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A Study on Regulatory Barriers Governing the Import, Export, and Marketing of Pharmaceutical Products in India and Selected ROW Countries"

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1.0. INTRODUCTION

Pharmaceutical Products are any substances resulting from preparing, preserving or compounding medicinal drugs, vitamins or other materials used to enhance personal health. Cannabis products, including any cannabis products intended for external use, are not pharmaceutical products health. Cannabis products, including any cannabis products intended for external use, are not pharmaceutical products. [1]

1.1. TYPES OF GLOBAL MARKET [1] [2]

- **Regulated Market**: US, EU (UK, Germany, France, Ireland, Sweden etc.), Japan, Canada, Australia, New Zealand, South Africa
- **Semi regulated Market**: (ROW Countries)

(a) Asia (Sri Lanka, India, Bangladesh,; ASEAN: 10 Countries group - Philippines, Vietnam Singapore, Malaysia, Thailand, Indonesia, Laos,
Cambodia, Brunei Darussalam, Myanmar

(b) African countries (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc.)
(c) Middle East countries (Gulf Co-operation Council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE)
(d) Latin America (Mexico, Brazil, Panama, Peru, Guatemala, Argentina, Chile, Dominican Republic)
(e) CIS (common wealth of independent states): Russia, Ukraine, OFSUs (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirghizstan, Moldova, Tajikistan,

Turkmenistan, Uzbekistan etc.)

1.1.1. *Emerging market.*

A country's economy that is developing toward being more advanced, typically through rapid expansion and industrialization, is referred to as an emerging market economy. The "BRIC" economies—Brazil, Russia, India, and China—are the most frequently mentioned emerging markets. There is no comprehensive list of emerging markets, but among the nations that are frequently grouped under the term are Mexico, Indonesia, South Korea, Turkey, South Africa, Nigeria, and Saudi Arabia.[3]

1.1.2. *ROW as an Emerging market*

Companies' regulatory affairs departments are expanding and expanding, and they are the ones that are least affected by changes in the regulatory environment. Mergers and acquisitions, as well as during a recession. Global standardization has resulted in a uniform approach to regulatory submissions and, consequently, to their assessment. Systematic formulation development serves as the foundation for all export registration dossier preparation. There are various registration requirements in various nations. It is challenging for any business to create products for every region. Therefore, when submitting technical data that will aid in export registration, we need to take the majority of requirements into account. Regions, however in these nations, they are all national registrations. Although there is a huge variety of regulatory needs, harmonisation happens as clusters, such as the ASEAN and Gulf.[3]

1.2. IMPORT

An import is a good or service bought in one country that was produced in another. Imports and exports are the components of international trade. If the value of a country's imports exceeds the value of its exports, the country has a negative balance of trade, also known as a trade deficit. [4]

1.2.1. Import Export data

In the worldwide pharmaceutical and vaccine sector, India is significant. It is the world's biggest supplier of generic medications. The nation supplies 20% of the world's total supply volume and about 60% of the world's vaccinations. India is the third-largest country in the world by volume and the fourteenth-largest by value. OTC drugs, generics, APIs, vaccines, biosimilar, and custom research manufacturing are significant sectors of the Indian pharmaceutical industry. In terms of providing vaccines like DPT, BCG, and measles, India leads the world. Additionally, it has the most US FDA-approved plants outside of the USA. India is

sometimes referred to as the "Pharmacy of the World" due to its inexpensive prices and excellent quality pharmaceutical products, which are its main USPs. In 2019–20, the industry had a $36.7 billion annual revenue total as shown in Figure 1.1 .Access to reasonably priced HIV medications is one of the great accomplishments of the Indian pharmaceutical industry. India is also one of the biggest international suppliers of inexpensive vaccinations Drug formulations and biologicals account for the majority of India's pharmaceutical exports, or around 75% of the total.

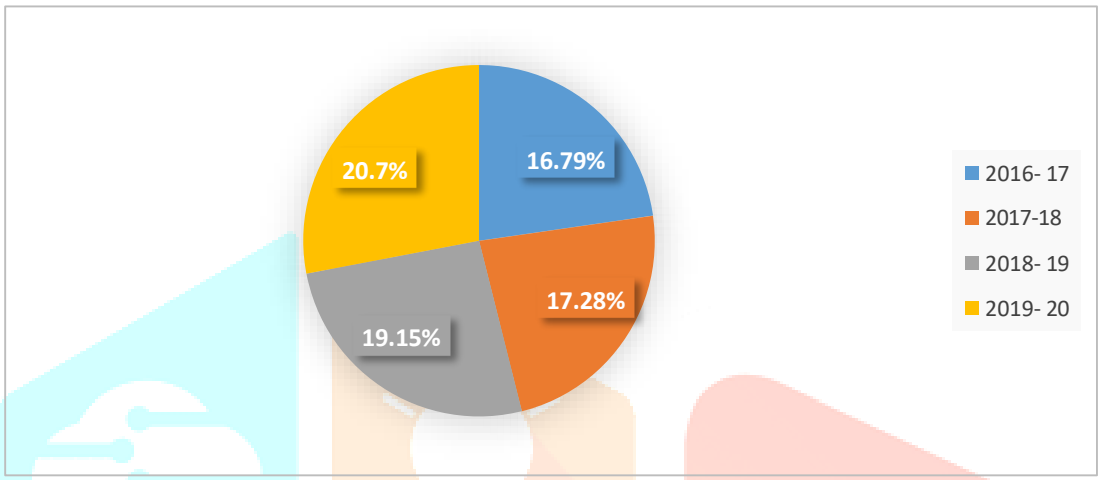

Figure 1.1 India's category wise export share data.

India accounts for 5.92% of the global market for pharmaceuticals and drugs. Formulations and biologics made up the majority of India's exports, accounting for 73.31% of total exports, followed by drug intermediates and bulk medications. A flat increase over the prior year, the nation exported pharmaceutical products worth US$24.62 billion in 2021–22. Exports increased by 18% YoY in 2020–21, reaching $24.4 billion. Despite lockdowns, global supply chain disruptions, and muted manufacturing, this strong performance was accomplished. A 23% increase from US$ 1.97 billion in February 2022 to US$ 2.4 billion in March 2022 was recorded by India in terms of pharmaceutical and drug exports. India's top five export markets are the USA, UK, South Africa,

Russia, and Nigeria.[4] India accounts for 5.92% of the global market for medicines and medications. Formulations and biologics made up the majority of India's exports, accounting for 73.31% of total exports, followed by drug intermediates and bulk medications. A flat increase over the prior year, the nation exported pharmaceutical products worth US$24.62 billion in 2021–22. Exports increased by 18% YoY in 2020–21, reaching $24.4 billion. Despite lockdowns, worldwide supply chain interruptions, and muted manufacturing, this strong result was accomplished and shown in Figure 1.2 . A 23% increase from US$ 1.97 billion in February 2022 to US$ 2.4 billion in March 2022 was recorded by India in terms of pharmaceutical and drug exports. India's top five export markets are the USA, UK, South Africa, Russia, and Nigeria.[4]

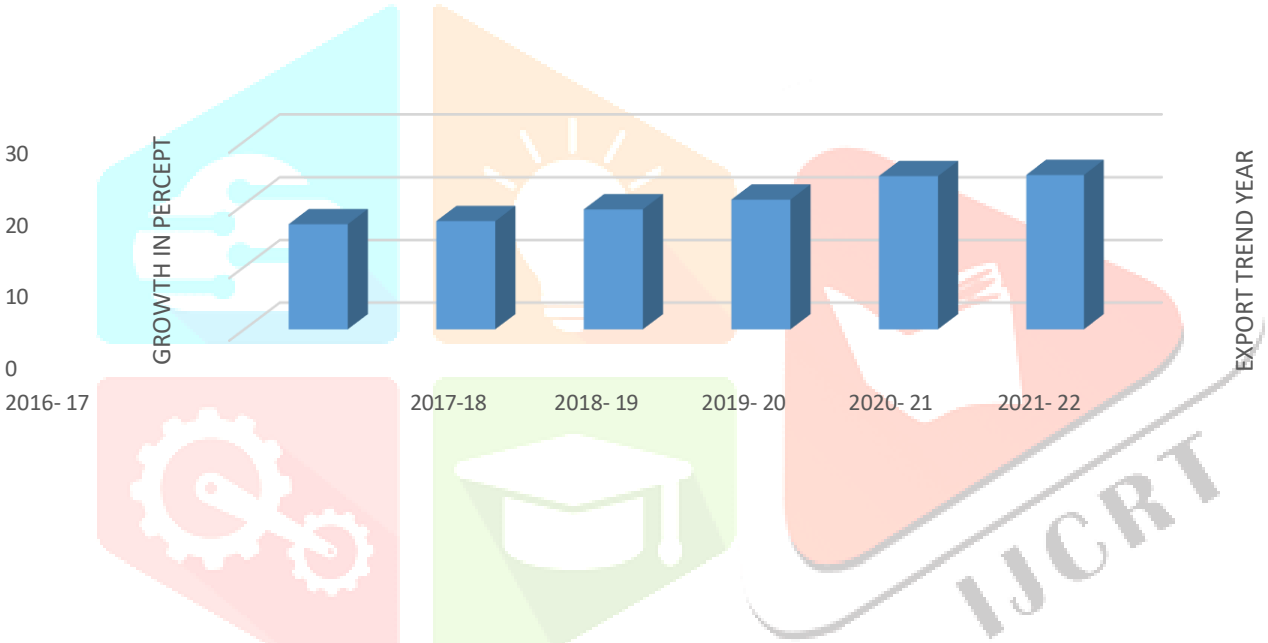

Figure 1.2 India Drug and Pharmaceutical drugs export trend.

1.3 EXPORT

The word “export” is well-known in business world. Export provides good amount of opportunities. Even among the youngsters, international trade is consider as, a good career option. The Foreign Trade (Development and Regulation) Act 1992, defines export as “taking out of India any goods by land, sea or air.” A flat increase over the prior year, the nation exported pharmaceutical products worth US$24.62 billion in

2021–22. In figure 1.3 the Exports increased by 18% YoY in 2020–21, reaching $24.4 billion. India's top five export markets are the USA, UK, South Africa, Russia, and Nigeria. Among the top importers from India in 2021–22 are the USA, the UK, and Russia, with shares of 29%, 3%, and 2.4%, respectively. In FY21–22, India exported pharmaceutical items to the following nations: USA ($7,101.6 million), UK ($704.5 million), South Africa ($612.3 million), Russia ($597.8 million), and Nigeria ($588.6 million). Over the past three years, the value of India's pharmaceutical exports to the USA increased at a CAGR of 6.9%. Additionally, over the same time period, it increased at a CAGR of 3.8% for the UK and 7.2% for Russia, respectively.[4]

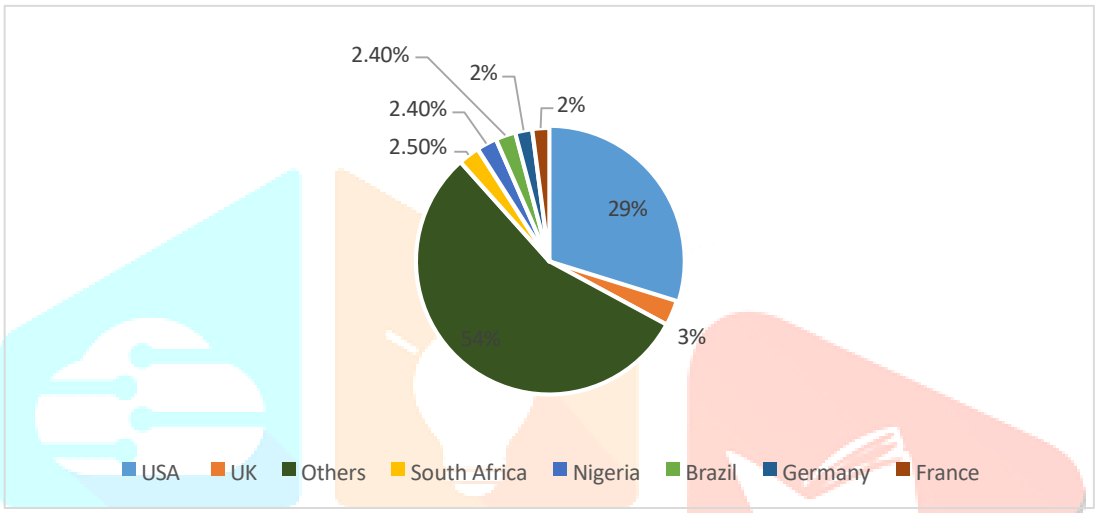

Figure 1.3. Country wise share of drugs, pharmaceutical product

2.0. AIM

To understand and overcome the Regulatory Challenges for Import, Export and Sale of Pharmaceutical Products in India and ROW Countries.

2.1. OBJECTIVE

1) Regulatory rules and regulations in ROW countries should be studied and assessed.
2) To present an overview of the requirements for submitting a request for a medical import or export permit
3) To specify the conditions that must be met in order for a permit to import or export medicines to be considered complete.
4) Provide an overview of the obligations of the parties engaged in the import and export of pharmaceuticals.
5) To map the legal and administrative frameworks for drug control in a few countries.
6) To understand the Act's or your responsibilities under the law, they should get legal counsel for assistance on the regulations.

2.3. RATIONALE

To explore or access the responsibilities of regulatory organizations and any potential dangers related to the export of pharmaceutical products.

2.4. PLAN OF WORK

1. Selection of topic for Dissertation.
2. Literature Survey.
3. Selection of major literature for basic structure and challenges.
4. Study of Registration process requirement According to the regulatory Authorities.
5. To study the Challenges and aspects for Import, export and sale.

3.0. INDIA

Regulatory bodies

In different parts of India have 11 Port offices, which are working under the Central Drugs Standard Control Organization (CDSCO) to import and export of pharmaceutical products in a regulated manner. World health organization (WHO) has issued regulatory guidelines to import Pharmaceutical products on the basis of the following conditions:

3.1. REGULATORY FRAMEWORK

Drugs Sector Under the current Indian legal and regulatory regime, the manufacture, sale, import, exports and clinical research of drugs and cosmetics is governed by the following laws:-

1. The Drugs and Cosmetics Act, 1940
2. The Pharmacy Act, 1948
3. The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954
4. The Narcotic Drugs and Psychotropic Substances Act, 1985
5. The Medicinal and Toilet Preparations (Excise Duties) Act, 1956
6. The Drugs (Prices Control) Order 1995 (under the Essential Commodities Act.
7. The Industries (Development and Regulation) Act, 1951
8. The Trade and Merchandise Marks Act, 1958
9. The Indian Patent and Design Act, 1970
10. The Factories Act.

3.2. PROCEDURE FOR IMPORT AND REGISTRATION OF DRUGS

Form and Manner of Application

3.2.1. Import License

1. An application for an import License shall be made to the licensing authority in Form 8 for drugs excluding Schedule X, and in Form 8-A for Schedule X drugs; either by the Manufacturer or by the Manufacturer's agent in India who is having the wholesale license for sale or distribution of drugs and shall be accompanied by a License fee of one thousand rupees for a single drug and one hundred rupees for

Each additional drug and by an undertaking in Form 9 duly signed by or on behalf of the manufacturer.

2. Any application for an import license in Form 8 or 8-A, which shall be accompanied by a copy of the Registration Certificate issued in Form 41 under Rule 27-A; in the case of emergencies the issue of Import License by the central government in Form 10 or 10-A without issuance of Registration Certificate under Rule 27-A, for reasons to be recorded in writing. A fee of two hundred and fifty rupees shall be paid for a duplicate copy of licence, if the original is defaced, damaged or lost.[6]

3.2.2. Registration Certificate

1. Application for issue of a Registration Certificate shall be made to the licensing authority in Form 40, either by the manufacturer or authorized agent in India under this rule and shall be specified in the sub rule (3) and the information and undertakings specified in Schedule D-1 and Schedule D-II duly signed by on behalf of the manufacturer.

2. The authorization by a manufacturer to his agent in India shall be documented by a power of attorney executed and authenticated either in India before a First Class Magistrate, or in the country of origin before such an equivalent authority, the certificate of which is attested by the Indian Embassy of the said country, and the original of the same shall be furnished along with the application for Registration Certificate

3(i). A fee of one thousand and five hundred US dollars shall be paid along with the application in Form 40 as registration fee for his premises meant for manufacturing of drugs intended for import and use in India.

(ii) A fee of one thousand US dollars shall be paid along with the application in Form 40 for the registration of a single drug meant for import into and use in India and an additional fee at the rate of one thousand US dollars for each additional drug. The fees shall be paid through a Challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110 001 or any other branch or branches of Bank of Baroda, or any other bank, as notified, from time to time, by the Central Government, to be credited under the Head of Account "0210-Medical

and Public Health, 04- Public Health, 104- Fees and Fines"; in the case of any direct payment of fees by a manufacturer in the country of origin, the fees shall be paid through Electronic Clearance System (ECS) from any bank in the country of origin to the Bank of Baroda, Kasturba Gandhi Marg, New Delhi, through the Electronic Code of the bank.

The applicant shall be liable for the payment of a fee of five thousand US dollars for expenditure as may be required for inspection or visit of the manufacturing premises or drugs, by the licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority under rule 22.

4. The applicant shall be liable for the payment of testing fee directly to a testing laboratory approved by the Central Government in India or abroad, as may be required for examination, tests and analysis of drug.

5. A fee of three hundred US dollars shall be paid for a duplicate copy of the Registration Certificate, if the original is defaced, damaged or lost.

6. No Registration Certificate shall be required under these rules in respect of an inactive bulk substance to be used for a drug formulation, with or without Pharmacopoeial conformity.[6]

3.2.3. Packaging and Labelling

Imported Drugs: Drug shall be packed and labelled in conformity with the rules parts IX and X and also Schedule F (1), in the case of drugs for Veterinary use is Part XII. Packing of Patent or Proprietary Medicine: Patent or proprietary medicines shall be imported in bulk containers, applicant need to get permission from the licensing authority at least three months prior to the date of import and the not to dispose of the drug without the permission of the officer authorized in this purpose.[4] The drugs specified in Schedule D shall be exempt from the provisions of Chapter III of the Act and of the Rules made there under, and subject to conditions specified in that Schedule.

Drugs, consignments of which are in transit through India to foreign countries and which shall not be sold or distributed in India shall be exempted from the requirements of Chapter III of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the rules made there under. The importers shall produce documents at the time of import in India to get import license 4. Common Submission Format for Import and Registration of Bulk Drugs and Finished Formulations of Bulk Drugs and Finished Formulations in India: Requirements for Registration of Drugs in Form 40.

1. **Covering Letter**: This contains the list of documents shall be submitted and any other information provided, it shall be duly signed and stamped by the authorized signatory along with the name and address of the firm.
2. **An Authorization Letter**: An Authorization letter in original issued by Director/Company Secretary/Partner of the Indian agent firm revealing the name & designation of the person authorized to sign Form 40, Power of Attorney, etc., it shall be submitted at the time of registration along with duly self-attested photocopies.
3. **Form 40 & TR 6 Challan**: It shall be filled as per Drugs & Cosmetics Rules, signed and stamped along with name & designation and date of the Local Authorized Agent. Performa shall be enclosed at Annexure-I. Payment shall be paid through Electronic Clearance System (ECS) from any bank in the country of origin to the Bank of Baroda, New Delhi, through the electronic code of the bank. 4. Power of Attorney: The authorization by a manufacturer to his agent in India shall be documented by Power of attorney authenticated in India or by country of origin, the certificate shall be attested by Indian Embassy of the said country and original copy shall be submitted along with the application for Registration Certificate (RC). Performa for Power of Attorney (POA) is enclosed at Annexure III. The authorized agent will be responsible for the manufacturer's business activity, in India. While submitting the Power of Attorney, the following shall be needed It shall be signed and stamped by the manufacturer as well as the Indian Agent indicating the

name & designation of the authorized signatories. It shall be clearly lists the names of all the proposed drugs if possible along with their uses. Further, the names of the proposed drug should correlate with Form 40, Free Sale Certificate or Certificate of pharmaceutical product (COPP) as per WHO-GMP certification scheme.The names & addresses of the manufacture and the Indian Agent stated in the Power of Attorney should correlate with the Form 40. Multiple sites are in tabular form. And the Fresh POA shall be submitted at the time of Re-Validation of RC.

4. Wholesale License

A duly attested and valid copy of Wholesale License for sale or distribution of drugs under Drugs and Cosmetics Rules in Form 20B & 21B or its renewal in Form 21C issued to the manufacturer or its agent by the State Licensing Authority in India.

5. Undertaking: Signed & stamped by the manufacturer/Authorized agent indicating the name and designation of the authorized signatory required to be submitted as per Performa for Schedule D (I) is enclosed at Annexure IV along with CTD module 1 covering the Schedule D (I) requirement. The requirements for Plant Master File are enclosed at Annexure Modules 2-5 Covering the schedule D (II) requirements: Standard of the Drug: Second Schedule of the act explains Imported drugs shall be compile with the standard which are there in IP, USP, BP, EP, etc.,

6. Label Submission: True copy of the Label as per Rule 96, if it is in IP means as per label claim in IP. Testing of Drugs: For Registration of Bulk Drugs, the consecutive three batches shall be submitted to the laboratory for the analysis and reanalysis along with specifications, Method of analyses, COA tested in their laboratory, impurity Standards, marker compounds, Reference Standard along with its COA where ever applicable.

7. Free Sale Certificate (FSC): Free Sale Certificate should state that the proposed drug is freely sold in Country of Origin and can be legally exported.

8. Certificate of Pharmaceutical Products (COPP): The valid copy of GMP Certificate or COPP as per WHO scheme for each drug issued by the National Drug Regulatory Authority of the country of origin. Format for COPP is enclosed at Annexure VII.

9. Manufacturing License: The valid copy of the Manufacturing License or Market Authorization certificate issued by the National Drug Regulatory Authority of the Country of origin. If available, free sale certificate also be submitted.

10.Product Registration Certificate: The valid copy of Product Registration Certificate wherever applicable in respect of the foreign manufacturing sites.

a. Soft copy of the Plant Master File and Drugs Master File shall be submitted along with the application.

b. All certificates submitted shall be within the valid period. All the regulatory and legal documents in separate file and Plant Master File and Drug Master File as separate files.

c. In case, the item considered as drug as per the definition of section 3 (b) of the Act in India but not registered as drug in the country of origin a legal undertaking from the manufacturer and approval from the competent authority of the country of origin duly notarized and apostle should be submitted.

d. The application of r-DNA products should be made separately as per the guidance document for submissions of biological.

e. In case of bulk drug, if the same is approved in EU/USA etc. DMF approval number may mention on the covering letter itself.

f. In case of toll manufacturer to be registered for a drug, the POA shall be signed by the legal manufacturer in the country of origin, this submitted as proof.

g. POA should be supplemented with declarations in respect of sites involved in the manufacturing and testing of the applied drugs as per the format given here under: [9]

3.2.4. Renewal of Registration or Re-registration

The application is to be made 9 months before the expiry of the Registration Certificate along with regulatory documentary compliance like Form 40, POA, GMP / COPP, Registration certificate, DMF, License etc. Undertakings by the manufacturer or his authorized agent in India in respect of any administrative action taken due to adverse reaction, market withdrawal, regulatory restrictions, or cancellation of authorization, not of standard quality report of any drug pertaining to this Registration Certificate declared by the Regulatory Authority of the country of origin or by any Regulatory Authority of any other country, where the drug is marketed/sold or distributed.[7]

3.2.4.1. Requirements for Registration of Drugs in Form 108

1) Covering Letter

2) An Authorization Letter

3) Form 8-Duly signed and stamped by the Indian agent along with the name & designation of the authorized signatory, Performa is enclosed at Annexure-XII.

4) Form 9-Duly signed and stamped by the Indian agent along with the name & designation of the authorized signatory, if the form 9 is issued by the manufacturer, it shall be authenticated from Indian Embassy of the country of origin, Performa is enclosed at Annexure-XIV.

5) Requisite fee: Rs.1000 for 1 proposed drug and Rs.100 for each additional drug shall be paid at Bank of Baroda, New Delhi.

6) Wholesale license

7) Registration Certificate

A Manufacturer holding valid license copy in Form-25 and Form-28 can obtain No Objection Certificate for export purpose only for approved / unapproved new drug / banned drug in India. The requirements are as per guidelines issued by Ministry of Health and Family Welfare for Export purpose and Rule 94 of the Drugs and Cosmetic Act, 1940.

3.4 GUIDELINES FOR THE EXPORT OF DRUG ISSUED BY MINISTRY OF HEALTH AND FAMILY WELFARE

During the issue of NOC‟s for manufacture of new (Unapproved) drug solely for export, the following conditions shall be taken into consideration The application shall provide copy of valid export order and NOC will be issued on a case by case basis against each such order. The applicant shall identify the premises where the drug will be manufactured for export. The applicant should mention whether the batch to be exported has undergone Quality control testing or shall be tested at the destined site. The applicant shall ensure that the drug(s) manufactured on the basis of NOC given as per the first condition and it is exported and that no part of it is diverted for domestic sale in India. The applicant shall make available for inspection of the appropriate authorities, on completion of the export orders, information regarding each consignment despatched, remaining stock of drug and related raw materials and intermediates in hand. The applicant shall ensure physical destruction of all un exported quantity of drugs. This should be included as a condition of manufacturing license issued to the applicant by the State licensing authority.

The applicant shall ensure that the drug for which NOC has been given shall cease to be manufactured or exported if the drug is prohibited in future in the country or in the importing country.

3.4.1 Requirement for Common Submission Format for Issue of NOC for Export

The following documents are required in the following manner and order for the issue No Objection Certificate (NOC) for export of drugs from India

3.4.1.1. Covering letter

Purchase Order: Order from the foreign buyer either in the name of the manufacturer or trader with the 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. It should be signed by the authority with a valid purchase order no. and recent date not more than 6 month prior to the application made by the firm Manufacturing License.

Performa Invoice: 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, it shall be duly signed by the competent

4.0. UNITED STATES OF AMERICA

The US will continue to reinforce its position as the leading pharmaceutical manufacturer. The majority of the largest drug makers are based in the country, and these firms are outperforming rivals in Western Europe and Japan considerable investments in R&D by US companies are resulting in the introduction of increasing numbers of new products, which are produced locally for domestic demand and exported for foreign markets.

4.1 CRITERIA OF AN EXPORTER AS PER USFDA.

Exporters are responsible for determining whether export is permitted under the Act and whether their exports meet the requirements of inspection 802(f) of the Act. FDA will evaluate compliance with the relevant export provisions as appropriate. FDA's export notification requirements must be fulfilled by the product. FDA recommends that firms intending to export drugs under section 802(b)(2) of the Act provide to the agency documentation showing that the drug complies with the foreign country's laws and has valid marketing authorization. FDA recommends that the firm obtain documents indicating that the authorities in that country do not object to the product's marketing.

FDA cannot make the necessary determinations concerning the foreign country's statutory and regulatory requirements, and the firm cannot export the drug under section 802(b)(2) of the Act. FDA has 60 days to act on a request to export a drug under section 802(b)(3) of the Act.The agency plans to begin the 60-day period on the date that it receives a complete petition containing the certification and evidence required by the Act. The Act does not allow exportation to proceed if FDA has not responded within 60 days.

4.1.1. *Basic requirements for the product which can be exported according to section 802(f) of the act.*

The product must be manufactured, processed, packaged, and held in "substantial conformity" with cGMPs or meet international standards as certified by an international standards organization recognized by

FDA. The product must not consist in whole or in part of any filthy. putrid, or decomposed substance and must not have been prepared, packed, or held under insanitary conditions where it may have been contaminated with filth or have been rendered injurious to health. The container for the product must not be composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health. The product must have the strength, purity, and quality that it purports or is represented to possess for drugs, no substance may be mixed or packed with the drug that would reduce the drug's quality or strength or may substitute in whole or in part for another substance in the drug. The product cannot present an imminent hazard to the public health of the country to which it would be exported. The product must be labelled in accordance with the requirements and conditions of use in the listed country in which it received valid marketing authorization. [8]

4.2 AUTHORITIES

Drug Regulatory Authority means the government authority responsible for the regulation of the research, development, testing, manufacturing, processing, storage, labelling, sale, marketing, advertising, distribution and importation or exportation of drug products and drug product candidates.

4.2.1. National Regulatory Authorities (NRA)

NRAs are national regulatory agencies responsible for ensuring that products released for public distribution (normally pharmaceuticals and biological products, such as vaccines and medical devices including test kits) are evaluated properly and meet international standards of quality, safety, and efficacy.

4.2.2. International Regulatory authorities

International regulatory agencies and organizations play an essential role in all aspects of pharmaceutical regulations worldwide as the pharmaceutical industries throughout the world are moving ahead towards becoming increasingly competitive, regulatory agencies are

being established in various countries across the globe. Regulatory agencies and organizations play a vital role to meet the requirements of legal procedures related to drug development process in a country in the present scenario, pharmaceuticals are considered as the most highly regulated industries worldwide. The regulatory body ensures compliances in various legal and regulatory aspects of drug every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the drug development process, licensing, registration, manufacturing, marketing, and labelling of pharmaceutical

4.3 FDA IMPORT REQUIREMENT

All imported FDA-regulated products must:

- Be manufactured, processed, packed, and held under sanitary conditions.
- Not be forbidden or restricted for sale in the country the product is produced or exported from.
- Not be adulterated (e.g., contaminated with a harmful or filthy substance or other substance prohibited by US law).
- Not be misbranded (e.g., must meet all federal labelling requirements.)
- Not otherwise be a product prohibited by federal law for distribution in US commerce e.g., unapproved drugs.
- Meet any registration, listing, and other filing requirements.[9]

4.3.1. Importance of import requirements

FDA's import requirements hele ensure that foods, drugs, cosmetics, medical devices, and other FDA-regulated products are safe for use and that the product's labelling is truthful and not misleading and correctly bears all required information such as an appropriate statement of identity, any required warning/caution statements, nutrition labelling and allergen declarations for foods, etc. The product is deemed to be in violation when it is in some way adulterated or misbranded. If the product is in violation of the FDA law, the FDA notifies the initial

importer, or the consignee of the specific reason or misbranding charged.

4.4. EXPORT OF DRUGS

Exports are any resources, intermediate goods, or final goods or services that a buyer in one country purchases from a seller in another country. In general, Export is selling drugs or pharmaceuticals, medical devices, etc. to other countries crossing the geographical frontiers of the country. A good example is the USA selling the drugs to India and England. Export earns a country lot of foreign exchange and helps in tilting the balance of payment. FDA is responsible for enforcing the Federal Food, Drug, and Cosmetic Act (FD&C Act), including those provisions concerning FDA-regulated products that are exported from the United States firms exporting products from the U.S. are often asked by foreign customers or foreign governments to supply a certification relating to products subject to the Federal Food, Drug, and Cosmetic Act (the Act) and other statutes FDA administers. FDA's export certification provides the agency's official attestation concerning a product's regulatory or marketing status, based on available information at the time FDA issues the certificate.

4.4.1. Documents for the export of drugs as per FDA

The guidance document provided by FDA summarizes and explains the basic requirements and procedures under the FDA Export Reform and Enhancement Act of 1996 for exporting human drugs, animal drugs, biological products, devices, food, food additives, colour additives, and dietary supplements that may not be sold or distributed in the United States.It explains the basic requirements and procedures for exporting human drugs (also drug components) and biologics that may not be sold or distributed in the United States also summarizes and explains the requirements for exporting drugs that are approved for marketing in the United States, but which are being exported for an unapproved use.[10]

4.5. SALE OF DRUG

The sale may be defined as the process of passage of articles from the manufacturer to the customers in practice two kinds of Sales are recognized, wholesale and retail sales. Manufacturer supply their article to selected agents who act as stockiest for their goods. These stockiest, then sell the goods to the shopkeeper. The sale of goods by the stockiest to the shopkeeper is known as wholesale while the sale of goods by the shopkeeper to the public is retail. The entire process of passage of materials from manufacturer to consumer can be illustrated by the following figure

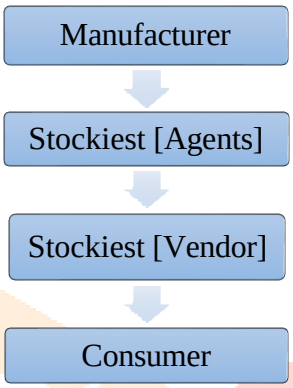

Figure 4.1 : Passage of manufacturer to consumer

It is a recognized fact that while the sale of ordinary goods is an open trade where the consumer selects the goods of his choice, the sale of drugs is a technical job that must be performed by persons who have received specialized training on this behalf of drug companies seeking to sell a drug in the United States must first evaluate it. The company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the company's data and proposed labelling. If this independent and unbiased review establishes that a drug's health benefits outweigh its known risks, the drug is approved for sale. The centre does not evaluate drugs itself, although it does conduct limited research in the areas of drug quality, safety, and effectiveness standards.

4.6. POLICIES APPLICABLE TO IMPORT AND EXPORT OF DRUGS

Laws, regulations, and policies applicable to imports and exports, domestic and overseas inspections for compliance, fraud deterrence plays a significant role. It protects public health by promoting supply chain integrity and working to ensure medicines imported to the U.S. and exported from the U.S comply with applicable legal and regulatory requirements. According to the 21CFR Part 1312 – Importation and Exportation of Controlled substances various guidelines.

4.7. IMPORT OF DRUGS

4.7.1 Requirement of authorization to import

a) No person shall import, or cause to be imported, into the customs territory of the United States from any place outside thereof (but within the United States), or into the United States from any place outside of, any controlled substances listed in Schedule I or II, or any narcotic controlled substance listed in Schedule III, IV, or V.
b) Person must be properly registered under the Act (or, in accordance with part1301of chapter, exempt from registration) and has filed an import declaration to do so.
c) A separate permit or declaration is required for each shipment of a controlled substance to be imported.

4.7.2. Application for import permit; return information.

a. Registered importers, other registrants authorized to import as a coincident activity of the registrations, and persons who in accordance with part 1301 of this chapter are exempt from registration, seeking to import a controlled substance in schedule I or II; any narcotic drug in schedule III, IV, or V any non-narcotic drug in schedule III that has been specifically designated by regulation in § 1312.30; or any non-narcotic substance listed in schedule IV or V that is also listed in schedule I or II of the Convention on Psychotropic Substances, 1971, must submit an application for a permit to import controlled substances on DEA Form 357All applications and supporting materials must be submitted

to the Administration through the DEA Diversion Control Division secure network application the application must be signed and dated by the importer and must contain the importer's registered address to which the controlled substances will be imported.

b. The applicant must include on the DEA Form 357 the registration number of the importer and a detailed description of each controlled substance to be imported including the drug name, dosage form, National Drug Code (NDC) number, the Administration Controlled Substance Code Number asset for thin part 1308 of this chapter, the number and size of the packages or containers, the name and quantity of the controlled substance contained in any finished dosage units, and the quantity of any controlled substance (expressed in anhydrous acid, base or alkaloid) given in kilograms or parts.

c. If desired, alternative foreign ports of exportation within the same country may be indicated upon the application (e.g., 1. Kolkata, 2. Mumbai). If a permit is issued pursuant to such application, it will bear the names of the two ports in the order given in the application and will authorize shipment from either port. Alternative ports in different countries will not be authorized in the same permit.

d. Application must also include the following:

- The name/ business name, address/ business address, contact information (e.g., telephone numbers, email addresses and business of the consign or, if known at the time the application is submitted, but if unknown at that time, the fact should be indicated, and the name and address afterwards furnished to the Administration as soon as ascertained by the importer.
- The foreign port and country of initial exportation (i.e., the place where the article will begin its journey of exportation to the United States).
- The port of entry into the United States.
- The latest date's aid shipment will leave said foreign port or country.
- The stock on hand of the controlled substance desired to be imported.
- The name of the importing carrier or vessel (if known), or if unknown it should be stated whether the shipment will be made by express,

Freight, or otherwise, imports of controlled substances in Schedules I or II and narcotic drugs in Schedules III, IV, or V by mail being prohibited).

- The total tentative allotment to the importer of such controlled substance or the current calendar year.
- The total number of kilograms of said allotment or which permits have previously been issued and the total quantity of controlled substance imported during the current year to date.[10]

4.7.3. Import requirements

FDA verifies compliance with the following requirements as applicable for the imported drug:

- FDA approval
- Registration and listing
- Premarket submission information
- Declared manufacturer
- Declared importer/consignee
- Product description
- Affirmations of compliance
- Intended use codes

4.7.4. Affirmation of complicated codes

The Affirmation of compliance codes are three letter codes that can be provide date and time of import to facilitate FDA review of import requirements. Providing the correct codes reduces the likelihood that shipments will be held for further FDA entry review during FDA's import screening process. FDA uses these codes to assist in verifying that products meet the appropriate requirements Affirmation of compliance codes are only mandatory in some instances and are not required for all scenarios Submitting voluntary affirmation of compliance codes may expedite initial screening and review.

4.8. Export procedure

The exporting activity involves several commercial and regulatory procedure. These procedures also involve considerable documentation requirements. The export documentation involves the preparation of the

specified number of copies of the prescribed documents pertaining to the different procedures.

4.9. Preliminary steps

IEC number: The IEC numbers are normally allotted by the regional licensing authorities. Membership registration: Membership of certain bodies will help the exporters in several ways.

Inquiry and offer: An inquiry requested from a prospective importer to be informed of the terms and conditions of sale.

Confirmation of order: Once the negotiation is completed and conditions are acceptable to the buyer and seller, the buyer may place and order with the exporter.

Export license: The exports of some items are banned and of some items controlled by means of licenses, though many items are permitted to be exported freely.

Finance: If the exporter requires pre-shipment financial assistance, he should take the necessary steps to obtain it.

Production/procurement of goods: Once the order is confirmed, the exporter should take necessary steps to ensure the timely availability of the goods of the specifications required and execute the export order promptly.

Shipping space: As soon as the export order is confirmed, the exporter should contract the shipping companies which have sailings for the port to which goods have to be sent and book the required shipping space. *Packing and marketing:* Once the goods are ready, they are packed and marked properly.

Quality control and pre-shipment inspection: Needless to say, goods should be exported only after ensuring that they are of proper quality *Excise clearance:* As a matter of policy, the government has granted excise duty exemption for export products. [11]

4.10. DOCUMENTATION REQUIRED

Proper documentation helps seller and overseas buyer in handling transactions in all means including time management, payment production, claim on loss etc. Most crucial components of a successful

international business transaction are the accurate completion of required export and import documentation. Failure to produce such documentation can hinder the dispatch of products by a manufacturer or supplier and can ultimately impede the timely receipt of goods by the customer.

4.10.1 Documentation required for import

The most important pieces of paperwork you will required to include:

- Packing List
- Bill of Lading
- Importer Security Filing (ISF)
- Commercial Invoice
- CBP Form 3461
- CBP Form 7501
- Arrival Notice
- Customs Bond
- Commodity Specific Documentation

4.10.2 Documentation required for export

AUXILLARY DOCUMENTS	REGULATORY DOCUMENTS	PRINCIPLE EXPORT DOCUMENTS
• Performa invoice. • Intimation for inspection • Shipping instructions • Insurance declaration • Shipping order • Mate receipt • Application for certificate of origin • Letter to the bank for collection or negotiation of document.	• Prescribed by Central Excise Authorities – i] Gate pass 1/2 ii] Bill of export iii]F-form • Export Application/ Dock Challan -Prescribed by Port Trust. • Receipt for payment of Port Charges • Vehicle Ticket • Exchange control declaration • Freight Payment Certificate • Insurance premium Payment	• Commercial invoice • Packing list: • Bill of lading • Combined transport document • Certificate of inspection / quality control • Insurance certificate /policy • Certificate of origin • Bills of exchange and shipment advice

Table 4.2. Auxillary, Regulatory and principle documents.

4.10.3. Form number

There are four FDA forms (Form FDA 3613, 3613a, 3613b, and 3613c) related to exporting FDA regulated products.

FORM	FOOD AND DRUG ADMINISTRATION FORMS
3613	Supplementary Information Certificate to Foreign Government Request
3613a	Supplementary Information Certificate of Exportability Requests
3613b	Supplementary Information Certificate of a Pharmaceutical product
3613c	Supplementary Information Non- Clinical Research use only certificates

Table 4.3 FDA FORM and regulated products.

4.11. FEES

Fee of one thousand US dollars shall be paid along with the application in Form 40 for the registration of a single drug meant for import and export into and use in and an additional fee at the rate of one thousand US dollars for each additional drug. [12]

5.0. BRAZIL ANVISA

Anvisa's role it to promote the protection of the population's health by executing sanitary control of the production, marketing and use of products and services subject to health regulation, including related environments, processes, ingredients and technologies, as well as the control in ports, airports and borders.

5.1 *MISSION* "To protect and promote health, ensuring the hygiene and safety of products and services and taking part in developing access to it."

5.1.1 *VISION* The National Health Surveillance Agency was established by Law 9.782, of January 26, 1999. The Agency is designated an autonomous agency operating under a special regime. This means that ANVISA is an independently administered, financially-autonomous regulatory agency, with the security of tenure for its directors during the period of their mandates. The Agency is managed by a Collegiate Board of Directors, comprised of five members.

5.2. IMPORT

Import are any resources, goods, or services that producers in one country sell to buyers in other countries in general, when a country purchase drugs from other country and brings them into the country crossing the geographical borders of the country. An IEC number (Import Export Code number) is required to act as an Importer or Exporter in India. Likewise, in almost all countries, a onetime licensing procedure to act as an Exporter/Importer is required to be completed. Brazil is one of its most important trading partners of India in the entire LAC (Latin America and Caribbean) region.

5.2.1 Import Requirements and Documentation

Includes import documentation and other requirements for both the U.S. exporter and foreign importer and Brazilian importers must register with the Foreign Trade Secretariat (SECEX), a branch of the former MDIC now

a branch of the Ministry of Economy. Depending on the product, Brazilian authorities may require more documentation.

For instance, the Ministry of Health controls all products that may affect the human body, including pharmaceuticals, vitamins, cosmetics and medical equipment/devices such products can only be imported and sold in Brazil if the foreign company establishes a local Brazilian manufacturing unit or local office, or the foreign company appoints a Brazilian distributor who is authorized by the Brazilian authorities to import and distribute medical products.

- Such products must be registered with Brazil's Health Regulatory Agency, ANVISA.

The entry of several imported products to Brazil is subject to permits issued by the respective Brazilian authorities that regulate the entry and commercialization of these goods.

- Goods that require an import license require approval from one or more of sixteen authorities, composed mainly of ministries or regulatory agencies. Usually, these licenses
- must be requested before the shipment, but in certain cases, they can be obtained after the shipment of goods, but prior to customs clearance.[13]

5.3. EXPORT

Exports are any resources, intermediate goods, or final goods or services that a buyer in one country purchases from a seller in another country. In general, Export is selling the drugs or pharmaceuticals, medical devices etc. to other countries crossing the geographical frontiers of the country. Exporting products regulated by Anvisa to Brazil might include the need for specific premarket authorizations issued by regulatory bodies in Brazil. Also, for some classes of products, manufacturers might have to be certified by Anvisa, a process which might include inspections at the place of origin. Requirements vary depending on the Products regulated by Anvisa are subjected to approval at borders when entering Brazil, and might be subjected to physical inspection. Please note that some classes of products may require authorizations prior to their embarkation in the exporting country. The main regulation about border control to which

products regulated by Anvisa are subjected to is the Resolution RDC 81/2008 (available only in Portuguese). There are other product-specific norms that must be observed by companies that wish to export to Brazil. There are other import regulations applicable to specific case such as:

- Products that enter Brazil for events and fairs: Resolution RDC 13/2004
- Health Services provided during Mass Gathering events: Resolution RDC 02/2013
- Products that enter Brazil during Mass Gathering events: Resolution RDC 41/2015
- Medicines that enter Brazil for use in clinical trials: Resolution RDC 09/2015[14]

5.4. POLICIES

Brazil has become a large market and more attractive to the pharmaceutical industry, thus the desire to entering this market became more evident. It is helpful to know the regulatory institutions that are involved with the clinical trials conducted in Brazil and to be awarded of related documents. In Brazil, three different institutions CONEP (Central), CEP (local committee), and ANVISA, are responsible for reviewing and approving regulatory documents to initiate a clinical study in this region. The CONEP and ANVISA processes happen in parallel.

5.4.1. Institution involve in approval process

- CONEP (Central)
- CEP (local and state committee)
- ANVISA 1. National Research Ethics Commission (CONEP),

Comissão Nacional de Ética em Pesquisa (CONEP), translated from Portuguese as National Committee of Ethics in Research: this committee is the Central Ethics Committee, which is related to the Ministry of Health, is responsible for review and approval of the ethical aspects of a clinical trial in Brazil.

5.4.2. Research Ethics Committee (CEP)

Comitê de Ética em Pesquisa (CEP), translated from Portuguese as Committee of Ethics in Research: these are local ethics committees that are registered with CONEP (the central committee). They can review and approve clinical trials conducted at an institution each company should have a list of documents and information required for the clinical trial.These documents and information are received from the sponsor and the study sites. These documents may contain templates of forms, documents, and statements required for the study. They also include statements related to general study information. For the first three study sites, one of these sites is selected as Coordinating Site; then its CEP is designated as the Coordinating CEP. All documentation must be provided in Portuguese; any translated document must be accompanied by the corresponding certificate of translation.

5.4.2.1. National Health Surveillance Agency

Agência Nacional de Vigilância Sanitária (ANVISA): this is the Brazilian Regulatory Agency. This group is responsible for reviewing all technical aspects and issuing the Import License for a clinical trial. Two types of dossiers are reviewed by ANVISA.

A. Processo de Anuência (Consent Process): the main application dossier for initial submission. This dossier will receive a unique specific number from ANVISA to be used for all updates.

B. Processo de Inclusão de Centros (Inclusion Centers Process): the dossier for adding sites when every site other than the one submitted in the Processo de Anuência. This document will carry the same number as the one previously assigned Regulatory regime.The basis for market regulation is Law No. 6360/76, which has been updated on several occasions since its introduction. Pharmacovigilance in Brazil is considered as fairly well-developed in comparison with many emerging markets, with standards largely comparable to those in developed markets. To obtain product registration, the manufacturer, importer or merchant must have either an 'Operating Authorisation' or a 'Special Operating Authorisation' issued by the MoH, a prior condition of which is an 'Operating Licence'. It

is also important to note that Brazilian legislation does not recognise companies that are dedicated exclusively to the commercialisation of drugs on behalf of third parties.[14]

5.5. POLICY

The Brazilian government is keen to support the development of the domestic pharmaceutical industry. Public procurement of goods produced outside South America, including pharmaceuticals, is set to decrease as a result of a new law that has recently come into force –
Lei No. 12.349/2010 – which amends the bidding law Lei de Licitação No 8.666/93.[16].The new legislation grants preference in public tenders to goods and services provided by domestic or foreign companies installed within the Mercosur economic block, even if their prices exceed those offered by foreign firms by up to 25%.The government's industrial policy is to foster domestic generic production of essential medicines, in particular vaccines and insulin as well as ARVs (HIV/AIDS), and it has invested substantial sums to boost local production technology and capacity 67% of its imports during 2010 were from USA (23%), Rest from Switzerland, Germany, France and Ireland showing high dependency on patented drugs. Brazilian govt. did not hesitate to exercise compulsory licensing to help their large HIV patient population.26% of Brazilian population suffers from either hypertension or Diabetes. Generic suppliers, be it domestic or foreign origin has a high chance of business from this sector.[17]

5.6. REGISTRATION AT ANVISA

The registration request must be made by the interested company through the Petitioning System, following the steps below:
1st STEP - REGISTRATION

The Company Registration is the first step to have access to the Petitioning System and should be used to register private companies that provide products or services regulated by Anvisa and to register users with a representation link with these companies.

STEP 2 - CHANGE OF THE COMPANY'S PORT

The companies should then promote the change, if necessary, of the Company Port, which will determine the amount of the fees to be paid by the interested party.

STEP 3 - REQUEST

Before accessing the Requesting System it is recommended that the interested party identify the Subject Code related to their request, since it is from this code that the entire transaction of the request will develop.During the process, the interested party will be guided to the type of petition of the chosen Subject Code.

STEP 4 - FEES

At the end of the petition process, the Union Recruitment Guide (GRU) will be generated to pay the Sanitary Surveillance Inspection Fee (TFVS) related to the chosen subject. The amount of the fee is determined by Interministerial Ordinance No. 701, of August 31, 2015.

STEP 5 – Protocol

After payment of the GRU, the interested party must gather all the requested documentation, according to the *checklist* of thechosen Subject Code and file with Anvisa, either in person or by mail.

The documents forwarded to Anvisa by mail must contain the following address, and no fax or copies thereof are accepted:

To the National Health Surveillance Agency

Board of Directors or General Management or Management or Unit to which the document is addressed

Care (A / C) of Document Management

Ref: Number of the Process or File or Petition, when applicable. Address: SIA, section 5, special area 57

CEP 71.205-050

Brasilia DF

STEP 6 - FOLLOW - UP

After filing the application, the interested party can follow the progress of their request, through the system of Consultation to the Situation of Documents.

ANVISA has established eight categories for the registration of medicines. These include new medicines, generic medicines, similar medicines, botanic medicines, biological & biotechnological medicines, parenteral medicines in bulk, homeopathic medicines and medicines that do not need registration criteria for the granting and renewal of drug registration with synthetic and semi-synthetic active ingredients, classified as new, generic and Similar, and other measures published by the ANVISA vide Board Resolution - RDC No. 200, OF 26 OF 2017 DECEMBER can be identified.

Reference Product - innovative product registered at the federal agency responsible for sanitary surveillance and marketed in the country, whose efficacy, safety and quality have been scientifically proven by the competent federal agency, upon registration (Law No. 9.787 of 10/02 / 1999).

Generic Drug - drug product similar to a reference or innovative product, which is intended to be interchangeable with it, usually produced after the expiration or waiver of patent protection or other exclusivity rights, proven its effectiveness, safety and quality, and designated by DCB or, in his absence, by the DCI (Law No. 9,787, of 10/02/1999).

Similar Drug - one that contains the same or the same active ingredients, has the same concentration, dosage form, route of administration, dosage and therapeutic indication, and which is equivalent to drug product registered at the federal agency responsible for health surveillance, which may differ only features relating to size and shape of the product, shelf life, packaging, labelling, excipients and carriers must always be identified by its trade mark; (Provisional Measure No. 2190-34, 2001).

New Medicine - Medicine with Input Active Pharmaceutical API again in the country.

Innovative Drug - Drug with incremental innovation, developing improvements in relation to a drug already registered in the country,

including novel salts, isomers or mixture of isomers, esters or ethers molecules previously registered.

List of Instruction Documents.

- Duly completed FP1 and FP2 petition forms.
- Proof of payment, or exemption, of the Health Surveillance Inspection Fee (TFVS), by means of a specific Union Recruitment Guide (GRU).
- Copy of the Operating License of the Company (Health Permit) updated Copy of the Authorization for Operation of the Company published in the DOU or, where applicable, the Special Functioning Authorization, published in the DOU.
- Statement of Simultaneous Registration of a similar and generic drug, 1315/05, if applicable. Copy of the updated Good Manufacturing and Control Certificate (CBPFC) issued by Anvisa for the production line in which the drug will be manufactured.[18]

5.6.1. Imported medicines

Proof of registration in the country of origin for imported medicines i.e Copy of the Certificate of Registration of the Medication issued by the sanitary authority of the country of origin, or equivalent document, or justification for exemption from this document. Sworn translation of the Certificate of Registration of the Medication, or justification for exemption from this statement with the global regulatory situation. Certificate of Pharmaceutical Product (CPP) in accordance with the standard adopted by WHO or a copy of the letter of approval of the registration in the country of origin, pursuant to article 18 of Law 6360/76. Sworn translation of the Certificate of Pharmaceutical Product (CPP) or the letter of approval of the registration in the country of origin, pursuant to article 18 of Law 6360/76. Specify the phase of the drug to be imported as a finished product, bulk or in the primary packaging. Copy of the Certificate of Good Manufacturing Practices and Control (CBPFC), issued by ANVISA, for the production line in which the drug, object of registration, will be manufactured , or a copy of the protocol for requesting inspection for the purpose of issue of the BPFC certificate accompanied by

a copy of a document certifying good manufacturing practice of pharmaceutical products by a valid production line issued by the body responsible for the Sanitary Surveillance of the manufacturer country and the respective sworn translation.

4.7. FEE STRUCTURE [19]

- For Originator Drug: 2700 USD – 27000 USD depending on the size of manufacturer.
- For generic drug: 2000 USD.
- For Similar product: 7000 USD.

6.0. AUSTRALIA

Therapeutic Goods Administration (TGA) approval is required for drug marketing applications (TGA) in Australia. The Therapeutic Goods Act 1989 (TG Act) and the Therapeutic Goods Regulations 1990 , both of which are a component of the Australian Government's Department of Health, govern the import and supply of pharmaceuticals in Australia (TG Regulations). A product must be registered on the Australian Register of Therapeutic Goods (ARTG) before it may be marketed in Australia, with few exceptions.[28]

6.1 AUTHORIZATION REQUIREMENTS

The TGA must be certain that a drug complies with all Australian legal criteria before it may be approved. The Therapeutic Goods Orders are a few of the statutory requirements under the TG Act (TGO). According to the TG Act, the following are considered default standards. As a result, any of these pharmacopoeias apply if a TGO does not specify a relevant standard:

- Therapeutic Goods Orders (TGO).
- British Pharmacopoeia (BP).
- European Pharmacopoeia (Ph Eur).
- US Pharmacopoeia-National Formulary (USP).

With the Secretary of the Department of Health's approval, a request for an exemption from the TG Act's provisions may be made. If drugs are brought into, exported from, or provided in Australia and don't adhere to the necessary criteria, there are offences and civil penalties that apply (sections 14 and 14A, TG Act).

6.2. REGULATORY BODY OF COUNTRY

The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Almost any product for which therapeutic claims are made

must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia. [29]

6.2.1. TGA

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods. The TGA uses social media to share links and information about safety alerts, recalls, current issues and events.

6.3. AUSTRALIA PHARMA MARKET

During the year 2016 Australia's total pharma market was $ 10.03 bn. The market is expected to touch $ 10.6 bn by the end of 2017 with just
0.78 % growth. The forecast for the next three years indicates market may stagnate or at best minimal growth. It is one of the most developed market in Asia-pacific region. Australian society has an ageing and affluent population, and this section mostly requires medicines of Central Nervous System & Cardiovascular System. India's exporters excel in the manufacture of generics of this therapeutic group and have record number of market authorizations. However, it is considered a Saturated market with very few sub-populations lacking access to medicines thereby chances of its growth in volumes is very moderate. In the government's announcement on September 30 2017, a list of 1,400 medicines that will be subjected to the price disclosure cycle from October 1 2017 was announced. These medicines will receive extra subsidies under the Pharmaceutical Benefits System (PBS). [30]

6.3.1. *Import of pharmaceuticals in Australia*

Buyers imported 2.3K pharmaceutical and HSN Code 30049069 import shipments to Australia. HSN Code 30049069 is the first product category of pharmaceutical imports in Australia. HS: Other progestogen and oestrogen group hormones, diazole, prednisolone, dexamethasone, and pituitary hormones. The majority of the pharmaceuticals with HSN

Code 30049069 in Australia are imported from India. Australia is the biggest import market for pharmaceuticals with HSN Code 30049069. With 2,255 shipments, Australia is the top importer of pharmaceuticals with HSN Code 30049069. Australian businesses have the option to include the importation of goods from abroad in their operations. Businesses thinking about importing should be aware of any applicable permits, duty levies, quarantine requirements, or other treatments. The Australian Department of Immigration and Border Protection has the authority to confiscate imports that don't comply with these regulations.[31]

6.3.2. *Import of Controlled Substance*

Narcotic, psychotropic drugs, some precursor chemicals, and several other drugs require import permission into Australia. These are several types of controlled substances which may be imported in Australia:

- Narcotic/Psychotropic drugs
- Anabolic/Androgenic
- Other controlled drugs
- Precursor chemicals

6.3.3. *Import of Drug for Personal Use.*

Some medications may be imported for you or a member of your close family under the personal importation scheme. This covers numerous medications that are not Australian-approved following guidelines must be followed, though: You need a legitimate Australian prescription or written authority if the medication is only available by prescription in Australia. You should make arrangements so that a copy of the prescription or written authorization is included in the shipment of the medication the majority of medications made with human or animal materials cannot be imported. One exception to this is insulin, which can be imported with a prescription. It is prohibited to import controlled substances. Even though there are prescription s for controlled

substances, they are not allowed for personal importation. The medication must not be given or sold to anybody other than members of your immediate family. You cannot provide a prescription medication to someone else. One order is limited to 3 months' worth of imports. Throughout a 12-month period, no more than 15 months' worth of supplies. When importing, u must retain imported medications in their original container with all of the labels still intact. Before an individual import a medicine, they should always seek advice from a medical professional on the appropriate treatment for your condition. A medical professional can also provide advice on appropriate access to a medicine. If after consulting a medical professional they decide to import: Check whether any of the ingredients in the medicine are listed in Schedule 4 of the Poisons Standard. Provided they have a valid Australian prescription, most Schedule 4 medicines can be imported for personal use - but not all.Check whether any ingredients are on the Office of Drug Control's list of controlled and prohibited substances. Some substances are not eligible for personal importation. Controlled substances can only be imported by a medical professional on behalf of a patient, while prohibited substances can only be imported with an appropriate license or authority be aware that other factors such as how a medicine is packaged or the dose size can influence how a medicine can be imported. Finally, if the medicine is of biological origin, check with Biosecurity at the Australian Department of Agriculture and Water Resources on whether you will need prior quarantine approval to import. It is the responsibility of anyone importing a medicine to ensure that they comply with all relevant legislation. If requirements are not met, the medicine could be seized and destroyed. Heavy penalties can apply for illegal importation of a medicine. [32]

6.3.4. *Import of Counterfeit Medicines*

It is prohibited to import a drug for personal use if it contains an unlisted component or substance.Therapeutic goods that are imported into Australia for export purposes only, are exempt from being included

in the ARTG if the goods remain subject to customs control under the Customs Act 1901 (Item 4, Schedule 5 of the *Therapeutic Goods Regulations 1990*).If the sponsor holds the medicine in a storage facility in Australia (outside of customs control), the medicine must be included in the ARTG prior to export. [33]

6.4. EXPORT OF PHARMACEUTICALS FROM AUSTRALIA

The export of therapeutic products from Australia is governed by the Therapeutic Goods Act 1989 (the Act). The Act, which establishes a standard national framework for the import, production, supply, and export of therapeutic products, is administered by the Therapeutic Goods Administration (TGA). The act is supported by Therapeutic Goods Regulations of 1990, the Therapeutic Goods (Medical Devices) Regulations of 2002, and other pieces of legislation complement the Act.

6.5. WORLD HEALTH ORGANIZATION (WHO) SCHEME [34]

Australia takes part in the World Health Organization's (WHO) certification programme for pharmaceutical goods that are traded internationally. The WHO Certification Scheme is an international voluntary agreement to provide assurance to participating countries about the quality and safety of pharmaceutical products moving in international commerce. According to the Scheme, one participating Member State must certify the following to the authority of another participating Member State (the recipient country) The manufacturing facilities and operations adhere to Good Manufacturing Practice (GMP) as advised by the WHO. [33]

6.5.1 *Export Only Medicines*

Export Only medicines must be listed in the ARTG (under section 26 of the Act) and cannot be supplied in Australia, including Australian duty free outlets.
Export Only medicines must be:

- Listed in the ARTG before export.

- Safe for their intended purpose(s) of use.
- Manufactured according to manufacturing principles for medicinal products of acceptable presentation.
- Must comply with required quality and safety standards.

Subject to the advertising provisions in sections 42DKB, 42DLA and 42DLC of the Act [34].

6.5.2. *Export of Controlled Substances*

The Office of Drug Control, a division of the Australian Department of Health, controls and offers guidance about the export of restricted drugs from Australia. Under the Customs (Prohibited Exports) Regulations of 1958, it is illegal to export controlled drugs (such as narcotics, psychotropic, and precursor compounds) without a licence or authorization. You require a licence and authorization from the Office of Drug Control in order to export a medicinal product that includes a restricted drug.

6.5.3 *Other Legislation Applicable To Export*

One must adhere to any additional applicable Australian or state and territory law while getting ready to export medications for commercial supply, such as: [34]

- Corporations Act 2001
- Criminal Code Act 1995
- Customs Act 1901
- Narcotic Drugs Act 1967
- Industrial Chemicals Act 2019
- Environment Protection and Biodiversity Conservation Act 1999
- Food Standards Australia New Zealand Act 1991
- Gene Technology Act 2000 and the Gene Technology Regulations 2001
- Competition and Consumer Act 2010 and the Australian Consumer Law
- National Measurement Act 1960.

6.6. EXPORTING MEDICINES FOR COMMERCIAL SUPPLY [35]

According to the Act, unless they are exempt, therapeutic products must be registered in the Australian Register of Therapeutic Goods (ARTG) before they may be made, supplied, or exported from Australia. Any medication that is exported for commercial supply must typically either Listed in the ARTG as an Export Only medicine OR Registered or listed in the ARTG and authorised for supply in Australia.

6.6.1. *Medicines for commercial supply*

To export a medicine for commercial supply, you must be either:

The person (generally, this is the sponsor of the good) in relation to whom the medicine is registered or listed in the ARTG.OR An agent authorised to act on behalf of the person in relation to whom the medicine is registered or listed in the ARTG. The export of a medicine for commercial supply will breach section 19B and/or contravene section 19D of the Therapeutic *Goods Act 1989* in cases where the medicine is exported by someone other than a person in relation to whom the medicine is registered or listed in the ARTG (or other than someone authorised to act on that person's behalf). The medicine has not been registered or listed in the ARTG and is not an exempt or excluded good.

6.7. SALE OF MEDICINAL AND PHARMACEUTICALS IN AUSTRALIA

6.7.1. *According to import*

Imports of Medicinal & Pharmaceutical Products in Australia averaged

566.54 AUD Million from 1988 until 2022.It reached an all-time high of 1906 AUD Million in August of 2022.It records low of 44 AUD Million in December of 1988.Australia Imports of Medicinal & Pharmaceutical Products - values, historical data and charts Figure 6.2 - was last updated on October of 2022.

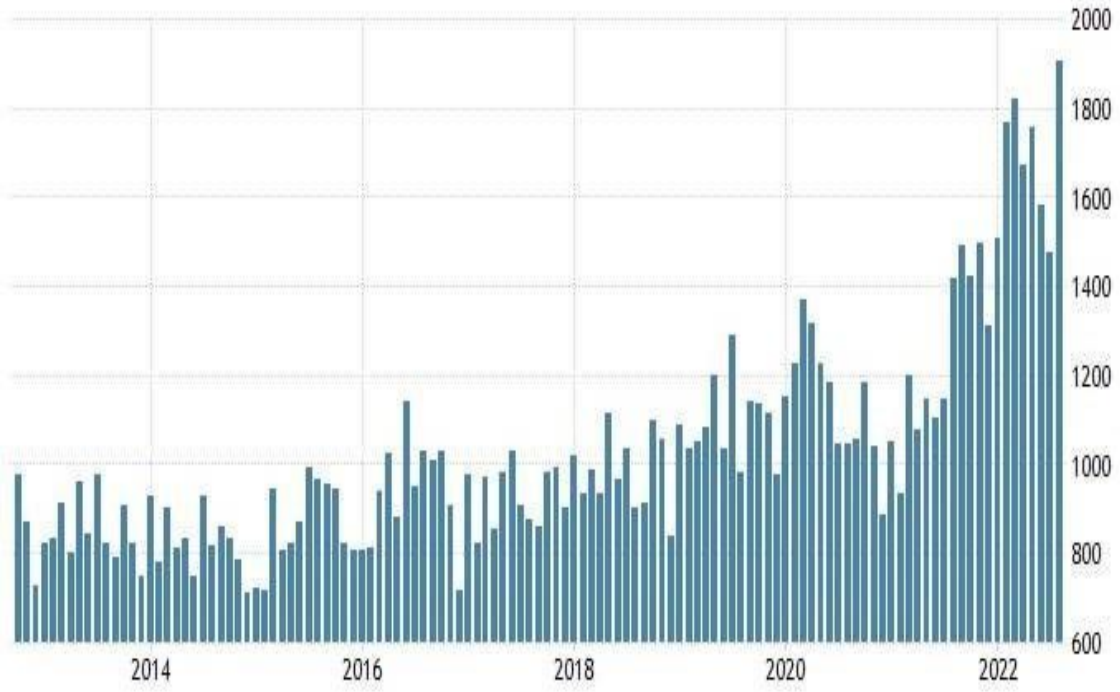

Figure 7.2 Statistics of Australia's Import of Medicinal & Pharmaceutical Products

- X axis represents the year
- Y axis represents the sale in AUD Million [35]

6.8. REGULATION

The Therapeutic Good Administration (TGA) is responsible for ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose. These include goods Australians rely on every day, such as vitamin tablets and sunscreens, through to goods used to treat serious conditions, such as prescription medicines, vaccines, blood products and surgical implants. The TGA is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods. The TGA regulates therapeutic goods through: pre-market assessment, post-market monitoring and enforcement of standards, licensing of Australian manufacturers and verifying overseas manufacturers' compliance with the same standards as their Australian counterparts.

The TGA is responsible for ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose. These

include goods Australians rely on every day, such as vitamin tablets and sunscreens, through to goods used to treat serious conditions, such as prescription medicines, vaccines, blood products and surgical implants.
The TGA regulates the supply of:

- Medicines prescribed by a doctor or dentist.
- Medicines available from behind the pharmacy counter.
- Medicines available in the general pharmacy.
- Medicines available from supermarkets.

Complementary medicines, these include vitamins, herbal and traditional medicines medical devices, from simple devices like bandages to complex technologies like heart pacemakers. Products used to test for various diseases or conditions (in vitro diagnostic devices), such as blood tests; and Vaccines, blood products, and other biologics and the manufacturing and advertising of these products.

6.9. POLICIES

Regulatory legal and policy services provide high quality and timely solutions-focussed legal services to the TGA. They also assist the Office of Drug Control (ODC) to support regulatory decisions, including implementation of business and legislative reforms compliance and enforcement activities. The Principal Legal and Policy Adviser is also responsible for providing leadership in delivering legally robust outputs for the regulatory process reviewing the legislative framework against government and stakeholders expectations of our regulatory functions Coordinating technical input for Freedom of Information (FOI) requests.[36]

6.9.1. *Regulatory Practice and Support Branch*

This branch provide operational regulatory policy advice and specific support services to Health Product Regulation Group (HPRG). This ensures efficient, best practice regulatory operations. Responsibilities for a range of functions including Activity-based pricing and billing

Business system help desk coordinating internal reviews of regulatory decision, labour hire and procurement regulatory impact statement advice. Data analytics support. Regulatory practice and support branch also includes the Office of Drug Control (ODC). They regulate and provide advice on the import, export and manufacture of controlled drugs to support Australia's obligations under the Narcotic Drugs Conventions Which includes administering licenses for access to controlled drugs implementing the regulatory framework pertaining to the cultivation, production and manufacture of medicinal cannabis.

6.9.2. *Regulatory Compliance Branch*

They are responsible for regulatory compliance activities relating to the offence provisions of the *Therapeutic Goods Act 1989, including:*

- Intelligence
- Compliance
- Enforcement action.

This includes unlawful advertising, import, export, manufacturing, and supply of therapeutic goods.

6.9.3 *Regulatory Engagement Branch*

They are responsible for providing a range of policy advice, communication and support services for TGA, including:

1. Regulatory guidance and education materials
2. Planning and performance reporting
3. Parliamentary processes
4. Media responses
5. External events and webinar programs
6. Library services
7. Scheduling relating to the Poisons Standard

6.9.4. *Medicines Regulation Division*

To evaluate applications to approve new medicines for supply in Australia Undertake safety monitoring of medicines and vaccines approved for supply in Australia after they are on the market. [37]

6.9.4.1. *International Regulatory Branch*

They are responsible for delivering two Department of Foreign Affairs and Trade (DFAT) -funded aid programs:
Regulatory Strengthening Program for regional medicines regulators Australian Expert Technical Advisory Program – Regulatory Support and Safety Monitoring for COVID-19 vaccine delivery in the region.
They also support The Asian Development Bank with their work to access and increase supply of vaccines for Developing Member.

6.10. PROCEDURE [37]

6.10.1 ***Export*** This is an outline of how the pharmaceuticals are exported in Australia.

6.10.2 *Applying for an export only medicine listing*

To apply for an Export only listing, the sponsor of the medicine must have a TGA Business Services account. After logging into the portal, the sponsor can apply for an export only listing using the online application form. Refer to: *User guide to apply for an Export only medicine listing.*

6.10.3. *Mandatory documentation*

There are three mandatory documents that must be included as part of a new export only application which will be assessed to determine the product's eligibility for listing in the ARTG
The product specification

- Product label and any other information packaged with the product prior to export from Australia
- Notification that 26B (1) certificate is not required (patent certificate).

6.10.4. *Applications* [37]

Narcotic, psychotropic drugs and some precursor chemicals required export permission from Australia. A list of these substances are provided as a guide.
Applications are grouped into two types:

6.10.4.1 Licence and permit to export

6.10.4.1.1 Pre-export notification

Narcotic, psychotropic drugs and some precursor chemicals required a licence and permit to export. The licence is valid up to 12 months and the permit is required for each export of each drug and/or preparation. Select the forms to *request a Pre-Export Notification Licence* and *Pre- Export Notification to export* which include precursor in the form title.

6.10.4.2. *Import*

There is no requirement for importers (companies or individuals) to hold an import licence to import goods into Australia. However, depending on the nature of the goods and regardless of value, importers might need to obtain permits to clear certain imported goods from customs control. Importers are required, amongst other things, to ensure that imported goods are correctly labelled. For example, imported goods that require a trade description must be marked with the name of the country in which the goods were made or produced, and where specified, a true description of the goods.[37]

6.11. FEES STRUCTURE

6.11.1. *Annual charges* [38]

Type of prescription medicine	Charge
Biological medicine	$7,120
Non biological medicine (chemical entity) - Subsection 3-10 of regulation 8	$4,060
Non biological medicine (chemical entity) – Otherwise	$3,290
Provisionally registered biological medicine	$16,100
Provisionally registered non biological medicine	$13,100

Table 6.11.1 Charges are in the Therapeutic Goods

These applications have both an application fee and an evaluation fee. These fees are in Schedule 9, Therapeutic Goods Regulations 1990.

These applications have both an application fee and an evaluation fee. These fees are in Schedule 9, Therapeutic Goods Regulations 1990.

Prescription medicine application type	Application fee	Evaluation fee
New chemical entity	$47,800	$191,800
Extension of indications	$28,500	$113,800
Major variations	$18,600	$74,200
Minor variation applications applied for under section 23 of the Act (Change in formulation, composition, design specifications, type of container or change of trade name)	$1,100	$4,360
Variations to an ARTG entry involving the evaluation of clinical, preclinical or bio-equivalence data, applied for under 9D(3) of the Act. Includes applications for changes to Product Information involving the evaluation of clinical, pre-clinical or bio-equivalence data	$1,100	$4,360
Additional trade name	$3,020	$12,100
New generic product	$18,400	$73,200
Extension of indications of a generic medicine to maintain currency with indications already registered to the corresponding innovator product and where clinical and/or bioequivalence data are not required	$1,100 $	$4,350

Table 6.11.2. Prescription medicine application and evaluation fees

7.0. GULF CO-OPERTAION COUNCIL

Saudi Arabia is among the Middle East's most attractive markets for multinational companies. The Kingdom's diversification plans bode well for local and regional companies, with 'Vision 2030' encouraging the expansion of manufacturing agreements in the country. Major interest to multinationals Key draws like the sheer market size, the sophistication of the demand and the favourable epidemiological trends. Local players will also find a fertile commercial base, given the need to satisfy rising volume demand for the established generic treatments. However, issues relating to patent approvals and the regulatory system remain a major issue for foreign research based pharmaceutical players. The market from the present USD 8.3 billion(in 2019) is expected to touch USD 8.8 billion by the end of 2020 with a year on year growth of 5.2%.[39]

Pharmaceutical market of Saudi Arabia: Saudi Arabia pharmaceutical market was valued at USD 8.3bn in 2019. Forecasts show by 2024 Market will clock $ 10.89 Billion with a CAGR of 5.4%.

7.1. REGULATORY REGIME [39]

The main regulatory authority in the country is the Ministry of Health (MoH), which requires all pharmaceutical companies to be registered. The registration process takes between six and 18 months to complete, although approval times have been steadily decreasing over the years. Registrations must be renewed every five years. Local producers or joint ventures are reported to enjoy far shorter product registration times. For imported products, the process often takes years, while for local items the approval time can take as little as three months. Once a product is registered, a price must be approved by the SFDA before it can be sold. Approval for pharmaceuticals new to the market is also undertaken by the SFDA, which follows the US FDA's Good Manufacturing Practice (GMP) guidelines. According to the World Health Organization (WHO), there were 6,541 pharmaceutical

products registered in Saudi Arabia in 2011. Legal provisions exist for the Medicines Regulatory Authority to make the list of registered products available publically and update it regularly. Medicines are registered by their international non-proprietary names (INN) or brand name and INN. There are no duties imposed on imported active pharmaceutical ingredients (APIs) or on finished dose pharmaceuticals. The SFDA also regulates imported and exported pharmaceuticals and drug manufacturing, [40] advertising and withdrawals. It maintains a list of registered and newly-registered pharmaceutical products, and is responsible for the Saudi National Formulary and over-the-counter (OTC) Formulary.

Products must gain SFDA approval before entering the market. Applications for approval, supported by the required certificates duly legalized by a Saudi Arabian consulate in the applicant's country, are examined and the samples are analysed by the authorities to ensure that they correspond to the specifications. If the regulatory body is satisfied with the results, a license is then issued to the applicant.

7.2. SAUDI FOOD AND DRUG AUTHORITY

The Saudi Food and Drug Authority (SFDA) was established under the Council of Ministers resolution no (1) dated 07/01/1424 H, as an independent body corporate that directly reports to The President of the Council of Ministers. The Authority objective is to ensure safety of food and drug for human and animal, and safety of biological and chemical substance as well as electronic products. [41]

7.2.1. Authority's main objectives:

The main purpose of the SFDA establishment is to regulate, oversee, and control food, drug, medical devices, as well as to set mandatory standard specifications thereof, whether they are imported or locally manufactured. The control and/or testing activities can be conducted in the SFDA or other agency's laboratories. Moreover, the SFDA is in

charge of consumer's awareness on all matters related to food, drug and medical devices and all other products and supplies.

The main objectives of SFDA can be outlined as follows:

1. Observe the safety, security, and effectiveness of food and drug for humans and animal.

2. Observe the safety of complementary biological and chemical substances, cosmetics and pesticides.

3. Observe the safety of medical devices and its impact on public health.

4. Ensure accuracy and safety of medical and diagnostic devices.

Launch clear policies and procedures for food and drug, and plan to achieve and implement these policies. Gulf Cooperation Council regulatory authorities Gulf Central Committee for Drug Registrations (GCC-DR) Located in the executive office for Health Ministers, Riyadh, Saudi Arabia.

Drug registration: there are two processes of drug registration;

1. Centralized registration procedure

2. Decentralized registration procedure [42]

7.2.1.1. Centralized registration procedure

1. The executive office of GCC-DR assumes the receipt of registration files after ensuring the fulfilment of registration requirements and upon duly filling the following forms:

- The drug companies' registration form.
- A pharmaceutical chemical entity/ preparation registration form.

Eight complete files for each chemical entity and 17 samples have to be submitted to the executive office and two samples shall be dispatched to each country along with registration file.

2. Every country shall study the registration files forwarded to it and then return those files with its recommendation to the committee.

3. The company needs to provide the laboratory for the analysis of standard materials, methods etc.

4. The executive office dispatches the samples of chemical entity to reference-accredited laboratory for the analysis.

5. After approving the registration of company and or chemical entity centrally, the remaining authentication and documentation, fees are finalized on country basis, as per their prescribed and established policies.

6. The executive office issues the registration certificate.

7. The companies reserve their rights to lodge their grievances to the executive office within a period of two months effective from the date of notification about the registration by GCC-DR.

7.3. FEES

The validity of the central registration

- The central Gulf committee's resolutions for drug registration are binding for the consolidated purchasing.
- All countries must sanction and approve the export price, which has been approved by the committee upon completion of the registration procedures in the country.[43]

7.3.1. Issue of Centralization of registration of drugs [45]

It is not mandatory to centralize the registration of drugs in GCC, as of now. But for special classes of drugs, registration through the centralized process is necessary. These are as follows: Generic drugs

for which bioequivalence studies cannot be done, e.g. inhalable medicines and some nasal inhalers. Drugs supported by biotechnology for which bioequivalence studies cannot be done and which require clinical or pharmacodynamics studies. Drugs with narrow therapeutic spectrum, which are administered orally.

7.3.2. Decentralized registration procedure

Registration regulations in major countries of GCC Although there is a centralized and quite harmonized process for drug registration in GCC countries, the regulatory requirements of a few big countries like Saudi Arabia and UAE are separate. These countries have their well- established regulatory system and its enforcement.[44] In this study, we will discuss briefly the registration requirements of multi-source generic products of the following GCC countries:

- Saudi Arabia
- Bahrain
- Kuwait
- UAE

Agent

↓

File application form and enclosures

↓

Registration form

↓

Technical Committee for evaluation

a) Pending for more information
b) Approved
c) Not approved

↓

Analysis (Central laboratory for Food and Drug analysis)

↓

Technical committee for evaluation (TCE (21))

a) Pending for more information
b) Approved
c) Not approved

↓

Pricing section

↓

Technical committee for evaluation

↓

Acceptance or non – acceptance

Final approval or rejection

7.4. STABILITY DATA REQUIREMENTS.

SFDA recommends the GCC guidelines for stability study data preparation. GCC countries come under climatic Zone III and IVa (Hot and dry and hot and humid). Three primary batches are recommended by the GCC guidelines. For generic drug product long- term stability study supporting the complete proposed shelf-life should be submitted. [46]

7.5. KINGDOM OF BAHRAIN-DRUG REGISTRATION REQUIREMENTS.

The regulations for pharmaceutical registration in Bahrain are almost similar to the other GCC countries. All types of necessary information is required by the Ministry of Health, Bahrain but as compared to the other GCC countries, they also focus on the details of the company profile and several types of business activities like current business merger by the company, etc. The following table provides the basic information required for the registration of a drug in the Kingdom of Bahrain and other GCC countries. [47]

7.6. KUWAIT: DRUG REGISTRATION REQUIREMENTS

Medicines in Kuwait are regulated for quality, safety and efficacy standards, price control, and patent protection. Kuwait has 40 years of experience of a regulatory system and plays a prominent role in the GCC. The Kuwait food and drug authority (KuFDA) is the head regulatory agency, which follows the ministerial decree 302/80 to register pharmaceutical products. [48]

8.0. ZIMBABWE

The Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03] and its Regulations, S.I 150 of 1991, established the Medicines Control Authority of Zimbabwe (MCAZ). Following consultations with the Authority in accordance with Sections 38 and 74 of the MASCA, the Minister of Health and Child Care issued the Medicines and Allied Substances Control (Import and Export of Medicines) Regulations, 2008 [S.I 57 of 2008]. The Medicines and Allied Substances Control (Import and Export of Medicines) Regulations, S.I. 57 of 2008, were used to develop these rules.[49]

These recommendations attempt to describe the procedures for obtaining an import or export permission for registered medicines, as well as the clearance of imported medication consignments at ports of entry. The rules also clarify the roles and duties of the parties involved in the project. The importation and exportation of recognised medications.[50]

8.1 APPLICATION

These guidelines apply to all registered medicines except:

1. Dangerous Drugs controlled under the Dangerous Drugs Act [Chapter 15:02];
2. Psychotropic substances controlled under the Medicines and Allied Substances Control (General) Regulations, 1991;
3. Medicines imported for a named person under section 75 of the MASCA.

8.1.1. Application for a medical import or export permit

Medicines may be imported or exported by:

- A wholesale dealer's permit holder who has been duly appointed by the principal as an authorised importer or exporter of that medicine;

- A medical practitioner or veterinary surgeon who holds a dispensing licence;
- A licenced pharmacy;
- A licenced manufacturer; and
- Any person or organisation approved by the Authority.

8.2 ISSUE OF IMPORT/EXPORT PERMITS

- Application forms and accompanying documents are submitted to the Authority at No. 106 Baines Avenue, Harare. An electronic version of the same application
- It should be submitted through electronic mail to the email address - imports@mcaz.co.zw. Hard copies are submitted to the Director-General.
- An application for an import permit shall be made in the Form

I.E 2 and should be accompanied by a copy of the pro-forma invoice from the supplier.

- Proof of consent by the principal or his duly authorized distributer to import the medicine to which the application relates.
- An application for an export permit shall be made in the Form

I.E 3.

- All applications shall be accompanied by an application fee as stated in the current fee schedule.
- Using Form I.E.1, a wholesale dealer should provide notification of their appointment as an authorized importer or exporter by the principal that is in respect to the medicine they intent to import or export. Form I.E 1 shall be accompanied by a letter from the principal stating the products that the applicant is allowed to import or export. This letter should be dated and on a letter head of the principal.

- All applications for an export permit shall include the following details [Reference: Section 5(2) and Section 5(4) of S.I 57 of 2008] [51]

8.2.1. An application for an import permit shall include the following:

a) The name and address of the importer; and

b) The trade name or proprietary name of the medicine, if any;

c) The International Non-Proprietary Name (INN) or generic name of the medicine
d) Its strength;

e) The total quantity of the medicine;

f) Name and address of the supplier; and g) the name and address of the manufacturer, if not the same as the supplier;
h) The Zimbabwean registration number;

i) The cost, insurance, freight (CIF) value of the consignment;

j) The port of entry.

Conditions for Amendment of Permit

If an applicant, for justifiable cause, wishes to amend an issued permit, he or she may submit any such request to the Director- General in writing. The letter should state the area(s) the applicant wants amended. This letter should be dated, stamped, signed and with a letter head.
4.3.2 The letter of request shall be accompanied by an amendment fee as stated in the current fee schedule.

- The applicant must also submit the original permit which is to be amended together with the letter of application for amendment.

Note: A used permit, whether exhausted or partially, may not be amended. There are no conditions whatsoever that a permit may be amended if the applicant does not submit the original copy of the import or export permit. If the applicant is unable to declare the

original copy, they will be required to reapply for the issuance of another permit. [52]

8.3. VALIDITY OF PERMIT

1. Upon successful application a permit shall be issued in the Form

I.E 4 (for imports) and I.E 5 (for exports).

2. Permits shall, in terms of section 9 of SI 57 of 2008, be valid for a period of six months from date of issue.

3. A permit is valid if it has the MCAZ seal and Director-General's signature, or designate

8.4. CLEARING OF CONSIGNMENTS

- Ports of entry
- The importation of all consignments of medicines should be done through the designated ports of entry, which are:
- Harare International Airport
- Bulawayo Airport
- Harare Customs
- Bulawayo Customs
- Plumtree Border Post
- Beit bridge Border Post
- Forbes Border Post

Note: No importations through ordinary or registered post shall be sanctioned. [53]

8.4.1. Clearing of Imported Consignments

- On arrival of the consignment, the importer shall notify the Director General of the importation using Form I.E 6 and shall pay a verification fee of 0.5% of the Cost Insurance and Freight value (CIF) before the consignment can be cleared.
- To expedite the process of consignment clearance, importers are encouraged to pay the verification fee prior to the arrival of

the consignment. No notifications or payments shall be accepted at the port of entry.

- It remains the responsibility of the applicant to ensure that imported medicines meet
- The Zimbabwean labelling requirements. If the medicine does not meet the conditions of belling under which it was registered, the importer may;
- Apply for approval to affix stickers with the product's registration details onto the medicine package as provided for by section 75 of the Act, and
- Pay a fee, as stated in the current fee schedule, for every product that needs stickers affixed and present the receipt at the point of physical examination and verification of consignment.
- For imports via Harare International Airport, consignment verification shall be conducted during week days between 10.30am and 12.30pm.
- Verification of consignments that come through Harare Customs, Bulawayo

Airport, Bulawayo Customs, Plumtree Border Post and Forbes Border Post: Any such consignments shall be cleared by the Authority within 3 days of receipt of the notification of importation.

- Port Health officials with the assistance of ZIMRA officials will carry out verification and physical examination at the port.
- The consignee shall keep the consignment sealed and under quarantine at approved premises, until it has been cleared by the Authority.
- The consignee and an inspector from the Authority shall organize for physical examination of the consignment, and this shall be done at the Authority's premises, No. 106 Baines Avenue, Harare.

The physical examination of consignments shall be done between 1400hours-1600hours.

- The consignee can only remove medicines from quarantine when the consignment has been cleared by the Authority.
- A Regulatory Officer stationed at Beit bridge Border Post shall carry out consignment verification and clearance.
- In the case of exportation, upon the successful exportation of medicines, the exporter shall notify the Director General in the Form IE 7 within 30days of exportation. [54]

9.0. SOUTH AFRICA

South Africa represents one of the most advanced and regulated pharmaceutical markets in the African continent, playing a strategic role in regional and global medicine supply chains. The country has a mixed pharmaceutical landscape comprising local manufacturers, multinational companies, importers, exporters, wholesalers, and distributors that collectively ensure the availability of medicines for both domestic consumption and export to neighbouring African countries and international markets. However, the import, export, and sale of pharmaceutical products in South Africa are governed by a stringent regulatory framework that presents several operational, administrative, and compliance-related challenges.

The regulation of medicines in South Africa is primarily governed by the **Medicines and Related Substances Act, 1965 (as amended)**, which aims to ensure that all pharmaceutical products available in the market meet acceptable standards of **quality, safety, and efficacy**. The **South African Health Products Regulatory Authority (SAHPRA)** serves as the national regulatory authority responsible for licensing, registration, inspection, market surveillance, and enforcement activities related to pharmaceutical products. SAHPRA oversees the approval of medicines, clinical trials, import and export permits, manufacturing licenses, and post-marketing surveillance.

Despite efforts to modernize regulatory systems, including the adoption of reliance pathways, digital submission platforms, and backlog-clearance initiatives, pharmaceutical companies continue to face challenges related to regulatory delays, capacity constraints, administrative complexity, and evolving compliance expectations. These challenges directly affect patient access to essential medicines, investment decisions by pharmaceutical companies, and South Africa's position as a regional pharmaceutical hub.[55]

Therefore, understanding the regulatory challenges associated with the **import, export, and sale of pharmaceutical products in South Africa** is essential for stakeholders including regulators, manufacturers, importers, exporters, and policymakers. A comprehensive evaluation of these challenges provides valuable insights for improving regulatory efficiency, strengthening pharmaceutical trade, and ensuring sustainable access to quality medicines within South Africa and across ROW markets.[56]

9.1 Regulatory Framework for Pharmaceuticals in South Africa Regulatory Authority & Legislation

The **South African Health Products Regulatory Authority (SAHPRA)** is the national authority responsible for regulation of medicines, scheduled substances, clinical trials, and related products under the **Medicines and Related Substances Act, 1965 (as amended)**. SAHPRA issues licences for manufacturing, importation, exportation, distribution, and sale of pharmaceuticals.

SAHPRA replaced the older Medicines Control Council (MCC) with a mandate to modernise and streamline drug regulation.

Import & Export Guidelines

Only **registered products** or those authorised under strict conditions (e.g., Section 21 authorisation for unregistered medicines) may be imported or exported.

Import/export applications must comply with SAHPRA **administrative and technical standards** intended to protect quality, safety and efficacy.[57]

9.2 Key Regulatory Challenges in South Africa

1. Lengthy Approval Processes and Backlogs

Historical backlogs and slow regulatory reviews have significantly delayed market access for pharmaceutical products — especially new drugs, generics, and biologics. Approval times have been reported to take multiple years historically, discouraging market entry. Even with ongoing backlog clearance projects and process improvements, delays continue to be cited as a critical barrier.

Impact:

- Delays in bringing products to market reduce patient access to treatments.
- Increased costs and investment uncertainty for both local producers and foreign suppliers.

2. Resource Constraints and Regulatory Capacity

Limited human and financial resources at SAHPRA affect timely evaluations, inspections, and compliance monitoring.

Technical capacity constraints contribute to slow dossier reviews, especially for complex products like biologics, or for manufacturing site inspections. Pharm regulatory.

Impact:

- Firms face unpredictable timelines and may defer submissions or investment decisions.

3. Complex Technical Requirements

Requirements such as **Good Manufacturing Practice (GMP) certification**, country-specific labelling, bioequivalence data, and local trial data increase compliance burden.

Compliance with these stringent technical standards often involves significant cost and documentation. Non-compliance can lead to delays or rejection.

Impact:

- Smaller firms, especially those in emerging markets, may struggle to meet these requirements, reducing competition and access.

4. Import/Export Administrative & License Hurdles

Import permits, customs documentation, and SAHPRA licensing are necessary for pharmaceutical imports and exports. Missteps in classification (e.g., Harmonized System codes), documentation, or permits can delay customs clearance.

Only authorised local entities can import registered products — foreign companies must partner with SAHPRA-licensed importers

Impact:

- Administrative complexity adds to costs and creates barriers for new market entrants.
- Exporters also face documentation burdens before products can leave the country.

5. Market Entry Barriers & Export Challenges

Regulatory requirements vary across **African and global markets**, making export compliance difficult and costly. Meeting diverse standards beyond SAHPRA (e.g., EU, US FDA regulators) adds complexity for South African exporters.

Harmonising standards across African markets (e.g., under AfCFTA) is ongoing but incomplete, slowing cross-border pharmaceutical trade.

Impact:

• High technical and regulatory barriers limit South African pharmaceutical exports within Africa and globally.

6. Pricing Controls & Economic Constraints

Policies such as **Single Exit Pricing (SEP)** cap prices locally, impacting profitability. When combined with export pricing dynamics and currency volatility, this creates economic pressures for manufacturers and importers.

Impact:

• Reduced incentives for companies to introduce innovative or imported medicines at scale.

7. Compliance & Enforcement Challenges

Monitoring compliance at **ports of entry**, preventing counterfeits, and controlling illegal sales are ongoing enforcement challenges for SAHPRA.

Ensuring that products imported and sold meet quality standards remains a resource-intensive task.

Impact:

• Risks of substandard or counterfeit medicines entering the supply chain, undermining public health and trust.[58]

10.0. GLOBAL CHALLENGES

In recent years, the global pharmaceutical export business has experienced remarkable growth. While the market for healthcare items to combat pandemics increased, some products experienced a decline.

Controlling strong export and distribution lines in the pharmaceutical sector is difficult. Although the pharmaceutical sector employs several methods to ensure effective export management, the following are some dangers and problems in pharma export.

10.1. SUPPLY CHAIN DISRUPTIONS

One of the biggest challenges globally since the start of the pandemic has been the disruption in the supply chain. This has also been one of the hardest-hitting disruptions for the pharma industry. The pharmaceutical industry relies heavily on importing and exporting raw materials and generic medicine production. China and India account for 31% of the FDA- registered facilities around the globe.

The shortage of resources has also halted pharmaceutical production, as a delay in PPE exports and medical supplies/ingredients has impacted companies that rely on offshore products in everyday operations.

10.1.1. Keeping proper storage conditions during shipment maintaining suitable storage conditions, whether for an API, an excipient, or finished goods, is a critical parameter for the safety and efficacy of pharmaceutical products. Storage requirements differ from one product to the next. For example, most drugs must be stored at room temperature, however other special products must be stored cold.

Assume that proper storage conditions are not controlled during exports. In that instance, it has a direct impact on the product's quality and the consumer's health. Furthermore, imagine the products degrade during transportation. In that instance, it may result in a market recall, hurting the manufacturer's reputation and resulting in waste. As a result, maintaining storage conditions throughout export from the warehouse to the destination becomes a difficult operation.

10.1.2. Keeping track of the distribution line

The pharmaceutical distribution line is a well-organized network of manufacturers, wholesalers, and distributors who work together to make products available to customers. Companies must ensure proper product distribution in order to survive in the market for an extended period of time. However, in poor nations where many pharmaceutical companies have not embraced digital supply handling modes, it is difficult to track all transactions. Shipment records are not always carefully kept, and there are no documentation of missing merchandise during travel. Furthermore, one main impediment to this system is that health authorities have not implemented stringent and comprehensive standards for medication distribution. As a result, there is a lack of control over the distribution chain, making it difficult to trace the exports. Many obstacles exist in this process, such as timely product delivery, temperature maintenance, inventory management, tracking of expired products, and so on.

Supply networks around the world have been damaged, disturbed, and some have even come to a halt as a result of nationwide lockdowns, closed borders, and suspended air traffic. The pharmaceutical industry drives its operations by ensuring the seamless operation of the supply chain in order to deliver pharmaceuticals and vaccines all over the world by:

- Rapid procurement of raw materials and chemicals for medication
- Manufacturing controlling research and production equipment
- Optimised warehouse management inventory management through track and trace on time in full shipments to clients
- Executives in the pharmaceutical sector will need to lessen their pharmaceutical supply chain issues by shifting tactics and maximising existing resources. [59]

10.2. CLINICAL TRIALS

Trials were suspended after the Indian Ministry of Health and Family Welfare revised rules requiring participants who claim to have been injured as a result of a clinical trial to get greater compensation. The Drug

Controller General of India (DCGI) recently declared that, in addition to getting written informed consent, audio-visual recording of each subject's permission is essential in a clinical trial, effective immediately. Uncertainty in the clinical trial regulation procedure jeopardises the overall clinical research environment in India, as well as the availability of novel therapies and vaccinations for Indian patents. [60]

10.3. GOVERNMENT PRICE CONTROL

The Department of Pharmaceuticals (DoP) has suggested an international reference price model including a purchasing power parity adjustment for patented medications purchased by the government and patented medicines covered by health insurance. This proposal would establish an unsustainable government pricing system and business climate for medications, the prices of which are already low in India in contrast to other countries.

10.4. RDP STANDS FOR REGULATORY DATA PROTECTION.

The Government continues to apply a flexible interpretation of Article 39 of the TRIPS Agreement, allowing government officials to give marketing authorization based on test and other evidence submitted by our member companies to show the safety and efficacy of their products. While some beneficial steps have been made to avoid inappropriate disclosure of government data, additional efforts are required to ensure certainty that test and other data will be adequately protected against unauthorised use in order to achieve marketing authorisation for a set length of time. Our member companies' efforts to achieve data protection through the judicial system continue, with minimal success. The heated argument in the Brazilian judiciary reveals the legal framework's lack of clarity about RDP protection for pharmaceuticals. While federal statute 10.603/02 protects veterinary and agriculture products, legislation does not give comparable protection for pharmaceutical items for human use, resulting in discriminatory treatment.[61]

Overall, country does not provide enough protection for data submitted for novel biopharmaceutical medicines. A term of data protection is required to prevent from relying on the innovator's data in approving a follow-on

medication application. Although lawsuits have been filed seeking to establish a term of data protection for specific items, the cases are currently ongoing in the courts. Courts have failed to provide innovators with adequate regulatory data protection. A fruitful interaction between US and Brazilian officials could result in a suitable RDP regime for pharmaceutical items in Brazil by ensuring that domestic legislation satisfies high requirements.

10.5. COST OF INNOVATION AND EVOLUTION

With the increased demand for innovation that the pandemic now demands, many companies have been financially impacted. It can be challenging to secure funding at this time if a company hasn't dealt with the fallout of the pandemic effectively. Many companies have used all available resources to help vaccines get developed much quicker, but even that came with a cost. Many companies do not conserve funds because of this need for quick solutions (as with the pandemic). Most of these companies use their capital to resolve the problem at hand and now have low money for other manufacturing processes.

10.6. DATA BREACHES AND OTHER CYBERSECURITY THREATS

Consumer data is constantly becoming more valuable, and as a result, cyber-attacks are also becoming a trend. Pharmaceutical companies are especially vulnerable to these cybersecurity threats, which can cost them a lot of money. The increased usage of internet-connected manufacturing technology can also make manufacturing facilities increasingly vulnerable to attacks.This creates a need for increased investment into cyber security solutions and policies in their office and remote workers. If companies do not invest in these crucial cyber security measures, they run the risk of falling victim to costly data breaches.[62]

The regulatory authority of India is one of the major obstacles to establishing a uniform export and distribution system in the country. At the international level, this authority is not acknowledged. There aren't any rules or regulations that should be applied to the supply chain to track down exports or exert control over them.A systematic and

standardised distribution method cannot be implemented because of illegal storage practices and ambiguous temperature regulations.

Managing the last-mile costs, getting medications to patients quickly, and keeping track of all transactions between the manufacturer and the consumer are all tasks involved in managing the drug distribution system in developing nations. This brings us to the next challenge standing in our way: India's administrative structure. We continue to operate in the old-fashioned system where most transactions take place on paper. Although technology has advanced significantly, our government continues to act as a hindrance. Companies must clear licences and compliances over several years.

Unsecure storing poor warehousing, for example, is another problem that causes the quality of the medicines to decline, which disrupts the cycle of distribution and causes the producer inconvenience. Any chemical that loses its effectiveness becomes ineffective and the maker is held accountable. For instance, a damaged or unattended soda can that is kept open for an extended period of time loses its fizz. This results in the product's quality being compromised, and as a result, consumers accuse the producer of delivering subpar goods. Consequently, proper warehousing can significantly reduce wastage.

Supplying medications Even the emergency drug delivery service in our nation is ineffective. Despite the best efforts of assistance organisations, non-governmental organisations (NGOs), and private and public funders, the disorganised supply chain is unable to keep up with the chaos that arises during humanitarian situations. As a result, false, inferior, and other inadequately regulated medical products frequently proliferate.[60] In most healthcare facilities, minimal information about patients, their diagnoses, or medical histories is gathered during emergencies. When infrastructure is interrupted, it might be challenging to identify drug quality signals since patients are seen rapidly and little information is kept on file.Even the emergency drug delivery service in our nation is ineffective. Despite the best efforts of assistance organisations, non-governmental organisations (NGOs), as well as private and public funders, the

reconstructed supply chain cannot withstand the instability that comes with humanitarian situations. As a result, false, inferior, and other inadequately regulated medical products frequently proliferate.[63]

10.7. DIFFICULTIES IN EXPORT

The USFDA has recently taken action against the Indian pharmaceutical business for failing to comply with a regulatory framework. Notably, many local generic medication manufacturers have experienced the effects, notably Sun Pharma and Wockhardt. Even though the Indian pharmaceutical industry exports a large amount of its products, it nevertheless faces difficulties. Campaigns against harmful generic products, which fall under the purview of intellectual property rights violations in India, suspect generic medicines leaving India with subpar quality standards, dependence on pharmaceutical raw materials ingredients, and pricing models that force exporters to fix lower margins for their quality products are just a few of the challenges. To ensure the tag of product made in India, bar-coding for all export products other than primary packaging which has made compulsory from July 01, 2015.[64]

10.7.1. RECENT EXPORT CONCERNS

Recently, the European Union (EU) tightened its trademark laws by enacting enforcement procedures for products in transit. Within of its borders. This means that even if goods are intended for a third nation, customs officers may still seize them at EU ports and airports. Additionally, goods with logos that are identical to those registered in the EU countries will not be allowed to be sold in the union.

As trademark registration is territorial and producers in other countries might not be aware that they exist, the official argued that the new trademark legislation was unjustified and unfair. A pharmaceutical producer in India that sells goods in Latin America or Africa may unintentionally be utilising a logo that is similar to a registered trademark in the EU, the Indian delegation claimed in its meeting with EU regulators. According to the official, "it is wrong to confiscate such things while they

Are being transported to other markets on the grounds that they breach the trademark protection assigned to a specific item in the transit country."[65]

11.0. CASE STUDY INDIA

Bulk Drug Industry in India: Challenges and Prospects An Overview of the Indian Pharmaceutical Industry

The Indian pharmaceutical sector is regarded as one of the most dynamic and vigorous in the world, ranking third by volume and tenth by value.

1 Continuing to grow at a rapid pace. The industry is divided into two parts: medicines and medical devices. Active Pharmaceutical Ingredients (APIs) or Bulk pharmaceuticals,

2 Formulations, and Vaccines are all part of the pharmaceuticals sector. This includes both patent-protected and generic medications. For many decades, generics have been the mainstay of Indian medicines.

The pharmaceutical industry is the lifeline of healthcare. The expectations from the industry, therefore, stem from that perspective. Meeting the health care needs of the country and the world are the foremost task before the industry. All manufacturing, be it in agriculture or industry, is to meet individual needs and higher societal objectives. In the larger societal context, pharmaceutical industry is well placed as a producer of essential items for human wellbeing. Indian bulk drug industry has the challenges to meet the domestic requirement and the global demand for affordable medicines. From an industry perspective, it opens a big market for it.Depending on the complexity of the molecule to be manufactured, APIs might need multistep complex chemistry using a range of processing technologies that pose major technological challenges.

APIs represent 40-50 per cent of the total value of generic drugs and hence form a critical component of any pharmaceutical industry, 6 particularly setup in a competitive environment. API supply chains

spread across the globe. The APIs used in medicines prescribed either in the US or Europe are as likely to have been produced in an Asian country as to have been locally produced. Different producers and suppliers try to extend their dominance in the global market by attempting to manipulate drug industry demand mostly through price and regulatory compliance. Some suppliers target the low cost API market and produce large volumes of comparatively cheap APIs with high cost efficiency whereas some others focus on producing specialised and expensive active ingredients. In this competitive fast- paced global market, the efficiency of each of these strategies determines the market share that can be potentially captured by these suppliers.Given the scarcity of countries with adequate pharmaceutical manufacturing capacity, this presents hurdles for the pharmaceutical industry in countries such as India to improve their production.

The domestic and global market for pharmaceuticals is huge, but the industry is faced with several challenges in increasing production and export. They relate to regulations, both national and international, export policy measures, environmental regulations, tax regime, credit crunch, and inadequacy of R&D support.The early growth of Indian pharmaceutical industry was on the strong foundation of a robust indigenous API industry. However, the recent crisis caused by COVID- 19 epidemic has brought out certain weaknesses in the sector.Indian pharmaceutical industry is deemed to be a success story with strong trade dominance and a competitive edge over its other counterparts as far as generic drugs are concerned. However, one of the biggest challenges faced by the industry currently is its continued heavy dependence on imports for its API requirements, mostly on China followed by USA and Italy, and in case of certain crucial APIs over 90 per cent dependence on China alone, exposes India to the risk of disruptions in raw material supply and volatile price levels, which in

turn can have strong adverse effects on the high riding generic formulation production 29 as well.

To meet those challenges huge investment in technology and quality control measures is required. Coupled with the same is the challenge of R&D. Cyber security, employment of digital technologies and Artificial Intelligence (AI) in drug discovery create new concerns. Fully automated medical science literature monitoring process may soon become the norm. Technology and R&D also raise the challenges of IPRs. While, so far it has been able to meet with those challenges, continued expansion without a strong foundation in R&D and with a large patent portfolio is a major challenge. This would necessitate huge investment in R&D and technology. Currently India's public investment in R&D does not create confidence in the area. Massive public investment over many years leading to invention of new chemical entities is required for development of new drugs.

China has invested heavily in the next generation drugs- mainly in biologics and biosimilar along with constant investment in new technologies like installing cold chain storage and continuous processing.

11.1. Conclusion

At first wrong policy decision or a disaster can lead to the rapid fall of an industry, but its growth will take time, as in the case of organic life. The policy approach to the current crisis in API industry has to bear this in mind.

What is required is avoidance of knee jerk reactions and adoption of well-considered policies with a long term perspective. The current disaster caused by a pandemic may raise in the minds of many doubts about the wisdom of globalisation.

A third important point is the need for integration of local MSMEs as primary suppliers to large manufacturers. This can become possible

only if they are able to produce and supply materials and products in required quantity and with quality but in a globally competitive price, that would require certain facilitations in provision of basic infrastructure like road and railways, energy and so on, referred to in earlier sections.

The essentiality of greater focus on innovation cannot be overstated. Innovation is really successful exploitation of novel ideas, but a conducive environment for generation of ideas and their experimentation will have to be created. This necessitates much higher public investment in R&D.

In policy making in the API sector, all these will have to be factored in for the best result in the long run. At the same time, a number of immediate measures may have to be taken. These, among others, include:

- Expeditious regulatory clearances,
- Ensuring easy availability of finances at low interest rates,
- Prescribing liberal eligibility conditions for government schemes,
- Setting up of large number of common facilities for MSMEs,
- Subsidised and priority movement of APIs from production units in view of role in public health,
- Simplification and restructuring of GST for APIs, and
- Identification of high potential API markets and special trade agreements with them. These measures may be needed to ensure that the industry does not collapse in the future and make India Atmanirbhar in its domestic 40 medicine requirements, as well as promote India's status as the pharmacy of the world, supplying affordable quality medicines.

11.2. CASE STUDY UNITED STATES OF AMERICA

Drug shortage is a global issue affecting low, middle, and high-income countries. Many countries have developed various strategies to overcome the problem, while the problem is accelerating, affecting the whole world. Among all pharmaceutical dosage forms, sterile injectable products have a higher risk of shortage than other forms. The causes of shortage are multifactorial, including supply issues, demand issues, and regulatory issues. Drug shortage has prevailed throughout the globe affecting high, middle, and low-income countries. In high-income countries, the drug shortage has been in excessive focus compared to other regions. The causes include manufacturing problems, business decisions, raw material unavailability, and regulatory issues. Unlike high-income countries, low-middle income countries (LMICs) have several new causes for drug shortage, including licensing of manufacturers/products, shortage of raw material for a local manufacturer, drug smuggling, and lodging tax government policies.

Low-income countries have few research studies and lack policies to deal with this event. A few studies reported a stock-out of essential medicines in Malawi, Egypt, and Uganda. Different countries have developed various strategies to address the drug shortage. These strategies vary depending upon the financial condition, the health system strength, and research studies, such as increased reporting systems, changes in policies, drug shortage platforms, and accelerated drug approval. Some authorities evaluate drug shortages and deliver guidelines directly to health stakeholders while some hospitals purchase extra inventory as a buffer stock to prevent shortages. Some regulatory authorities establish platforms for tracking and reporting shortages and some countries are trying to strengthen their food and drug institutions.

11.2.1 DRUGS REPORTED IN SHORTAGE

Nearly all types of drugs have been reported in shortage, including

Antibiotics (A07AA/D01AA/G01AA/J02AA/S01AA), antiretroviral drugs (J05AR), anti-protozoal (P01), antineoplastic agents (L01), cardiovascular medicines (C), analgesics (N02), etc.Different countries or areas encounter different drugs in shortage depending upon health conditions. However, essential medicines and emergency medicines are more liable to shortage than other medicines.

Antimicrobial agents are the most affected class by drug shortage (Mazer-Amirshahi et al., 2017), along with oncology drugs (both chemotherapeutic (D06B/ D06C/D06BX) and non-chemotherapeutic drugs) (Woodcock and Wosinska, 2013; Costelloe et al., 2015). Benzathine Penicillin G (J01CE08) shortage occurred in the United States (2014), and the reason reported by ASHP was a delay in manufacturing (Organization, 2016). A study in Iran found 73 cancer drugs in shortage, covering most areas. Many oncology drugs were reported in shortage in the US, for example, Mechlorethamine, Leucovorin (L01BA), Daunorubicin (L01DB02), PEGylated liposomal Doxorubicin (L01DB01), etc.

Cardiovascular drugs like Labetalol (C07A G01) and Metoprolol (C07AB02), Methyldopa (C02AB), and pindolol (C07AA03) are found in the United States FDA drug shortage list. Currently, the United States FDA shortage drug list still includes Ketoprefen (M01AE03) The most affected drugs in the United States in 2016 were antibiotics, followed by electrolytes, chemotherapy medicines, cardiovascular drugs, and CNS agents. But in 2020, analgesics, sedatives, paralytics were short due to their increased demand in COVID-19. Moreover, cardiovascular and CNS agents in injectables were also short (Pharmacists, 2020). On the other hand, a study of EU in 2014 found that CNS drugs were most short, followed by anti-infective drugs, cardiovascular drugs, antineoplastic/immunomodulatory agents,

and GIT drugs (Pauwels et al., 2014), but the EAHP survey in 2019 found that antimicrobial agents were on the top with oncology medicines second, followed by anaesthetic agents.

Table No. 12…. Drugs Reported on shortage

Therapeutic class	Reason of shortage & Challenge	Impacts
Antibiotics	Manufacturing issues (Supply chain)	First-line agent for many nosocomial infections, alternative drugs with greater risk
Anti-retroviral drugs	Price increasing of raw material (Market Barrier & Patent)	Use of alternative drugs
Analgesics	Opioid epidemic quality issues (Regulatory Policies)	Switch to other dosage form
Anti- protozoal	Delayed tendering/ procurement process, economic issues (Supply chain)	Delayed treatment and associated loss
Anaesthetics	Pandemic, increased demand (Policies)	May put patients' health in severe condition as both medicines.

11.3. Supply chain

Supply issues mean manufacturers are unwilling or unable to produce enough medicines to satisfy the demand. It can be classified into manufacturing problems, unavailability of raw materials, business reasons (economic reasons like low-profit margin, low market size, cost raise of raw materials, capacity constraints), and logistic problems.

11.4. Manufacturing Issues

The manufacturing issues include quality problems and competing priorities. The EMA is associated mainly with medicine shortages due to manufacturing issues, shortages of injectable products with disregarded quality due to decreased incidence of some diseases and the availability of other valued alternatives.

1. Quality problems
2. Competing priorities
3. Unavailability of Raw Material
4. Business Issues
5. Logistic Issues

11.5. Regulatory issues

One important factor is the lack of a unified definition of drug shortage. Drug shortage affects all stakeholders from economic, clinical, and humanistic aspects. WHO established global mitigation strategies from four levels to overcome drug shortages globally

10. CONCLUSION

The pharmaceutical products available in different countries vary significantly. Most nations required additional evidence that is not included in CTD modules 2-5, some of which may be difficult to get. The principal problems in the drug exportation process noticed, as well as some essential recommendations for success in the region, are as follows. Knowledge of drug exporting processes and submission material for a certain country is required for effective global regulatory strategy planning and implementation.

Any export market requires high-quality dossiers, which can be produced through rigorous Formulation Development.

Proper formulation development planning and execution will aid in the production of a high-quality dossier and the resolution of regulatory inquiries.

Because of the huge differences in regulatory requirements, it is impracticable to obtain global marketing authorisation and launch the product simultaneously in all regions.

As a result, one should thoroughly analyse and develop a clear regulatory plan by considering the target locations, various patent terms and their extensions, numerous application possibilities, data needs, and probable timelines for marketing launch in various regions. This avoids redundant investigations, reduces drug approval and subsequent launch delays, and lowers total development costs.

Because the world is divided in drug approval procedures with technical data as explained above, it is critical for generic manufacturers, in particular, to carefully analyse the market need, Development Costs, target regions, and regulatory requirements before developing medications. As a result, it is vital to plan and coordinate all actions in order to successfully launch a product into the market on time.

DES is regulated by CDRH in the USA, EMA in the EU, MDA in Malaysia, and CDSCO in India. It is classified as the highest risk in all four countries and is regulated as a single entity in the USA, as an

integral product in the EU and Malaysia, and as a medical device in India. ISO 13485, ISO 14971, ISO 10993, ISO 10555, and ISO 25539 are the common regulatory requirements followed in the EU, Malaysia, and India for DES, whereas the USA follows CFR 820 for quality management. Even after having regulations, every country has its own challenges for approval. Early classification in cases of new developments is the challenge in the USA; information exchange between CA and NB is a complex process in the EU; and identifying primary and secondary agencies is the challenge in Malaysia. India requires 6–9 months for evaluation; the US requires 180 days for the review of class III devices; approval in the EU is based on the Notified Bodies of member states; and Malaysia requires 60 days for evaluation. From all the countries mentioned above, Malaysia has the fastest approval process as compared to the US, EU, and India.

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