 of directive 2001/83/EC and the labelling, package leaflet according to the articles 54, 55, 59 and 63.

The legal requirements and the procedures for making an application for a marketing authorisation are set out in Directive 2001/83/EC and in Regulation (EC) No 726/2004.

A brief description of Articles referred in marketing authorization applications where applicable

- Article 8(3) of Directive 2001/83/EC; relating to the particulars and documents accompanied with the application;

- Article 10 of Directive 2001/83/EC, relating to generic medicinal products, "hybrid" medicinal products and similar biological medicinal products;
- Article 10a of Directive 2001/83/EC, relating to applications relying on well-established medicinal use supported by bibliographic literature;
- Article 10b of Directive 2001/83/EC, relating to applications for new fixedcombination of active substances in a medicinal product;
- Article 10c of Directive 2001/83/EC, relating to informed consent from a marketing authorisation holder for an authorised medicinal products.

3) Quality

European Commission (EC) has passed new mandatory regulations for APIs imported from outside the European Union. Under the new laws, which will come into effect on July 2013, APIs imported into the EU must comply with the good manufacturing practice (GMP) standards used by the EU, as stipulated by the International Conference for Harmonisation (ICH Q7).

Manufacturing plants exporting to the EU must be inspected and, for each API they export, presented with a written document.(written confirmation).

The manufacture of Active Substances are performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC.

ICH Q7 guidelines are intended to provide guidance regarding Good Manufacturing Practice (GMP) for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they are represented to possess.

Quality should be the responsibility of all persons involved in manufacturing.

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be

defined and documented.

The persons authorised to release intermediates and APIs should be specified. All quality related activities should be recorded at the time they are performed.

Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented quality system incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management.

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the active substance. It can be applied both proactively and retrospectively.

The quality risk management system should ensure that

- The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient through communication with the user of the active substance.
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

APIs and intermediates should only be released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (Contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

The Pharmaceutical manufacturer must have evidence of appropriate audit being performedon all API manufacturers (Manufacturing, packaging, repackaging, mixing labelling,).

Practical steps to establish a quality culture should include

- Create management visibility; messages by senior management
- Create positive message about quality, GMP, Data integrity etc
- Use banners and posters to drive quality messages
- Establish quality recognition awards for work well done
- Publicize metrics using visual means-look at measures such as CAPA'S, warning letters, inspection reports etc, look at year on year trends.
- Challenge employees with fun competitions and recognition of quality principles
- Perform self-audits

Internal Audits (Self Inspection)

In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completedin a timely and effective manner.

Challenges faced

Non -compliance during regulatory Inspections. Many countries for the last 5 years facing GMPCompliance issues. The non- compliance sometimes may lead to warnings.

4) Impact of Multiple Languages

One of the biggest challenge when entering the European market is the multiple languages, which results in many associated country-specific pack formats. Within the 2member states of the EU, there are 150 regional and minority languages, of which 23 are recognized working languages. Labeling and packaging must be in the member state language, requiring design, generation, and management of all packaging components, e.g., labels, Patient Information Leaflets (PILs).

Packaging and Labelling

According to Article 54, Article 55 and Article 59 of Directive 2001/83/EC of the European

Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use1 (hereinafter: "Directive 2001/83/EC") medicinal products must be accompanied by outer and/or immediate packaging information (labelling) and a package leaflet.

Article 56 of Directive 2001/83/EC requires that the particulars to be included in the labelling shall be easily legible, clearly comprehensible and indelible.

Article 56a of Directive 2001/83/EC requires the name of the medicinal product to be expressed in Braille format on the packaging, and the marketing authorisation holder to ensure that the package leaflet is made available on request from patients organisations in formats appropriate for the blind and partially sighted.

5) Patent Protection & Data Exclusivity

If a company chose to manufacture the same product by using a different process, it could do so without violating Indian patent laws. With the 2005 amendment being enacted, product patents and process patents have been permitted for a period of 20 years. The drug is covered under patent protection, which means that only the pharmaceutical company that holds the patent is allowed to manufacture, market the drug and eventually make profit from it.

Once the patent has expired, the drug can be manufactured and sold by other companies. At this point, the drug is referred to as a generic drug.

Directive 2004/27/EC, amending Directive 2001/83/EC, and Regulation (EC) No 726/2004 have introduced new rules (8+2+1) concerning the periods. The period of eight years from initial authorisation of the reference product provides a period of so-called "data exclusivity", after which valid applications for generic products can be submitted and lead to the granting of a marketing authorisation. The period of ten years from initial authorisation of the reference product provides a period of so-called "market protection" after which generic products authorised in this way can be placed on the market. The same periods of protection apply in the case of centrally authorised products pursuant to Article 14(11) of Regulation (EC) No 726/2004.

6) Written Confirmation

CDSCO has come up with guidelines for issue of "Written Confirmation" Certificate required for export of API to European Union countries.

EU is aiming at implementation of 'Directive on Falsified Medicines' to be effective from 2nd July, 2013 with the objective of preventing falsified medicinal products from entering EU from other countries, The directives required all non-EU countries, in order to export (Active pharmaceutical ingredients) APIs meant for medicinal products for human use in EU, to hold a "Written Confirmation" certificate for each such API unit to be issued by the enforcement authorities of that countries confirming compliance with GMP standards or rules 'equivalent to the rules applied in the EU', such as WHO GMP, 'ICH guideline on GMP, etc.

In this regards, Ministry of Health and Family Welfare, Government of India, have nominated "Central Drugs Standard Control Organization (CDSCO) as the competent Authority for the purpose of issue of "WC" certification. CDSCO have already come up with the guidelines forissue of "Written confirmation" certificate duly approved by the Ministry of Health and Family Welfare and published it vide notification 7-5/2013/ DCGI/Misc (EU) dated 10th April 2013.[9]

Procedure for written confirmation

Application for issue of "Written Confirmation" for active substances exported to EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC shall be made.

Initially, the application was prescreened at the time of receipt of application for its completeness of documents. The application is accepted if all the documents are in place. After the application is received it was scrutinized for the details as submitted by the firm.

Then CDSCO (HQ) request the concerned Zonal/Sub Zonal office of CDSCO to conduct the inspection. Zone/Sub Zonal office conduct the inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal productsfor human use. After conducting the inspection, report was prepared and forwarded to the CDSCO (HQ)The inspection report or investigation report was reviewed by CDSCO(HQ).

On the basis of recommendations of inspection report or investigation report submitted to DCG(I), necessary action was initiated for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

Non Compliances, if any, are communicated to the firm as per "Procedure for forwarding of Non Compliances to EU". DCG(I) is the "Competent Authority" to issue "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

The following standards are applicable for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC:

- GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
- WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No.957, 2010
- Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonized Triplicate Guideline stated as per ICH Q7.

❖ Written confirmation issued was valid for a period of 3 years from the date of issue. Surveillance inspections / Inspection for Cause/Sudden Inspection/ Inspection after major changes are conducted by the "Competent Authority (DCG(I))".

Written Confirmation Certificate format was enclosed below as per European Commission-Health and Consumers Directorate- General.[9]

European commission

Health and Consumers directorate-general

Health systems and products.

Medicinal products – quality, safety and efficacy

Annex: *Letterhead of the issuing regulatory authority.*

Written confirmation for active substances exported to the European Union (EU) for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC

Confirmation no. (given by the issuing regulatory authority):

……

……

1. *Name and address of site (including building number, where applicable):*

……

……

2. *Manufacturer's license number(s):*

……

……

Regarding the manufacturing plant under (1) of the following active substance(s) exported to the eu for medicinal products for human use

Active Substance (s)	Activity (ies)

The issuing regulatory authority hereby confirms that

The standards of good manufacturing practice (GMP) applicable to this manufacturing plant are at least equivalent to those laid down in the EU (= GMPof WHO/ICH Q7);

The manufacturing plant is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at leastequivalent to that in the EU; and In the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country without delay to the EU.

Date of inspection of the plant under (1). Name of inspecting authority ifdifferent from the issuing regulatory authority:

……

…… This written confirmation remains valid until

……

…… The authenticity of this written confirmation may be verified with the issuing regulatory authority.

This written confirmation is without prejudice to the responsibilities of the manufacturer to ensure the quality of the medicinal product in accordance withDirective 2001/83/EC. *Address of the issuing regulatory authority:*

……

……

Name and function of responsible person:

……

……

E-mail, Telephone no., and Fax no.:

……

……

Signature *Stamp of the authority and date*

4. SUMMARY

India is currently the third largest Pharmaceutical market in the world, in terms of production volume. It is the largest provider of generic drugs globally, accounting for about 20% of global exports in terms of volume. It is also among the major exporter's of Active Pharmaceutical Ingredients/API. The Indian Pharmaceuticals sector is highly fragmented, with more than 10,000 manufacturers from both unorganized and organized sectors. API's began to be produced in the country in the large scale from 1970 onwards.

India holds a significant position in the global Pharmaceuticals sector. It has gained the reputation of a preferred low-cost destination for manufacturing generic formulations and API's. It also has a rich pool of scientists and engineers who are playing a crucial role in driving innovation and developing newer formulations.

India's Pharmaceutical Industry has filed the highest number of CEP's with Europe and by the end of the year 2016, number of filings stands at 1458.

Over the past several years, Pharmaceuticals have emerged as one of the India's largest export items. The ability to manufacture at low costs while adhering to international quality standards has helped Indian drug manufacturer's gain market share in exports.

USA and Europe are the dominant markets in global Pharmaceutical industry. Duringthe year 2016, US is having the highest Pharmaceutical exports from India. The regulatory agency is

responsible for the safety regulation of food and drug products in their respective country.US is the single market having single regulatory authority whereas Europe is having multiple number of regulatory authorities and it is complex procedure for the approval of Drug products.

Drying the R&D pipelines have given opportunity to Indian Pharmaceutical producers to export their drug substance or drug products throughout the world. Regulatory process varies across countries. On the basis of established regulations and patent laws, the global pharmaceutical industry can be broadly classified into regulated and semi-regulated markets.

Regulated markets include the USA, EU and Japan that have established systems of patent laws and sophisticated regulatory systems for controlling drug quality. On the other hand, semi- regulated markets include countries such as China, India, South Africa and Brazil which have less stringent systems of patent laws and less sophisticated regulatory systems for drug quality control.

However, there is no single harmonized protocol for drug approval across countries. Countries have their own regulatory authorities and drug approval mechanisms.

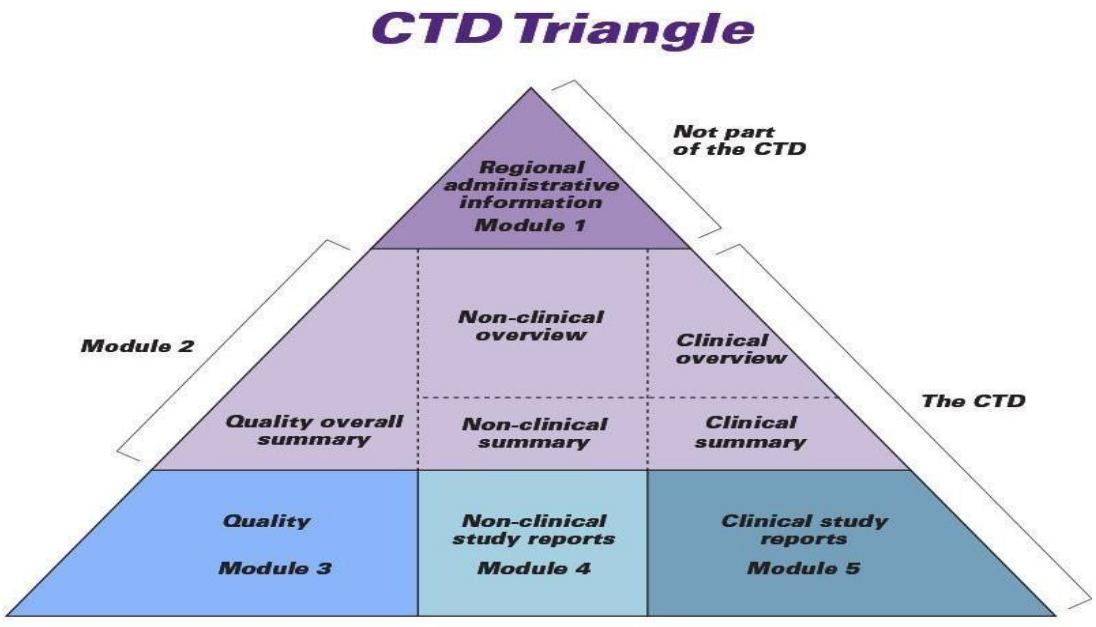
Historical overview of ICH

The first attempt to harmonize pharmaceutical regulatory requirements was undertaken by the European Commission (EC) member nations during the 1980's. Recognizing the mutual benefits to both industry and consumers, the EC decided to facilitate the trade of pharmaceutical products through the development of a single market. The undertaking was a success and demonstrated that Multilateral harmonization for pharmaceutical products could be accomplished without Jeopardi- zing consumer safety. Concurrently, the EC began bilateral discussions on possible Pharmaceutical harmonization with both Japan and the United States. It was not until 1989 that all three parties joined together and considered a trilateral harmonization. Specific plans began to materialize at the World Health Organization's (WHO) Conference on Drug Regulatory Authorities held that year in Paris. One year later ICH was formed to oversee and carry out harmonization plans. The European Federation of Pharmaceutical Industries and Associations (EFPIA) hosted the original meeting, which took place in Brussels. ICH headquarters would later be set up in Geneva, Switzerland and the International Federation of Pharmaceutical manufacturer’s Association (IFPMA) would take over administrative duties for ICH. ICH stands for The International

Conference on Harmonization of Technical Requirements for registration of Pharmaceuticals for Human Use.

It was started in the year 1990.Unique harmonization project involving the regulation and research based industries of US, EU and Canada.

According to the guidelines, such as E6 (GCP) and E3 (Clinical Study Reports), are concerned with the design, conduct, safety, and reporting of clinical trials. Quality guidelines, such as Q7 (GMP) include harmonization achievements in the areas of stability studies, defining relevant thresholds for impurities, etc. Safety guidelines, such as Sl (Need for Carcinogenicity Studies), include a comprehensive set of guidelines related to carcinogenicity, genotoxicity, and reprotoxicity, Multidisciplinary guidelines include ICH medical terminology (MedDRA, M1) and the CTD (M4). CTD is a common template designed by ICH to submit dossier related information to Agency for review and approval. The CTD Triangle contains the following elements:



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

USA and Europe are the dominant markets in Indian Pharmaceutical industry during the year 2016. The regulatory agency is responsible for the safety regulation of food and drug products in their respective country.US is the single market having single regulatory authority and it is easy procedure whereas Europe is having multiple number of regulatory authorities and it is complex procedure for the approval of Drug products.

Some of the challenges faced by the Indian Pharmaceutical industries while exporting of medicines to Europe. They are:

1) Regulatory Directive Differentiations
2) Impact of Multiple Languages
3) Marketing Authorizations Application (MAA) Submission
4) Quality

European Medicines Regulatory network is a partnership between the EuropeanCommission, the medicines regulatory authorities in EU Member states and the European Economic Areas and the European Medicines Agency works to ensure that patients in the EU have access to high- quality, effective and safe medicines. Medicines are authorized and monitored in the European Union.

The European Medicines Agency (EMA) is a Decentralized body of the EU. The mission of the Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health serving over 500 million users of medicinal products. Responsible for Centralized Procedure and co- ordination of EU network + plays a role in stimulating innovation and research in the pharmaceutical sector. A single market system has been developed in European Unionby the laws, this leads to completely different type of procedures for entering into EU market. European regulation has established and harmonized many aspects of regulating the production, distribution, and use of medicines in the EU.

To protect public health and ensure the availability of high quality, safe and effective medicines for European citizens, all medicines must be authorized before they are placed on the market in the EU. The European system offers different routes for such an authorization. They are:

1) Centralized Procedure
2) National Procedure
3) Mutual Recognition Procedure
4) Decentralized Procedure

On the basis of scientific assessments carried out by EMA, it grants or refuses, changes or suspends marketing authorizations for medicines. Once, the medicines gets granted in Eu by EC, it is valid for all member states.

However, the regulatory requirements related to the European Regulatory system for medicines are laid down to ensure that the patients in the EU have access to high- quality, effective and safe medicines. By exporting the drug substance or drug Product to various countries, India is growing its economy. Therefore, India is fastly growing country in the Pharmaceutical Sector. We need to get attention in this, which will increases the market size and also investments in India.

CONCLUSION

India is one of the fastest growing economies in the world and the Pharmaceutical industry has been an important constituent to the Pharma sector worldwide due to the recent changes in the patent laws, the rising use ofGenerics, API's, high cost competitiveness and availability of large scientific research force in the country. Participation of Indian Pharma companies in the international Pharmaceutical market has increased and with more formulations and Bulk Drug exports have been grown significantly.

The contribution of Indian Pharmaceutical industry for exports can increase by involving new exporters, exports to new countries. Pharmaceutical exports from India stood at US$16.4 Billion in 2016-17 and is expected to reach US$20 Billion by the year 2020.

Pharmaceutical Industries contributes to the welfare of humanity and provides significant socio- economic benefits to the society through creation of jobs, supply chains and community development.

From India, many of the Pharmaceuticals are exported to other countries because of the huge population with a large growing middle-class, low cost of production but high quality standards and existence of good infrastructure are the main strengths of Indian Pharmaceuticals. India is all set to become the leader of Pharmaceutical exports to the world. From the above information, we came to know that USA and Europe are the dominant in global Pharmaceutical industries and both are having drug approvals which are most demanding in the world. The primary purpose of therules governing the medicinal products in US and Europe is to safeguard Public health. It is the role of regulatory authority to ensure that Pharmaceutical companies comply with the regulations.

In this dissertation, we have explained about how Indian Pharmaceutical industry has evolved and how it was growing its economy in terms of exports by exporting to other countries. We

also explained about what are challenges facing by Indian Pharmaceutical industry and how they overcome those challenges. In current scenario, US and Europe are the highly regulated markets from India. To confirm that, by exporting the Pharmaceuticals from India, it is growing its economy and maintain the strategic relationship. So, in this present work we have taken the Europe which is comprising of different member states and complex marketing authorization procedures whereas US is having the single marketingauthorization procedure. It also explains about how the European Medicines Regulatory System works and different marketing authorization procedures. Moreover, we explained what information has to be submitted to the agencies while exporting the Pharmaceuticals from India to Europe.

BIBLIOGRAPHY

1. A brief report on pharmaceutical industry in India by ASA & AssociatesLLP
2. Indian Brand Equity Foundation - www.ibef.org ;http://www.mbaskool.com
3. http://managementstudyguide.com/porters-model-of-competetion.htm
4. Indian Brand Equity Foundation- www.ibef.org
5. Indian Pharmaceutical Industry Changing dynamics and road ahead-www.idembassy.com
6. India's leading pharmaceutical companies 2016-http://www.dnb.co.in/Publications/LeadingPharmaceutical2016/IndiasLeadingPharmaceuticalCompanies2016.pdf
7. Indian Pharmaceutical exports to various countries during FY 2016-www.mea.gov.in
8. Europa.eu- European directorate general for trade
9. Central Drug Standard Control Organization-www.CDSCO.nic.in
10. www.lexology.com / https://www.lexology.com/library/detail.aspx?g=42cd8e54-6cb2-4952-9bc9-b49f9865167e
11. International Journal of current Research- www.journal.cra.com
12. International Research Journal of Pharmacy- www.irjponline.com
13. International Journal of Pharma Professional Research-www.ijppronline.com
14. Journal of Pharmaceutical Sciences and Research-www.jpsr.pharma
15. World Journal of Pharmacy and Pharmaceutical Sciences
16. International Journal of Pharmaceutical Sciences-www.ijpsr.com
17. Journal of Pharmaceutical Sciences and Research-www.jpsr.com
18. International Journal of Pharma Sciences and Research-www.ijpsr.com
19. Asian Journal of Pharmaceutical and Clinical Research
20. European Medicines Agency-www.ema.europa.eu

21. European Commission- https://europa.eu
22. Heads of Medicines Agency- www.hma.eu
23. Guideline on summary of requirements for Active Substances inthe quality part of the dossier – www.europa.eu
24. Certificate of suitability-www.edqm.eu
25. Volume 2A Procedures for marketing authorizations- Chapter 1-marketing authorizations; December, 2016.
26. Volume 2A Procedures for marketing authorizations- Chapter 2- Mutual Recognition February, 2007.
27. Volume 2A Procedures for marketing authorizations- Chapter 4- Centralized Procedure; April, 2006.
28. Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QPdeclaration template"- www.europa.eu