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PHARMACEUTICAL INDUSTRY: REGULATORY LANDSCAPE AND OPPORTUNITIES FOR INDIAN EXPORTERS

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Project Team:

Mr. S. Prahalathan, Chief General Manager
Mr. Ashish Kumar, Deputy General Manager
Ms. Simaran Kaur, Manager

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INTRODUCTION

The Indian pharmaceutical industry is considered one of the fastest growing sectors in the country and has exhibited considerable growth in the recent years. It is one of the high performing knowledge based segments of the manufacturing sector. In addition to catering to the needs of the domestic demand, the pharmaceutical industry is also engaged in contract manufacturing, contract research, clinical trials, contract R&D, and direct exports to developed and developing country markets. In fact, the industry has an eminent position in the global pharmaceutical market and is one of the leading producers of generic pharmaceutical products in the world, catering to approximately one-fifth of the global generic pharma market. The Indian pharma industry exports its products to more than 200 countries in the world, including strictly regulated markets such as the US, Europe and Japan.

Regulatory supervision and quality monitoring of medicines and other pharmaceutical products is of vital importance. In this context, this study examines the regulatory landscape in highly regulated markets of the US, the EU as well as that of India and then analyses the trend in the world and India's international trade in pharmaceutical products, and suggests select measures which could help the Indian industry move higher up the export growth trajectory.

REGULATORY ENVIORMENT IN THE US AND THE EU

Regulations in the US

The US FDA (Food and Drug Administration) is the agency responsible for regulating the pharmaceutical market in the US, aiming to safeguard the health safety of the consumers. The Federal Food, Drug and Cosmetics Act is the basic food and drug law followed in the country. Every pharmaceutical drug marketed in the US has to pass through an approval process, which comprises four stages, viz. pre-clinical, clinical, new drug application review and post marketing. The various types of applications that need to be submitted to the US FDA for drug development and approval include:

- New Drug Application (NDA)
- Investigational New Drug Application (IND)
- Abbreviated New Drug Application (ANDA)
- Over-the Counter Drugs (OTC)
- Biologic License Application (BLA)

NDA is the primary means by which a drug sponsor puts forward to the US FDA for approval of marketing and sales of the drug in the United States. The entire information and data collected while the animal studies and human clinical trials are conducted constitute a part of the New Drug Application. In 2017, FDA's Centre for Drug Evaluation and Research (CDER) approved 46 novel drugs, either as new molecular entities (NMEs) under NDAs, or as new therapeutic biologics under Biologics License Applications (BLAs). From 2008 through 2016, CDER has, on an average, approved 31 novel drugs per year with 2017 being the year with the highest number of novel drugs approval over the last decade.

According to the Federal Law, the marketing application of a drug must be approved, before it can be transported or distributed across state lines. Nevertheless, the sponsor of an investigational drug is likely to ship the drug to clinical investigators across various states. So, the Investigational New Drug application is the means by which a pharmaceutical company acquires the permit to ship an experimental drug across state lines (typically to clinical investigators) prior to the approval of marketing application of the drug. The three types of INDs include an Investigator IND, Emergency Use IND and Treatment IND.

For marketing a generic drug, companies need to submit the Abbreviated New Drug Application to the FDA to gain approval. These applications are referred to as 'abbreviated' as there is no compulsion of incorporating the preclinical (animal) and clinical (human) data to demonstrate safety attributes. The matter of concern for the drug companies is to confirm scientifically that the performance of their product is comparable to that of the innovator drug.

Over the counter drugs, which refer to the drugs which are available to patients without the need of a prescription, constitute a substantially important segment of the American healthcare market. There exist greater than 80 therapeutic categories of OTC drugs, extending from drugs for the cure of acne to weight loss. CDER's Office of Drug Evaluation IV is essentially responsible for the assessment of the OTC drugs. FDA evaluates the active ingredients and the labelling of more than 80 therapeutic varieties of drugs such as analgesics or antacids, rather than reviewing individual drug products. FDA has developed an OTC Drug Monograph for each category of these drugs, which is published in the Federal Register.

Firms undertaking the manufacture of biologics for sale in interstate commerce are expected to hold a license for the product. These products receive an approval for marketing under the provisions of the Public Health Service Act. The application requires inclusion of detailed information about the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical impacts of that biologic product. On conformity with the FDA preconditions, a license is issued for permitting the marketing of the product.

Regulations in the EU

The European Medicines Agency (EMA) was established during the year 1995, with the objective of attempting the harmonization of processes in various member state regulatory agencies so that the expenditure incurred to the drug companies in obtaining approvals from each member state can be avoided. Nevertheless, the EMA does not supervise the entire list of drug approval processes as is the case with FDA in the US. There exist four ways/ paths through which a drug can be approved, conditional on the drug class as well as the priority and preference of the manufacturer which include the centralized process, national process, mutual recognition and the decentralised procedure.

The centralised procedure is monitored, controlled and regulated by the EMA. Each of the member states of the EU is represented on the EMA Committee for Medical Products that issues a license, which holds valid in each of the EU member states. One of the major advantages involved in undertaking the Centralized Process is that medicines are authorised for all EU citizens at the same time. For those category of drugs which are not subject to the requirement of undergoing the Centralised Process, each EU member state approves drugs by way of their individual procedures followed by them internally, following the national process.

Through the mechanism of mutual recognition, the drugs which have received approval from one member state through its individual state procedures, have the advantage and opportunity of achieving marketing authorization in another EU member state. By way of the decentralised procedure, the manufacturers have the option of applying simultaneously in more than one EU state for that segment of products which have neither been authorized in any of the EU states nor do they fall in the category of products which are necessitated to undergo the mandatory Centralised Process.

International Harmonisation of Regulations

In recent years, a trend of globalisation has been witnessed in the production, marketing and sale of pharmaceutical products. With the objective of targeting global markets, drug manufacturers are necessitated to seek approval for their products from the various regulatory bodies established in several countries. There is a need for global collaboration to guarantee that consistent and appropriate standards are being adhered by the drug manufacturers and regulatory authorities, irrespective of the country.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), established in the year 1990 by regulatory agencies as well as industry bodies in the United States, Europe and Japan, have been promoting global harmonisation of pharmaceutical regulations. The goal of the ICH is to facilitate increased harmonisation globally, and ensure the production and registration of safe and efficient drugs. The harmonisation is attempted by way of establishing ICH guidelines, which is developed by a procedure of attaining scientific consensus between the regulatory and industry experts.

Key Trends in Global Pharmaceutical Sector

PIC/S

Pharmaceutical Inspection Cooperation Scheme (PIC/S) is an informal collaboration among member economies spearheaded by the EU seeking to improve the standards of manufacturing requirements amongst its members. India is not currently a member, although PIC/S has identified India as one of the 'key players' in terms of the pharmaceutical industry. PIC/S entails membership candidates to bring their GMP systems up to international standards and the process of membership can be accomplished in two to three years. According to a few large pharmaceutical firms, the act of India joining this membership will increase the visibility of India in the global market. It is further viewed that if India becomes a member of PIC/S, the quality and capacity of the regulatory system in India will also improve and be aligned with the global standards. Approximately two thirds of the pharmaceutical products exported from India are being supplied to the PIC/S member countries. Thus, becoming a member of this association will lead to augmentation of exports. However, the medium and small sized pharmaceutical players, particularly those supplying to the domestic markets do not find this a favourable arrangement. This move will entail them to upgrade according to the global standards, incurring an expenditure of approximately Rs. 5 crore to Rs. 20 crore per unit, which may not be a viable option for them.

BEPS

On 5 October 2015, the Organisation for Economic Co-operation and Development (OECD) released the final action plan in relation to Base Erosion and Profit Shifting [BEPS]. The project is anticipated to impact the industry significantly. Impact on Indian pharmaceutical industry is, however, subject to the proposed Indian tax law and positions adopted by India in the multilateral instruments or bilateral tax treaties. Some of the key areas where the project is anticipated to impact are: on the status of Permanent Establishment (PE), tax treaties, intellectual property (IP), financial transactions and interest deductions on hybrid instruments, transfer pricing, contract research and manufacturing arrangements, and indirect taxes.

Substandard and Falsified (SF) Medical Products

WHO is working with stakeholders to minimize the risks from SF medical products by collecting data and transferring knowledge and good practices to various nations. During 2013, WHO launched the Global Surveillance and Monitoring System to encourage countries to report incidents of substandard and falsified medical products in a structured and systematic format, to help develop a more accurate and validated assessment of the problem. As of November 2017, WHO had issued 20 global medical product alerts and numerous regional warnings, and had provided technical support in over 100 cases. It has engaged in training a global network of over 550 regulatory staff in 141 Member States to report substandard and falsified medical products to the WHO Global Surveillance and Monitoring System.

Developments in African Healthcare Regulations

The African Medicines Regulatory Harmonisation Programme (AMRH) has been established to ameliorate the quality and improve standards related to regulations. In collaboration with the World Health

Organisation, it is designed to review the registration of a selected list of medicines and coordinate regional harmonisation systems on the continent. The AMRH, launched in 2009 with initial funds from the Bill and Melinda Gates Foundation and overseen by the World Bank, has contributed to reduce marketing authorization timelines in East African Community and the Southern African Development Community member states.

In order to address the barrier of weak regulations in African countries, the AMRH Initiative developed the African Union Model Law on medical products regulation to ensure effective regulation and promote harmonization. The objective of the Model Law is to have at least 25 AU Member States using a version of the Model Law on medical products regulation by 2020. In order to facilitate implementation of the AU Model Law, AMRH has established a continental Technical Working Group on Policy and Regulatory Reforms composed of regulators and legal experts to guide the domestication process. The Model Law endorsed by the African Union Assembly in January 2016, is at different levels of domestication and implementation by twelve African countries, viz. Ivory Coast, Burkina Faso, Seychelles, Zimbabwe, Lesotho, Namibia, Swaziland, Gambia, Tanzania, Rwanda, Burundi and Mozambique.

INDIAN PHARMACEUTCIAL INDUSTRY: REGULATORY OVERVIEW

In India, the import, manufacture, distribution and sale of drugs is regulated by the Drugs and Cosmetics Act of 1940. The Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945 list down detailed provisions to mitigate the manufacture of spurious or lower quality drugs. Definitions and explanations of adulterated and misbranded drugs have been clearly elaborated so that such improprieties can evoke legal action. Over the years, various revisions and amendments have been implemented taking into considerations the transformation in economic scenarios.

In India, the drug regulations are segregated into the Central Drug Authorities and the State Drug Regulatory Authorities. The Central Drugs Standard Control Organisation (CDSCO) is the apex national drug regulatory authority for carrying out the responsibilities allotted to the Central Government in accordance with the Drugs and Cosmetics Act. The functioning of the CDSCO is under the Director General of the Health Services of the Ministry of Health and Family Welfare and is headed by the Drugs Controller General of India, DCG (I). The primary objective of the CDSCO is to ensure the delivery of safe, superior quality effective drugs, cosmetics and medical devices to the public. The affiliated institutions under the governance of the CDSCO include the Central Drugs Laboratory in Kasauli, Himachal Pradesh and the Pharmacovigilance Programme of India at the Indian Pharmacopoeia Commission in Ghaziabad, Uttar Pradesh. The Central Government has established six zonal offices of the CDSCO, five Sub-Zonal Offices (including one created recently at Indore in Madhya Pradesh) with another being established at Guwahati in Assam, 13 port offices and eight laboratories under its control.

The regulatory authority at the state level comprises the Food and Drug Administrations (FDA) at each state and certain licensing authorities have been set up for the Union Territories. With reference to the Drugs and Cosmetics Act, 1940, there exists dual regulatory control, inclusive of both the Central and the State Government. The implementation and enforcement of the Act needs to be ensured by both the Central and the State Governments. Under the Act, the task of regulating the manufacturing, sale and distribution of drugs and other related products and issuing of licenses is entitled to the State Authorities, while the Central Government authorities are in charge of approving new drugs and clinical trials, listing standards for drugs, administering the quality of imported drugs as well as collaborating and co-ordinating with the State drug control organisations.

Drug Price Control Orders

The Government initiated the first drug price control on the pharmaceutical sector through the Drug (Display of Prices) Order 1962 and Drug (Control of Prices) Order 1963. Over the years, various amendments have been exercised on this regulation, which has resulted in variations in the proportion of control on prices as well as the essence of price control. The amendments which had a significant impact on the Indian Pharmaceutical industry were those introduced in the following years, viz. 1970, 1979, 1995 and 2013, respectively. The DPCO 2013, entailed that the prices of drugs that featured in the National List of Essential Medicines (NLEM) be monitored and controlled by the National Pharma Pricing Authority (NPPA). While under the DPCO (1995), 74 drugs were covered for price control, this figure rose to 348 drugs as all these appeared in the National List of Essential Medicines 2011; additionally approximately 628 formulations were also subject to price control. Prior to 2013, the pricing of drugs was fixed based on the manufacturing cost declared by drug manufacturers, while post that regime, prices were regulated through market based pricing. Under NLEM 2015, the government has increased the number of drugs subject to price control to over 800 formulations.

Patent Acts

India followed a product patent regime for its inventions under the Patents and Designs Act 1911. During the year 1970, the Government introduced the Process Patent instead of the Product Patent. This Act permitted Indian companies to produce patented drugs, under the condition that the process of production was not the same as the one adopted by the innovator company. This had a major favourable impact on the Indian pharmaceutical companies, who could develop cheaper versions of branded patented drugs, without the requirement of paying a license fee to the innovator companies.

Nonetheless, the Patent Act was amended, for the purpose of adhering to the WTO'S TRIPS (Trade Related Aspects of Intellectual Property Rights) regime. Taking this development into account, the product patent was re-established and the process-patent was abolished. Consequently, the sale of generic version of drugs which were patented after the year 1995 was considered illegal. Post the amendment in the Patents Act, the pharmaceutical firms were authorized to develop cheaper generic versions of the drugs which were off-patented or the ones patented before the period 1995.

Compulsory Licensing

In the provisions of a compulsory license, three years post the introduction of the patented drug in the country, a domestic manufacturer can attempt the production of the patented drug, on which the compulsory license has been granted. The grant of compulsory license can be attributed primarily to the unaffordability characteristic of the medicine.

Foreign Direct Investment

During the year 2016, the FDI Policy for the pharmaceutical sector was amended. FDI in brownfield pharmaceuticals sector was permitted up to 74%, under the automatic route, and a further increase, beyond the limit of 74% necessitated prior Government approval. This approach was envisaged to attract capital, enhance mergers and acquisitions, boost international best practices and draw updated technologies in the Indian pharmaceutical sector. For greenfield pharma investments, 100% FDI under the automatic route is allowed. During the period April 2000 to December 2017, the cumulative FDI inflow into the Drugs and Pharmaceuticals sector stood at US$ 15.6 billion, accounting for approximately 4% of the aggregate cumulative FDI inflow for the period, making it the seventh leading recipient of foreign direct investment.

INTERNATIONAL TRADE PERSPECTIVE

World Pharmaceutical Market

The global medicine spending was estimated at US$ 1135 billion during the year 2017, recording a CAGR of 4.6% during the period 2007 to 2017. According

to the forecast by IQVIA Institute, the worldwide spending on pharmaceutical markets is anticipated to touch US$ 1415 - 1445 billion by 2022.

While developed regions accounted for 73% of the total in 2007, their share fell to 66% in 2017. As against this, the share of the pharmerging countries have risen considerably – from 15% to 24% during the same time frame. The US, the Europe and Japan continue to remain the dominant markets in the global pharmaceutical space. The US market remained the single-largest market and accounted for 41.1% of the total medicines sales for the year 2017. In the pharmerging markets, China with sales of US$ 122.6 billion, was the leading country, followed by Brazil and India. With respect to therapy categories, oncology recorded a CAGR of 11.8% during the period 2012-17; this growth is projected to moderate to 7-10% over the 2017-22 period. Antivirals registered the largest CAGR of 25% in the five year period 2012-17, followed by Diabetes and Autoimmune categories, respectively.

International Trade in Pharmaceutical Products

The global exports of pharmaceutical products were valued at US$ 493.8 billion during the year 2016, registering a year-on-year marginal decline of (-) 0.4%. However, over a larger time frame, the exports of pharmaceutical products recorded a CAGR of 1.3% during the five year period 2012 to 2016. Germany continued to remain the largest exporter of pharmaceutical products in the world, with the value of its exports increasing from US$ 70.4 billion in 2012 to US$ 77.1 billion in 2016, accounting for a share of 15.6% in world exports during 2016. Switzerland was the second leading exporter, with its value of exports standing at US$ 67.5 billion (13.7% share) in 2016. The US, being the third largest exporter of pharmaceutical products in the world, had a share of 9.5% in world exports during 2016, with its exports registering a CAGR of 4.0% during the period 2012 to 2016.

In terms of imports, the US was the leading importer of pharmaceutical products in the world, with a share of 17.6% during the year 2016. The imports of pharmaceutical products from Germany, the second largest importer, increased from US$ 43.5 billion in 2012 to US$ 49.1 billion in 2016.

INDIA'S TRADE IN PHARMACEUTCIAL PRODUCTS

India's exports of pharmaceutical products, including drug formulations and biologicals were valued at US$ 16 billion during the year 2016-17, recording a year-on-year decline of 1.2%. During the seven year period 2010-11 to 2016-17, a negative growth rate in export of these products was observed for the first time only during 2016-17. The growth rate peaked during the period 2011-12, at 25.3%. Post this period, a decline in growth rates was witnessed up until 2014-15 after which it increased to 9.9% in 2015-16, as the value of exports stood at US$ 16.2 billion. However, in 2016-17, the growth actually entered the negative domain, declining by (-) 1.2%. The US was the leading export destination of bulk drugs and drug formulations, occupying a share of 33.8% in the aggregate exports during the period 2016-17. Other major export destinations were the UK, South Africa, Nigeria, Russia, Brazil, Kenya, Germany, Belgium and Australia with shares of 3.3%, 3.0%, 2.4%, 2.3%, 2.0%, 2.0%, 1.8%, 1.4% and 1.4%, respectively.

Bulk Drugs, Drug Intermediaries

In terms of value, the growth in bulk drug exports has remained anaemic, declining from US$ 3.6 billion in 2010-11 to US$ 3.4 billion in 2016-17. The per unit price realisation in the export market for bulk drugs and intermediaries has witnessed a decline over the period 2010-11 to 2016-17. Although, US remained the largest export destination of bulk drugs from India, the value of exports to this country recorded a negative CAGR of (-) 7.2% during the period 2010-11 to 2016-17. Germany continued to be the second largest export destination with the value of exports standing at US$ 361.1 million in 2016-17, although its share declined from 5.2% to 4.3% during this period. Brazil replaced Turkey as the third largest importer of bulk drugs from India, with its share increasing from 3.6% in 2010-11 to 3.8% in 2016-17.

The exports of bulk drugs to the African region was valued at US$ 372.2 million during the year 2016-17. Among the African countries, Egypt was the largest importer, with its value of imports being US$ 95.9 million. South Africa was the second largest African importer, with a share of 23.1% in the total African imports of bulk drugs from India.

The value of bulk drugs exports by India to the American region was US$ 758.1 million during 2016-17. In terms of country wise analysis, the USA was, by far, the leading export destination in the American region, with its value of imports at US$ 361.1 million (47.6% share). Brazil, the second largest bulk drug importer in the American region had a share of 16.8%.

India's exports of bulk drugs to Europe amounted to US$ 1066.8 million in 2016-17. Germany was the largest importer of bulk drugs from India in the European region, with a share of 13.6% in the aggregate European exports. Turkey was the second largest export destination with a share of 10.4% followed by Belgium, the UK, Italy, Ireland, Switzerland, Spain, the Netherlands and France.

The export of Indian bulk drugs to Asia were valued at US$ 1127.9 million during 2016-17. Japan was the leading Asian importer of bulk drugs with its imports standing at US$ 115.5 million while Bangladesh was the second largest export destination.

Drug Formulations

The exports of drug formulations have displayed a considerable growth over the years, with the value of exports more than doubling from US$ 6.3 billion in 2010-11 to US$ 12.7 billion in 2016-17. USA continued to be the largest export destination of drug formulations from India, with its imports having augmented substantially from US$ 1775.8 to US$ 5057.8 million in the period 2010-11 to 2016-17. The UK emerged as the second largest export destination in 2016-17 as compared to its fourth position in 2010-11, although its share in India's exports of drug formulations declined from 4.3% to 3.5% during this period. South Africa continued to be the third largest export destination of drug formulations, although its share in aggregate exports also fell from 4.3% to 3.1% during the period 2010-11 to 2016-17.

India's exports of drug formulations to Africa were valued at US$ 2.8 billion during the year 2016-17. In terms of countries, South Africa was the largest export destination for drug formulations in the African continent, with exports valued at US$ 389 million. Nigeria, the second largest export destination had a share of 12.4% followed by Kenya (10.4%), Tanzania (6.8%), Uganda (5.0%), Ethiopia (4.9%), Ghana (4.7%), Mozambique (4.3%), Congo D. Republic (3.0%) and Zambia (3.0%). In the American region, the US was, by far, the leading importing country, accounting for a share of 86.4% in the aggregate imports of drug formulation of the North American region from India. Brazil, the second largest importing country in this region, had imports valued at US$ 196.5 million.

European imports of drug formulations from India in 2016-17 were valued at US$ 1539.6 million, with the share of the European Union at 96.1%. The UK, with a share of 28.5% in the aggregate European imports was the largest importer in this region. The other major European importers of drug formulations from India included Germany (9.2%), France (8.8%), Belgium (8.5%), The Netherlands (8.2%), Hungary (4.7%), Malta (4.4%), Slovenia (3.3%), Finland (3.2%) and Turkey (3.2%). The imports of drug formulations by the Asian region from India stood at US$ 1923.1 million in 2016-17, with Australia being the leading import source, contributing a share of 10.9%.

CHALLENGES AND STRATEGIES

Pricing Pressures

The increased rate of wholesale consolidation in the US market has led to considerable decline in the bargaining power of exporting countries, and has especially impacted the Indian players leading to pricing pressures. During the year 2016, 3 players in the US pharma distribution market, viz. AmerisourceBergen Corp, Cardinal Health Inc. and McKesson Corp, together held nearly 85% of the

market share. The total revenues since 2012 for these three wholesalers' is estimated to have reached US$ 424 billion in 2017, a 4.5 percent increase from the 2016 figure. Over the past few years, these three companies have acquired many regional and specialty wholesalers within the United States leading to further consolidation and concentration in the distribution supply chain. Moreover, the increase in the pace of ANDA approvals caused by the implementation of Generic Drug User Fee Amendment has led to a huge inflow of players in the US market, driving pressure on realisations.

With the objective of addressing the present challenges it is important for the pharmaceutical firms to attempt a variation in their strategy. They could focus on the development of new and innovator drugs and undertake novelty in drug delivery mechanisms. It is beneficial to target complex and chronic diseases which are high in value and have lesser competitors. The pharmaceutical players could also focus on development of biosimilars which could provide new avenues of cost-effective growth, rather than restricting their attention to the generic drugs segment alone.

Regulatory Compliance

Regulatory compliance has emerged as a critical challenge for the pharmaceutical industry, particularly in the regulated markets. Noncompliance is cost intensive, and may expose the companies to revenue losses, reputational risks, patient safety issues, criminal sanctions, and can jeopardize the future of the entire business unit. Compliance issues facing the pharmaceutical industry include government policies, drug safety, counterfeiting, information security and privacy, intellectual property protection, corruption and adulteration, and other third-party risks.

Under such a scenario, meeting the evolving regulatory stipulations such as Current Good Manufacturing Practices (CGMPs) should be given prime importance by the pharmaceutical companies. Along with addressing the emerging legal requirements, the companies need to lay emphasis on following the policy of substantial compliance and risk management. The Indian pharma firms need to persistently evolve with the variations in the global regulatory compliances and accordingly adjust cost and resources to adhere to those standards.

The pharmaceutical firms should be facilitated with an updated repository enumerating regulatory requirements notified by each country's regulatory organisation. The repository can be formulated in a manner that lists down the common requirements as well as the variations in standards, such that minimum set of regulatory adherence can be identified to address the compliance across various global agencies. For ensuring the compliance to standards, skill development of various stakeholders is crucial. Preparedness and proficiency in documentation and following statistical techniques as per regulatory requirements are also of considerable importance in this regard. Moreover, to demonstrate and justify that the manufacturing process being applied by the firm is in compliance with good manufacturing practices, it is essential for them to have a comprehensive record of their production information, which can be presented to the inspectors and auditors.

Clinical Trials

The lack of appropriate regulatory guidance on certain issues, dearth of adequate lucidity on various legal terms and the deficiency of sound communication strategy from the drug regulators have had adverse impacts. The global multinational pharma companies have become sceptical about the operations in India due to this uncertainty and lack of clarity. There is a skewed distribution which can be observed in terms of medical research in the country. During the year 2016, out of a total of 1083 registered Ethics Committee (EC), Maharashtra had nearly 23.9% concentration followed by Gujarat (11.5%) and Karnataka and Tamil Nadu with 10.3% each. However, the number of registered ECs in Jharkhand, Jammu and Kashmir, Sikkim and Himachal Pradesh was only 1. Moreover, there are certain states and union territories which do not have a single EC. Another area of concern is

that various medical colleges which are approved by the Medical Council of India to run post graduate courses do not possess registered ECs. There is a requirement of an approval from a registered EC for academic non-regulatory studies; thus there is a need for such a transformation accordingly.

The development of an IT enabled platform would empower the EC to scrutinise the clinical trial project at various stages all along the life cycle of the project. These initiatives have proven to be successful in various countries. In this regard, the National Accreditation Board for Hospitals and Healthcare Providers and Forum for Ethics Review Committee (FERCI) can play a pivotal role in the progress of this plan of action. The requisite capacity building and training on Good Clinical Practices by way of online mentoring through modules is being used in various developed countries including the US and the EU. The specialists from FERCI and the Indian Council of Medical Research (ICMR) can be requested to establish the modules with updated information. There should be the establishment of Standard Operating Procedures for the reference of the ECs. This will facilitate the provision of a standard for the EC which can be used by them in their functioning.

Data Integrity

In the pharmaceutical industry, data integrity is a crucial component and the organisation should be able to proficiently exhibit the integrity of data on the occasion of a regulatory audit. The various ways in which data integrity is compromised includes falsification of data, inappropriate recording of activities, representing already existing data as new, and deleting the data. The breach of data integrity can lead to consequences of warning letters and import alerts apart from other kind of penalties. The major causes of data integrity issues include dearth of skilled manpower, preference of quantity over quality, lack of effective training and inefficiency in guidelines and regulations.

There should be provisions to attempt computerised audit trails, which keep an account of the date and time along with the sequencing of events. Moreover, if any modifications are made to the records, then a note should be maintained regarding the prior entries. To safeguard the integrity of data, ensuring the security of computer systems is indispensable. Further, the junior as well as mid-level staff should be imparted trainings in which the importance of data integrity and the FDA requirements should be highlighted. In this regard, an important strategy being adopted by countries across the globe is developing and transforming their domestic regulatory regime, with a view to put them in line with the global regulations. The attempt of aligning the domestic regulations with these global ones will make the task of data integrity more convenient and easy.

Excessive Dependence on China for Drug Imports

India is heavily dependent on China for bulk drug intermediates and APIs with the country accounting for nearly two-third of India's imports of such products. An over dependence on bulk drugs, active pharmaceutical ingredients and other raw materials from China, could have an unfavourable impact on the Indian pharmaceutical industry. Any discontinuance of supply could trigger a major loss for the pharma players. During the year 2016-17, China had a share of 66.7% in the aggregate bulk drug imports by India, valued at US$ 1.83 billion. In terms of quantity of imports, China contributed nearly 60.7% of the total bulk drug imports.

With respect to this issue, it is imperative for the Government and the industry body to strengthen the domestic active pharmaceutical ingredients market such that the need for imports can be circumvented. The Chinese market's competitive advantage lies in the ability to provide low cost raw materials. The creation of a scenario by policy makers in the country which is conducive for boosting the domestic API market can be beneficial. Greater incentives for encouraging investments and financial support for achieving a robust domestic API industry could be considered by the government.

Research and Development

India's gross expenditure on R&D has been low at just around 1 per cent of GDP. India currently ranks 60th out of 127 on the Global Innovation Index 2017, though this ranking has improved from 66th in 2016. Among the BRICS countries, only South Africa is behind India in R&D expenditure ranking. There is extensive scope to initiate an increase in scientific research, particularly in the healthcare and pharmaceutical sector. A vast majority of updated medical equipment and devices, diagnostics as well as examination and inspection tools are imported by India, with Indian patients getting an access much later than their availability in the advanced countries. If an ecosystem of nurturing and promoting R&D is created, the need for such imports could go down significantly.

Absence of Singular Lead Agency to Oversee Pharmaceutical Innovation

In the present scenario, there exists no single authority for the construction and performance surveillance of public pharmaceutical research centres. The National Institute of Pharmaceutical Education and Research and various other public sector undertakings are under the purview of the Department of Pharmaceuticals, while the biotech parks are overseen by the Department of Biotechnology. Moreover, approximately 20 centres are affiliated to the Council of Scientific and Industrial Research, and 32 research centres are governed by Indian Council of Medical Research. The absence of an apex institute to promote innovation is an important issue which needs to be tackled, as multiplicity of regulatory bodies only increases complications.

Infrastructural Issues

Indian pharmaceutical industry also faces the challenge of inadequate infrastructural support such as lack of animal breeding facilities and good laboratory practices. Moreover, the deficiency of skilled laboratory technicians to supervise and administer the activities and decipher the information from tests has also been unfavourable. In this regard, the success story of Korea can be studied, with respect to superior clinical trial infrastructure. The Korea National Enterprise for Clinical Trial (KONECT) provides upgraded clinical trial services. Moreover, collaborations between KONECT and several privately run contract research organisations have enabled significant developments in the innovation fields. India should replicate this model to ameliorate the clinical trial infrastructure and promote productive and pertinent course structure in colleges and organisations to improve the skills of personnel and staff.

Talent Pool Requirement

There is a mismatch between the supply and demand of skilled professionals which needs to be taken care of in order to restore India's competence in the pharmaceutical sector. According to the GCI Report 2017-18, India scores relatively low and ranks 97th among 137 countries in gross enrolment for secondary education, and ranks 88th in gross enrolment for tertiary education. India also scored relatively low in availability of specialized training. One of the major trends noted is the dearth of doctoral candidates as well as graduates and post graduates in the field of science, technology, engineering and mathematics. Moreover, retention of skilled workforce also intensifies the issue, as a vast majority of them migrate to the US and the UK.

There should be a rise in the funding program facilitating an augmentation in the amount of grants and scholarships as well as stipends being provided to researchers in this field. The availability of enhanced provisions for transfers and internships, wherein the scientists and researchers enrolled in an university can have the experience of working in labs and the research and development department of pharmaceutical firms, and even in other international research organisations can be hugely beneficial.

Intellectual Property Rights

The smaller enterprises are comparatively insignificant

in terms of their research and development as well as innovation endeavours, which can be attributed to the dearth of technological backing due to insufficient funds. Thus, the Indian pharmaceutical SME firms do not engage in the IP activity. It is crucial for the SME units to build associations and collaborations with the research wings of public as well as large sized private organisations and focus on R&D and innovation. It is very important to motivate and encourage Indian pharmaceutical firms to undertake an innovative approach concentrating on new drug discoveries, novel dosage forms along with new applications of already existing drugs. Measures or schemes from the government aimed at reducing the expenditure involved in filing and the maintenance of patents and also providing assistance in the cost involved in litigation and associated legal formalities can be helpful.

Data Exclusivity Issue

In the United States, the FDA approval of a drug is linked to the patent protection. Thus, on the occasion of a generic drug company application (ANDA), the application will be processed only on the condition that there is no valid patent on the same. This methodology of patent linkage creates hurdles in the entry of generic drug players in the market. This arrangement is beneficial for those countries who have companies which are majorly innovator drug producers. However, it can be unfavourable for countries like India, which typically have generic drug producing companies. In India, the marketing of a drug is not associated with its patent status. The advanced countries, triggered by the demands of their pharmaceutical lobbies, have been putting pressure on developing countries like India to observe data exclusivity, to continue their monopoly and prevent the generic companies to expand their market.

The application of DE implementation in all countries regardless of their socio-economic capabilities and manufacturing competencies is not a viable strategy. Taking into account, the economic incentives of originator companies and simultaneously giving priority to making affordable medicines accessible to the public, alternative approaches can be considered. These include preferential pricing, tax benefits and special benefits from originator companies for patients of least developed countries.

Technology Transfer

There are various important discoveries related to drugs which are initiated in the academic sphere. For the development of the pharmaceutical industry, it is vital to have a collaboration between academia and the industry. The transfer of technology between these two entities are essential and there should be adequate partnerships and arrangements to facilitate the same. In India, the earnings from technology transfer and the academia patenting rates are comparatively less. The Government of India has commenced the promotion and encouragement for commercialisation of intellectual property from the public research organisations; however, there are no acclaimed guidelines for the same.

In addition, it is important to attract foreign investments in the pharmaceutical sector, especially in greenfield ventures. Indian pharma companies could leverage the FDI policy by having in-house R&D with foreign investment. To encourage FDI in R&D into India, the Government could consider a fixed minimum per cent of FDI into the pharmaceutical sector mandated for R&D investments. This will make India a global leader in pharma R&D and further strengthen its position in the pharmaceutical space.

1. INTRODUCTION

The pharmaceutical industry plays a crucial role in the socioeconomic development of a nation, through the production of effective medicines and delivering healthcare services for the welfare of patients. At the same time, the pharma sector facilitates revenue generation and employment opportunities in other ancillary sectors, especially in the intermediary industries. There are several factors which have led to the growth of this industry including rapid urbanisation, rise in population, disease proliferation and improvement in the awareness level of citizens.

The key players in the pharmaceutical industry can be broadly categorised based on the kind of pharmaceutical items they produce – branded drug manufacturers, generic drug manufacturers, firms developing biopharmaceutical products, non-prescription drug manufacturers, and firms undertaking contract research. In addition, there are also enablers for the industry such as universities, hospitals and research centres that play an important and supplementary role in R&D activities.

The Indian pharmaceutical industry is considered one of the fastest growing sectors in the country and has exhibited considerable growth in the recent years. It is one of the high performing knowledge based segments of the manufacturing sector. In addition to catering to the needs of the domestic demand, the pharmaceutical industry is also engaged in contract manufacturing, contract research, clinical trials, contract R&D, and direct exports to developed and developing country markets. In fact, the industry has an eminent position in the global pharmaceutical market and is one of the leading producers of generic pharmaceutical products in the world, supplying to approximately one-fifth of the global generic pharma market. The Indian pharma industry exports its products to more than 200 countries in the world, including strictly regulated markets such as the US, Europe and Japan.

Table 1: Evolution of the Policies Associated with the Indian Pharmaceutical Industry in Post-Liberalised India

1990-2010	• Liberalisation of market occurred • Indian companies increasingly launched operations in foreign countries • India developed as a major destination for generic drug manufacturing • Approval of Patents (Amendment) Act 2005, led to the adoption of product patents in India
2010	• Leading pharmaceutical companies augmented their expenditure on research and development with the objective of manufacturing cost effective generics which would strengthen their presence across the global market • Increased patent filings by pharma players took place
2010- 2018	• Patent Amendment Act 2015 followed which included amendments in Patent Act 2002 • 100% FDI was permitted for the medical device industry through the automatic route in the year 2014 • Leading pharma companies raised funds for the purpose of acquisition in domestic and international markets with the aim of increasing product portfolios • In the Union Budget 2018, a new Flagship National Health Protection Scheme was announced for providing health insurance cover of Rs. 5 lakh per family per year. The Scheme will cover 10 crore vulnerable families, with approximately 50 crore beneficiaries • Broad measures like abolition of Foreign Investment Promotion Board, liberalisation of the FDI policy, reduced corporate tax for the small and medium enterprises will help the sector which has many multinational players as well as small manufacturers of generic medicines

Source: Ace Equity Database; Exim Bank Analysis

While consuming pharmaceutical products, a majority of the patients lack specialised knowledge required to assess the quality or safety of the medicine being consumed. There exist asymmetrical information between the producers of drugs, the medical practitioners prescribing those drugs and the patients who ultimately consume these medicines. The quality and safety of pharmaceutical products is of prime importance and is a priority in the process of amelioration of global health worldwide. Thus, regulatory supervision and quality monitoring of medicines and other pharmaceutical products is of vital importance. In this context, this study examines the regulatory landscape in highly regulated markets of the US, the EU as well as that of India and then analyses the trend in the world and India's international trade in pharmaceutical products, and suggests select measures which could help the Indian industry move higher up the export growth trajectory.

2. REGULATORY ENVIRONMENT: THE CASE OF THE US AND THE EU

The pharmaceutical industry is influenced by a host of practices, which may primarily relate to price regulations, patent laws, safety policies, promotion regulation, insurance, procurement regulation, etc. Hence, the regulatory mechanism plays a crucial role in the trade and development of the pharmaceutical industry. The regulatory environment of the US and the EU that significantly govern and impact the global pharmaceutical sector are discussed in this chapter.

REGULATIONS IN THE US

The FDA (US Food and Drug Administration) is an agency of the United States Department of Health and Human Services which is responsible for regulating the pharmaceutical market in the US. The aim of the FDA is to safeguard the health safety of the consumers and the Federal Food, Drug and Cosmetics Act is the basic food and drug law followed in the country. The objective of the FDA is to ensure that human as well as veterinary drugs, biological products and medical devices are appropriately labelled and safe for consumer usage. It enumerates the methodology for product approvals of generic and new drugs and implements the Federal Food, Drug and Cosmetic Act of the United States. The final regulations which are published by the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are brought together in the Code of Federal Regulations (CFR). The FDA's section of the CFR is related to the Federal Food, Drugs and Cosmetics Act and Section 21 of the CFR lists the various regulations concerned with the food and drugs industry. These regulations elucidate the actions which drug sponsors are expected to undertake as per the Federal Law rules.

Under this, every pharmaceutical drug marketed in the US has to pass through an approval process, as underlined below:

Stage One: Pre-Clinical: In this stage, the organisation sponsoring the drug discovers and screens the drug.

- Drug Developed and Animals Tested: Once the sponsor has developed a new drug and wants to have it approved by the FDA, they perform animal testing to gain information on the safety and efficacy of the drug compound.
- Investigational New Drug (IND) Application: The drug sponsor submits an IND application to the FDA to seek approval. This application includes information on the results of the animal tests, as well as on the composition and manufacturing of the drug.

Stage Two: Clinical: This stage consists of the drug sponsor's clinical studies and trials of the proposed drug.

- Phase 1 (20-100 volunteers): This testing phase is primarily concerned with identifying the most common side effects, and how the drug is processed within the human body. It emphasizes safety.
- Phase 2 (hundreds of volunteers): This phase emphasizes effectiveness, and tests how the drug affects a certain disease or illness.
- Phase 3 (thousands of volunteers): In this phase, testers gather more information about both the safety and effectiveness of the proposed drug. They also test it in combination with other drugs, different dosages, and different populations to understand the effects.

Stage Three: New Drug Application (NDA) Review: The FDA performs a comprehensive review on the new drug to ensure it meets requirements and is safe to approve.

- Review Meeting: The FDA meets with the drug sponsor to discuss the findings of the testing.
- NDA Application: The sponsor submits a formal application, and includes all data from the tests they have completed on both animals and humans.
- Application Review: The FDA has 60 days to review the NDA application and decide whether or not to file it.

- Filed: If the FDA files the NDA, it moves on to the next review step.
- Not Filed: The FDA can also choose not to file the NDA. At this point, the drug proposal is terminated.

Application Reviewed: If the FDA decides to file the NDA, they perform a review of the application to evaluate the sponsor's research and the drug itself.

- Approved: If approved, the drug moves on to the next step.
- Rejected: If rejected, the proposal is terminated.

Drug Labelling: The FDA reviews the official drug labelling and edits it to ensure the proper messaging and communication to health care professionals and consumers.

Facility Inspection: The FDA performs an inspection of the facilities where the drug will be manufactured to ensure safety.

FDA Drug Approval: The drug is formally approved by the FDA.

Stage Four: Post-Marketing: Ongoing efforts by healthcare industries to appropriately market the drug to the public.

The next section details the various types of applications that need to be submitted to the US FDA for drug development and approval.

Types of Applications

- New Drug Application (NDA)
- Investigational New Drug Application (IND)
- Abbreviated New Drug Application (ANDA)
- Over-the Counter Drugs (OTC)
- Biologic License Application (BLA)

<u>New Drug Application</u>

The regulations of new drugs in the United States have been based on the New Drug Application for ages. Each and every new drug has been the subject of an approved new drug application before being commercialised in the US ever since the year 1938.

Exhibit 1: The Drug Discovery, Development and Approval Process

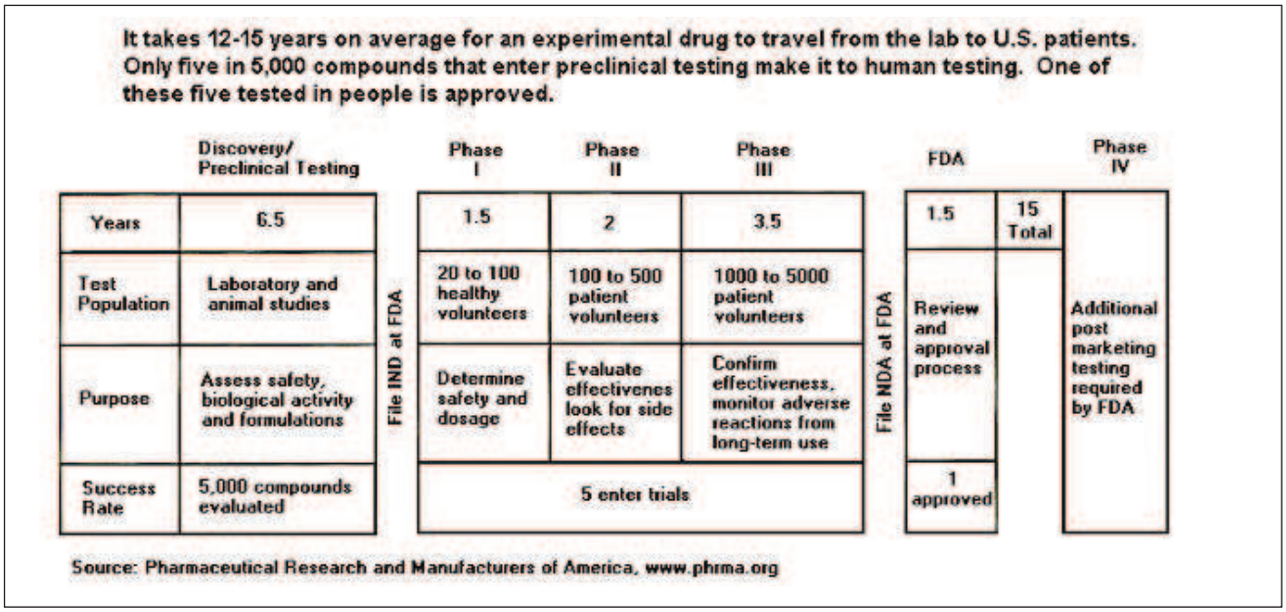


Table 2: New Product Approvals in the US

Year	New Drug Applications	New Molecular Entity
2001	66	24
2002	78	17
2003	72	21
2004	113	36
2005	78	20
2006	93	22
2007	92	18
2008	94	24
2009	96	26
2010	100	21
2011	137	30
2012	101	39
2013	102	27
2014	110	41
2015	127	45
2016	22	22

From the year 2004 onwards the figures include new biological approvals for therapeutic products transferred from Centre for Biologics Evaluation & Research (CBER) to Centre for Drug Evaluation & Research (CDER)
Source: CDER

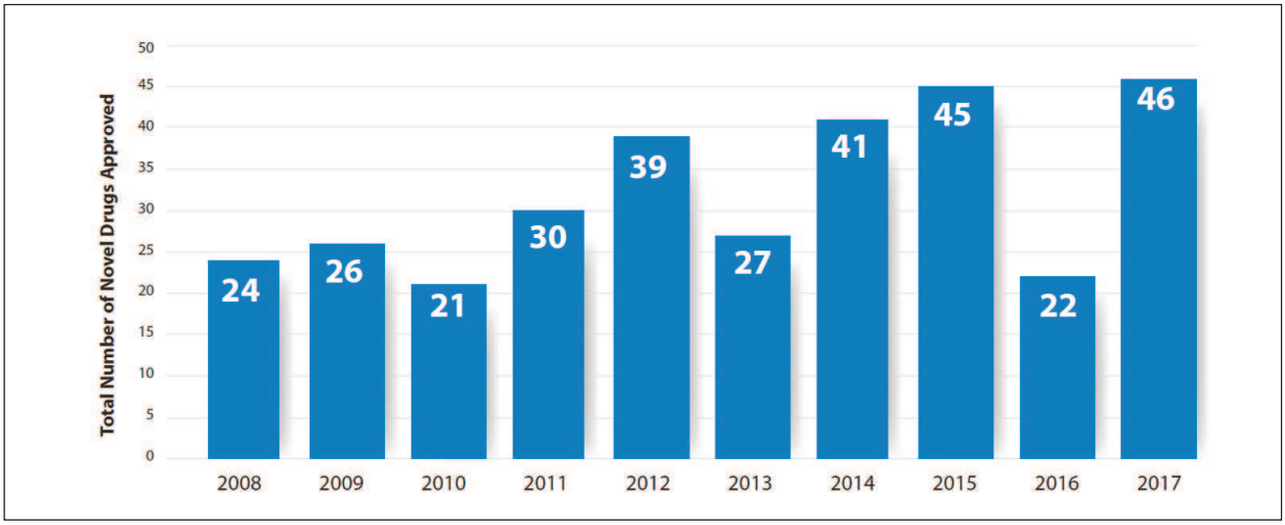
NDA is the primary means by which a drug sponsor puts forward to the US FDA for approval of marketing and sales of the drug in the United States. The entire information and data collected while the animal studies and human clinical trials are conducted constitute a part of the new drug application. The objective of this application is to furnish adequate information regarding the following:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drugs proposed labelling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

Typically, the documentation associated with the NDA should provide clarity regarding all crucial parameters including the description of clinical tests, ingredients of the drug, results of animal studies, process of manufacturing, processing and packaging.

In 2017, FDA's Centre for Drug Evaluation and Research (CDER) approved 46 novel drugs, either as new molecular entities (NMEs) under New Drug Applications (NDAs), or as new therapeutic biologics under Biologics License Applications (BLAs). From 2008 through 2016, CDER has on an average approved

Exhibit 2: Annual Novel Drug Approvals in the US: 2008 - 2017



Source: Advancing Health through Innovation 2017 – New Drug Therapy Approvals; CDER

31 novel drugs per year with 2017 being the year with the highest number of novel drugs approval over the last decade.

Investigational New Drug (IND) Application

According to the Federal Law, the marketing application of a drug must be approved, before it can be transported or distributed across state lines. Nevertheless, the sponsor of an investigational drug is likely to ship the drug to clinical investigators across various states. So, the investigational new drug application is the means by which a pharmaceutical company acquires the permit to ship an experimental drug across state lines (typically to clinical investigators) prior to the approval of marketing application of the drug.

There are three types of Investigational New Drugs:

An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Emergency Use IND gives FDA the permission to authorize the usage of an experimental drug in the case of an emergency situation, when there is lack of time for submission of an IND.

Treatment IND is a framework which grants permission to eligible subjects with investigational drugs, for the purpose of treating life threatening diseases, which do not have any alternative satisfactory treatment available. This is granted when adequate research has been conducted to demonstrate that the drug "may be effective" and there are no chances of any risks. Prior to the treatment IND being issued there are four conditions which must be fulfilled:

- The drug is targeted to cure a critical and immediately life threatening disease
- There is no satisfactory alternative treatment available
- The drug is already under investigation or the trials have been completed
- The trial sponsor has been putting in serious efforts for acquiring market approval

While applying for an investigational new drug application, detailed information regarding the following must be provided:

Animal Pharmacology and Toxicology Studies: This refers to particulars of the pre-clinical data to permit an investigation to test if the product is fit for initial testing in humans. There should also be a mention of any prior observance of the drug when used on humans.

Manufacturing Information: This includes listing down details related to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and drug product. The rationale behind enumerating this information is to assure that the company engaged is capable of appropriately producing and then supplying consistent batches of the drug.

Clinical Protocols and Investigator Information: This covers comprehensive protocols for the proposed clinical studies with the objective to evaluate that the preliminary phase of the trials would not present unwarranted risk for the subjects. There is also a requirement to provide information regarding the qualifications of clinical investigators who would be engaged in the supervision of the experimental compound. Moreover, it also includes commitments to achieve informed consent from the research subjects, to arrange for review of the study by an institutional review board and to comply with the investigational new drug regulations.

Subsequent to the Investigational New Drug application, the sponsor is expected to wait for a period of 30 calendar days before commencing clinical trials. During this period, the FDA makes an assessment of the application to verify and assure that the safety of the research subjects is guaranteed.

The regulations associated with the IND Application Process include:

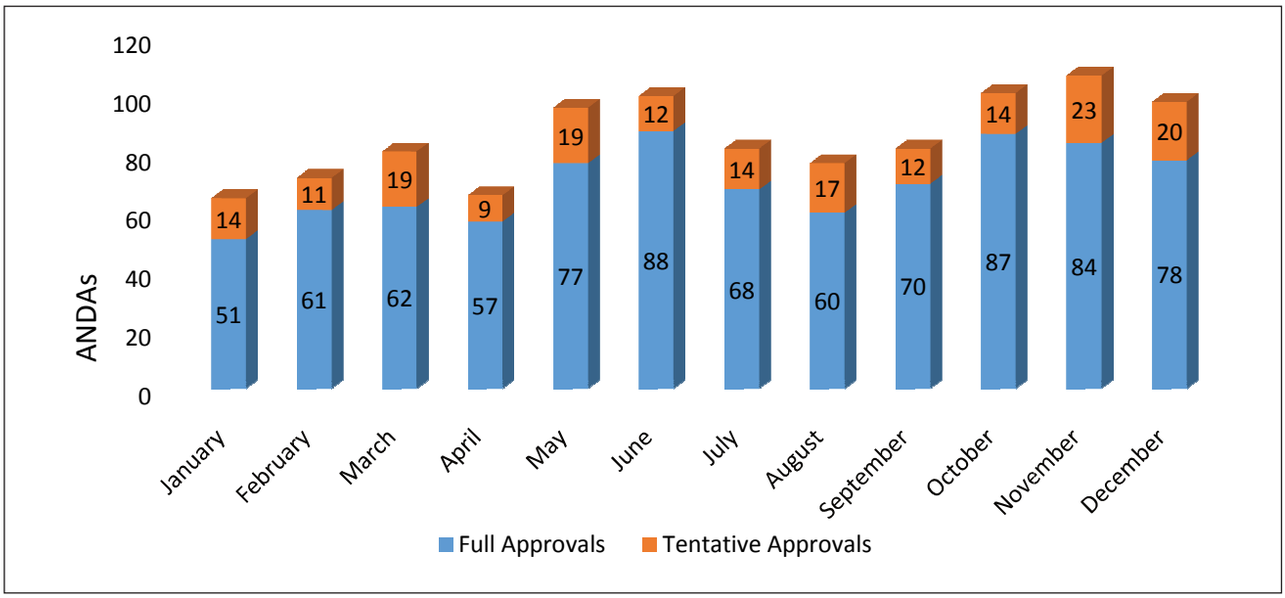
21 CFR Part 312- Investigational New Drug Application
21 CFR Part 314- INDA and NDA Applications for FDA Approval to market a new drug
21 CFR Part 316- Orphan Drugs[1]
21 CFR Part 58- Good Lab Practice for Nonclinical Laboratory (Animal) Studies
21 CFR Part 50- Protection of Human Subjects
21 CFR Part 56- Institutional Review Boards
21 CFR Part 201- Drug Labelling
21 CFR Part 54- Financial Disclosure by Clinical Investigators

Abbreviated New Drug Application (ANDA)

For marketing a generic drug, companies need to submit the Abbreviated New Drug Application to the FDA to gain approval. Generic drug products are the ones which are similar to the innovator drugs in terms of dosage form, strength, route of administration, quality, performance characteristics as well as intended use. These applications are referred to as 'abbreviated' as there is no compulsion of incorporating the preclinical (animal) and clinical (human) data to demonstrate safety attributes. The matter of concern for the drug companies is to confirm scientifically that the performance of their product is comparable to that of the innovator drug. With the intention of exhibiting bioequivalence, applicants record the amount of time employed for the generic drug to reach the bloodstream of healthy volunteers. This in turn gives the rate of absorption, or bioavailability of the generic drug to check for correspondence with the innovator drug. For the FDA to grant an approval, the generic version of the drug must deliver the same quantity of active ingredients in a patient's bloodstream, and it should also take the same amount of time as taken by the innovator drug.

This phenomenon of the usage of bioequivalence as the premise for granting approval for the manufacture of generic version of drug products was constituted by the Drug Price Competition and Patent Restoration Act of 1948, also referred to as the Hatch-Waxman Amendments. In this arrangement, the FDA can give

Exhibit 3: Generic Drugs Approved in the USA in the year 2017



Source: USFDA

[1]An orphan drug is a drug which is intended to treat a condition affecting fewer than 2,00,000 people in the US, or which will not be profitable within 7 years following approval by the FDA

approval for the marketing of the generic copies of branded drugs, without imposing the obligation of attempting expensive and duplicative clinical trials. This has given the brand name companies the opportunity to apply for an expansion of patent protection period to compensate for the amount of time taken by the FDA in their review procedure, and also obtain periods of market exclusivity. Likewise, the generic drug companies have acquired the capability to challenge patents in court before marketing and gaining the facility of 180 days generic drug exclusivity.

The regulations with regards to the ANDA process are:

21 CFR Part 314
21 CFR Part 320

The year 2017 had been considered a record- setting year for generic approvals and the US FDA approved 1027 new generic drugs. Amongst these, 843 approvals were full approvals, while the remaining 184 were tentative approvals.

Generic Drug Approval Process

FDA approved generic drugs account for nearly 89% of the prescriptions given by the doctors in the United States. While the branded drugs are the result of effective and prolonged research programs and extensive clinical trials, the producers of generic drugs can utilize the data of their branded peers and engage in relatively lesser exorbitant research and development arrangements. It is the responsibility of the generic drug developers to convince the FDA that generic copy of the drug is substitutable with a branded drug and is safe for consumer usage.

The submission of appropriate and exhaustive data is a crucial part of the application. The manufacturing process of the drug should be properly described as to how the generic drug will be produced by amalgamating the active and inactive ingredients, thus representing the superior quality of the product. The active ingredient should be the same as in the case of branded drugs and it has to be established that the inactive ingredients used are safe. Apart from this, another area of concern is to justify that the impact that the generic drug has on the patients is alike when compared with the effect that the branded drug has on them. To achieve this objective, trials are conducted on human volunteers. Patients are made to take the branded drug on one day and the generic drug on the following day, and experience the same treatment in both the scenarios. Moreover, other characteristics to be considered are to effectively verify that the quality of the generic drug will not degenerate over the passage of time and that the labelling will be similar to that of the branded drug. Post the submission of data, healthcare experts as well as scientists undertake a thorough evaluation to analyse the quality of the generic drug. The information gathered by the investigators in the process of examining the testing and manufacturing facilities are also considered. Even after the generic drug is approved, the FDA conducts regular exploration and check-up of the manufacturing plants and continues to scrutinize the quality of the generic drug. The time frame between the submission of application and the approval varies depending upon the complexity of the drug and also the comprehensiveness and completeness of the application. Several series of communications take place between the FDA and generic drug company for the investigators to be certain that the generic copy is safe and can be effectively substituted for its branded drug counterpart. The submission of a complete application including all the requisite data is critical for attaining an early approval. There have been instances in the case of priority drugs (drugs which the Centre for Drug Evaluation and Research (CDER) considers has the potential to result in a considerable advancement in the field of medical care) when the approval has been granted in a period of 6 months or even lesser. However, it might also take years for the FDA's investigation team to be satisfied about the effectiveness and safety of the generic drug and accord approval. FDA renders priority to the review of first generics by way of tracking the legal issues having an impact on the generic competition, deciding

the earliest date a first generic can be eligible for the approval procedures and also putting in efforts for expediting their approval.

Box 1: Generic Drug Application Submitted to the FDA for Approval must Demonstrate the Following:

- Generic drug is "pharmaceutically equivalent" to the brand.
- Manufacturer is capable of manufacturing the drug appropriately.
- Manufacturer is competent of making the drug consistently.
- The 'active ingredient' is same as that of the brand.
- Proper quantity of the active ingredient reaches the parts of the body where it would result in an effect.
- The inactive ingredients of the drug are safe.
- The drug does not break down over time.
- The container used for the shipping and selling of the drug is suitable.
- The label is same as the brand-name drug's label.
- Pertinent patents or legal exclusivities have expired.

Source: USFDA

Paragraph IV Drug Product Applications

The provisions of the Drug Price Competition and Patent Restoration Act, or the Hatch-Waxman Act, provides that a company can request for permission from the FDA, to market a generic drug, prior to the expiration of a patent, associated with the brand name drug, based on which the generic has been made. Under the provisions, the company which is the first one in the submission of an abbreviated new drug application with the FDA, achieves the exclusive grant to market the generic drug for a period of approximately 180 days.

The conditions to be fulfilled by the generic applicant include the following:

- Include in its ANDA Application, a certification verifying that the concerned patent is not infringed by the generic product (referred to as the paragraph IV Certification)
- Notify the patent holder about the submission of the ANDA

In case the patent holder files an infringement suit against the generic applicant within 45 days of the ANDA notification, then the FDA approval for marketing of the generic product is deferred for a period of 30 days, unless before completion of that period, either the patent expires or is determined to be not infringed.

Over the Counter Drugs

Over the counter drugs, which refer to the drugs which are available to patients without the need of a prescription, constitute a substantially important segment of the American healthcare market. There exist greater than 80 therapeutic categories of OTC drugs, extending from drugs for the cure of acne to weight loss. CDER's Office of Drug Evaluation IV is essentially responsible for the assessment of the OTC drugs. FDA evaluates the active ingredients and the labelling of more than 80 therapeutic varieties of drugs such as analgesics or antacids, rather than reviewing individual drug products. FDA has developed an OTC Drug Monograph for each category of these drugs, which is published in the Federal Register. These monographs contain details regarding acceptable ingredients, doses, formulations and labelling. On the implementation of a final monograph, companies can go ahead with the manufacture and marketing of the OTC product, and do not require a FDA pre-approval. New products which adhere to the final monograph may be marketed without the need of a further FDA review. However, in the case of non-conformity, review is conducted by way of the New Drug Application procedures.

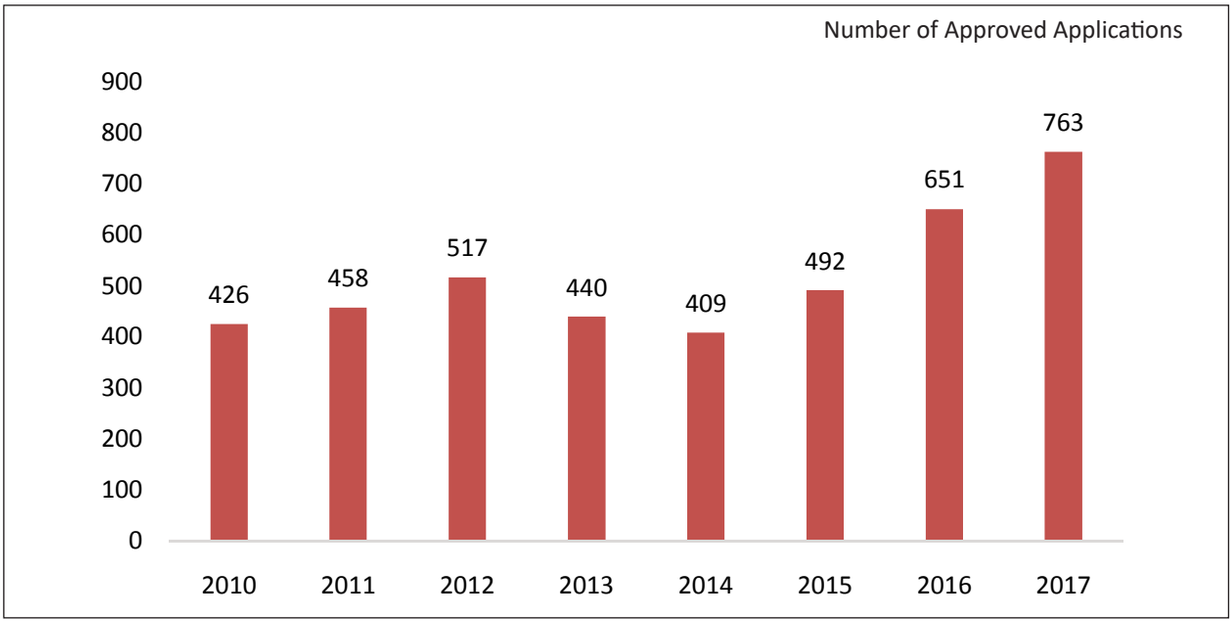
Biologic License Application

Firms undertaking the manufacture of biologics for sale in interstate commerce are expected to hold a license for the product. These products receive an approval for marketing under the provisions of the Public Health Service (PHS) Act. The application requires inclusion of detailed information about the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical impacts of that biologic product. On conformity with the FDA preconditions, a license is issued for permitting the marketing of the product.

Box 2: Generic Drug User Fee Amendments (GDUFA)

The generic drug industry has expanded significantly with approximately 89% of the prescriptions dispensed in the United States constituted by generic drugs, saving the healthcare system more than US$ 1.67 trillion over the last decade . The quantity of generic drug applications and the number of international facilities engaged in the manufacture of generic drugs has increased manifold. This in turn has caused the FDA's generic drug program to also expand in scope. Taking cognizance of this, the US FDA introduced the Generic Drug User Fee Amendments (GDUFA) in 2012, with the intention of intensifying and accelerating the speed of quality generic drugs to the public and also increasing the predictability of the review process. This regulation was implemented as a solution to various regulatory hurdles and with the objective of enhancing the efficiency of the FDA's generic drug program. The law obligated the industry to pay user fees to supplement the costs of evaluating generic drug application and scrutinising facilities. In return for the fees paid by the generic drug industry, FDA ensured to finish the review of these drugs at an estimated time bound manner. GDUFA needs to be reauthorized every five years, and the latest reauthorization happened in August 2017. The number of approvals post this measure have increased considerably with the US FDA having approved 1027 new generic drugs in 2017, 14 more than the previous record of 813 set in 2016. Of those, 843 were full approvals and 184 were "tentative" approvals, that is, applications that are ready for approval from a scientific perspective, but cannot be fully approved due to patents or exclusivities on the brand-name drug.

Number of Generic Drug Applications Approved



Source: USFDA

Drug Master Files

A drug master file is a collection of confidential and exhaustive details related to the facilities, processes, or articles that have been employed in the manufacturing, processing, packaging and the storage of one or more human drugs, which are submitted to the FDA. This document prepared by the drug manufacturer is not necessitated by law or any regulatory authority, but is submitted upon the individual judgement of the holder. The particulars detailed in a drug master file (DMF) may be used to substantiate an investigational new drug application, new drug application, abbreviated new drug application, an export application or another DMF; however, it does not serve as a substitute for any of these applications. A DMF is neither approved nor disapproved and the information contained therein is analysed solely in association with the assessment of an investigational new drug application, new drug application, abbreviated new drug application, and an export application, respectively.

There are five categories of DMF's:

Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel

Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III Packaging Material

Type IV Excipient, Colorant, Flavour, Essence, or Material Used in Their Preparation

Type V FDA Accepted Reference Information

Current Good Manufacturing Practices

FDA oversees the quality of pharmaceutical products vigilantly, and the major regulatory standards for assessing the quality of human pharmaceuticals is the Current Good Manufacturing Practice (CGMPs). CGMP includes systems that guarantee appropriate designing, monitoring, and control of manufacturing processes and facilities. The fulfilment of these regulation assures that the identity, strength, quality, and purity of drugs by necessitating that the manufacturers appropriately control their operations. These system of controls if observed are beneficial in deterring chances of contamination, mix-ups, deviations, failures and errors. While considering the new drug and generic drug applications, FDA takes into account an analysis of the manufacturer's adherence with the CGMP. The judgement regarding the compliance with these regulations are made depending on the examination of the facilities, analysis of samples and also determining the compliance history of the firm. These details are recorded in the form of reports which depict the history of the firm.

Regulations as well as guidance documents for the pharmaceuticals industry is published by the FDA in the Federal Register. Various other details including guidance documents and resources are available on the FDA's website for the reference of the pharmaceutical industry players. Moreover, FDA with the target of enriching the knowledge of the manufacturers, imparts information by way of presentations in national and international meetings and conferences. If a company is unsuccessful in meeting with the CGMP requirements, then the FDA might take punitive measures in the form of issuing warning letter or other regulatory actions. This can also induce the FDA to reject the application for the marketing of a drug.

Form 483 and Warning Letters

The drug companies which sell their medicines in the United States are expected to adhere to the regulations which are entailed by the FDA. The manufacturing units which are engaged in the supply of drugs are frequently inspected by the FDA. At the completion of the inspection, if the investigator concludes that there exist violations of the Food Drug and Cosmetics Act, then a FDA Form 483 is issued to the management of the concerned firm. This occurs on the occasion that an investigator deduces that any food, drug, device or cosmetic has been adulterated or is being prepared, packed, or held under conditions

Table 3: Interpretation of an Import Alert

Import Alert Section	Description
Import Alert #	This is the number issued by the FDA. The first 2 numbers are the industry code of the product.
Published Date	This is the last date that there was an update to the alert. This is not the original date the alert was published.
Type	This describes whether the alert is Detention Without Physical Examination (DWPE) or DWPE with surveillance. Import Alerts that are DWPE with surveillance include additional guidance for the field.
Import Alert Name	This is the name of the alert; it is a brief description of what the alert applies to.
Reason for Alert	This section describes why the alert was issued.
Guidance	This section describes what actions FDA may take and may provide guidance on how to be removed from the alert. This section can vary based on the type of alert.
Product Description	This section describes what products are subject to DWPE.
Charge	This section describes the FDA laws and regulations applicable to the import alert.
Countries	This section is included for country- or area-wide import alerts and includes the countries/areas subject to DWPE.
List of firms and their products subject to DWPE under this Import Alert (a.k.a. Red List)	This section lists the firms and/or products that are on the red list of the import alert. If a firm/product is on the red list of an import alert, it means they are subject to DWPE.
List of firms and their products that have met the criteria for exclusion from DWPE under this Import Alert (a.k.a. Green List)	This section lists the firms and/or products that are on the green list of the import alert. If a firm/product are on the green list of an import alert it means they are not subject to DWPE.

Source: US FDA

whereby it may become adulterated or rendered injurious to health. The FDA Form 483 apprises the company's management of the conditions which have resulted in the violation of the rules. The companies are then supposed to respond to this form in writing, elucidating their remedial measures, and commencing those initiatives promptly. The Establishment Inspection Report is a comprehensive narration of the activities and observations of the investigator at the establishment or facility.

The FDA expects a response to the Form 483 observations within a period of 15 days. In the circumstance when the FDA is unsatisfied with the response furnished by the manufacturer in reply of the Form 483, then the FDA might issue a warning letter to the firm. If the violations pose considerable threat to the safety of the consumers then a warning letter can be issued by the FDA even without the issue of Form 483. This warning letter leads to a constraint on the manufacturing unit to deliver goods to the US from that particular facility. Following this legal action, the manufacturer must seek the services of consultants to devise corrective measures and incorporate those techniques. The firm can then contact the FDA for the purpose of a re-inspection. If the investigators are convinced with the corrective measures, then a close out letter is issued.

Import Alert

FDA Import Alert signifies that the product does not comply with the FDA laws and regulations. As a result, the products will be detained at the border without physical examination, as there exist adequate evidence regarding the regulatory noncompliance of the product. The violations can be associated with the product, manufacturer, shipper or any other information. Prior to attempting to import into the United States it is advisable for importers to enquire if the products are subject to Detention Without Physical Examination (DWPE).

Table 4: Types of Import Alerts

Category of Import Alert	Instructions
Country- or area-wide	FDA may detain without physical examination certain products offered for entry from the specified country or area.
Manufacturer/ Product Specific	FDA may detain without physical examination certain products from specific manufacturers.
Shipper	FDA may detain without physical examination certain products from shippers.
Country/World Wide Alert	FDA may detain without physical examination certain products from all countries outside of the U.S.

Source: USFDA

Drug Supply Chain Security Act

Anti-counterfeiting has been a critical issue in the pharmaceutical industry and has been a major area of focus in the regulatory regime globally. The Drug Quality and Security Act (DQSA) was enacted by the Congress on November 27, 2013. Title II of the Drug Quality and Security Act, the Drug Supply Chain Security Act (DSCSA), outlines the steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. This measure has been taken to protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful. The system will also improve detection and removal of potentially dangerous drugs from the drug supply chain to protect U.S. consumers.

The Drug Supply Chain Security Act (DSCSA) outlines requirements for manufacturers, repackagers, wholesale distributors, dispensers, and third-party logistics providers (trading partners). Some requirements began in November 2014 and several key requirements began at various stages in 2015. The requirements, development of standards, and the system for product tracing is likely to continue until 2023.

A critical component of the product tracing scheme outlined in the DSCSA is the product identifier. Section 582 requires that each package and homogenous case of product in the pharmaceutical distribution supply chain bear a product identifier that is encoded with the product's standardized numerical identifier, lot number, and expiration date by specific dates. Under the statute, manufacturers were required to begin affixing or imprinting (adding) a product identifier to each package and homogenous case of a product intended to be introduced into commerce by November 27, 2017.Repackagers are required to do the same no later than November 27, 2018[2].

21st Century Cures Act

The 21st Century Cures Act, was signed into the law on December 13, 2016, designed to help accelerate medical product development and bring new innovations and advances for the patients. The Cures Act would drive modernisation of clinical trial designs and clinical outcome assessments, which would in turn expedite the development and review of novel medical products, inclusive of medical countermeasures. The Cures Act authorized US$ 500 million over a period of 9 years to help FDA cover the cost of implementing the law. This Law enables the FDA to improve its ability to retain scientific, technical

[2]US FDA

and professional experts and formulate innovative product development programs including:

- Regenerative Medicine Advanced Therapy (RMAT), to grant expedited options for certain eligible biologics product
- Breakthrough Devices Program, established to speed the review of certain innovative medical devices[3]

REGULATIONS IN THE EU

The various procedures involved in the drug approval process in the EU are similar to the ones followed by the US FDA. An investigator is required to acquire pre-authorisation for the usage of drugs in clinical trials. The Clinical Trials Directive of the European Commission (2001/20/EC), set down regulations for clinical trials; however, this was later repealed and replaced in the year 2014 by Regulation No 536/2014 of the European Parliament. Subsequent to this, the drug has to pass through three phases for further approval. Phase I trials are conducted on a small number of healthy subjects for the clarification of pharmacology and dose range. The purpose of holding the Phase II trials on hundreds of patients is to analyse the dose-response relationship. This is followed up by Phase III trials which includes the participation of hundreds to thousands of patients to justify for the safety and efficiency of the drug.

The European Medicines Agency (EMA) was established during the year 1995, with the objective of attempting the harmonization of processes in various member state regulatory agencies so that the expenditure incurred to the drug companies in obtaining approvals from each member state can be avoided. Nevertheless, the EMA does not supervise the entire list of drug approval processes as is the case with the FDA in the US. There exist four ways/ paths through which a drug can be approved, conditional on the drug class as well as the priority and preference of the manufacturer.

Centralized Process

This procedure is monitored, controlled and regulated by the EMA. It should be noted that each of the member states of the EU is represented on the EMA committee for Medical Products. In this case, the Committee issues a license, which holds valid in each of the EU member states. One of the major advantages involved in undertaking the Centralized Process is that medicines are authorised for all EU citizens at the same time. Moreover, information related to the product is made available in all the various languages used in the EU.

Medicines approved via the Centralised Process are:

- Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune dysfunctions and viral diseases
- Medicines derived from biotechnology processes, such as genetic engineering
- Advanced therapy medicines which include gene-therapy, somatic cell therapy or tissue engineered medicines
- Officially designated 'orphan medicines' (medicines produced to cure rare diseases)

National Process

For those category of drugs which are not subject to the requirement of undergoing the Centralised Process, each EU member state approves drugs by way of their individual procedures followed by them internally.

Mutual Recognition

Through this mechanism of mutual recognition, the drugs which have received approval from one member state through its individual state procedures, have the advantage and opportunity of achieving marketing authorization in another EU member state.

[3]US FDA

Decentralised Procedure

By way of the decentralised procedure, the manufacturers have the option of applying simultaneously in more than one EU state for that segment of products which have neither been authorized in any of the EU states nor do they fall in the category of products which are necessitated to undergo the mandatory Centralised Process. Majority of the drug manufacturers prefer this route of drug approval, and this method attracts leading number of applications for the purpose of approval.

Table 5: Drug Approval Process in the US and the EU: A Comparison

United States	European Union
Application Application to FDA for permission to conduct clinical studies and transport drugs across states	**Application** Application within one or more states of the European Union for approval to conduct clinical studies; each state designates its own regulatory body which undertakes approval procedures
Clinical Trial Phase Phase 0 and 1 trials: Small number of healthy subjects, to clarify pharmacology and dose range Phase II trials: Several hundred patients with the target condition, to determine dose/response relationship Phase III trials: Several hundred to thousand patients to demonstrate safety and efficacy	**Clinical Trial Phase** Phase 0 and 1 trials: Small number of healthy subjects, clarify pharmacology and dose range Phase II trials: Several hundred patients with the target condition, to determine dose/ response relationship Phase III trials: Several hundred to thousand patients to demonstrate safety and efficacy
Emergency Use and Orphan Drugs "Orphan Drug" Applications: Special approval processes for drugs produced to treat illness that affects fewer than 2,00,000 patients in the United States EIND (Emergency Drug Application) Process: This is designed for dealing with emergency and life threatening situations; this requires shorter duration as compared to IND approval; IND approval must be initiated, but treatment can proceed after EIND approval Treatment IND Process: This application is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place	**Emergency Use and Orphan Drugs** "Orphan Drug" Applications: Special consideration for drugs to treat conditions experienced by small segment of population Emergency Drug: The safety of these drugs produced to treat life threatening diseases must be tested by way of clinical trials
Drug Approval New Drug Application to FDA	**Drug Approval** There are four pathways to drug approval in the EU • Centralized Process • National Process • Mutual Recognition • Decentralized Process

Source: Comparison of European and US Approval Processed; Gail A. Van Norman, MD

Differences in the EU and the US drug Approval Process

Extent of Time Taken: It is crucial to expedite the launch of drugs in the market, both for the patients and the sponsor. A vast majority of time is spent in clinical trials, which have resulted in expenditure adding up to millions and billions of dollars. It has been observed that the amount of time involved in drug review procedure is relatively lesser at the US FDA as compared to the EMA. According to a study[4], the median time taken in the initial review stage for similar drugs was 303 and 366 days by the FDA and the EMA respectively. In case of full review, the period of time taken by the FDA was 322 days while that of the EMA was 366 days. Owing to a relatively brief review time, the drugs that were approved by the FDA and the EMA, were made available to the patients in the US, in lesser periods of time as compared to the EU.

INTERNATIONAL HARMONISATION OF REGULATIONS

In recent years, a trend of globalisation has been witnessed in the production, marketing and sale of pharmaceutical products. With the objective of targeting global markets, drug manufacturers are necessitated to seek approval for their products from various regulatory bodies established in several countries. The variations in the data requirements which are demanded by different countries, results in a rise in cost associated with trials and delays the availability of medicines to patients. Subsequent to the drug approval procedures, the difference in the regulatory system ensuring the ongoing safety of drug consumption, creates hurdles and is time consuming. The current scenario has created the need for global harmonization of the various international pharmaceutical regulations. There is a need for global collaboration to guarantee that consistent and appropriate standards are being adhered by the drug manufacturers and regulatory authorities, irrespective of the country.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been pivotal in assembling the varied regulatory bodies in pharmaceutical industry and organising discussions related to the scientific and technical aspects related to drug registration. The ICH was established in the year 1990, by regulatory agencies as well as industry bodies in the United States, Europe and Japan have been promoting global harmonisation of pharmaceutical regulations. The goal of the ICH is to facilitate increased harmonisation globally, and ensure the production and registration of safe and efficient drugs. The harmonisation is attempted by way of establishing ICH guidelines, which is developed by a procedure of attaining scientific consensus between the regulatory and industry experts.

ICH Members

Regulatory Members

- European Commission (EC)
- US Food and Drug Administration (FDA)
- Ministry of Health, Labour and Welfare of Japan (MHLW) also represented by the Pharmaceuticals and Medical Devices Agency (PMDA)
- Health Canada
- Swissmedic
- Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
- Ministry of Food and Drug Safety (MFDS, Republic of Korea)

Industry Members

- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- International Generic and Biosimilar Medicines Association (IGBA)
- World Self-Medication Industry (WSMI)
- Biotechnology Innovation Organisation (BIO).

Source: International Council for Harmonisation, US FDA and Health Canada Regional Public Consultation PPT

[4]Comparison of European and US Approval Processed; Gail A. Van Norman, MD

Box 3: ICH Guidelines

Quality Guidelines: These guidelines include the undertaking of stability studies, which list down the permissible limits for the testing of impurities and an adaptable and flexible perspective towards the quality of the pharmaceutical products, built on the basis of Good Manufacturing Practice (GMP). These guidelines are associated with chemical and pharmaceutical quality assurance.

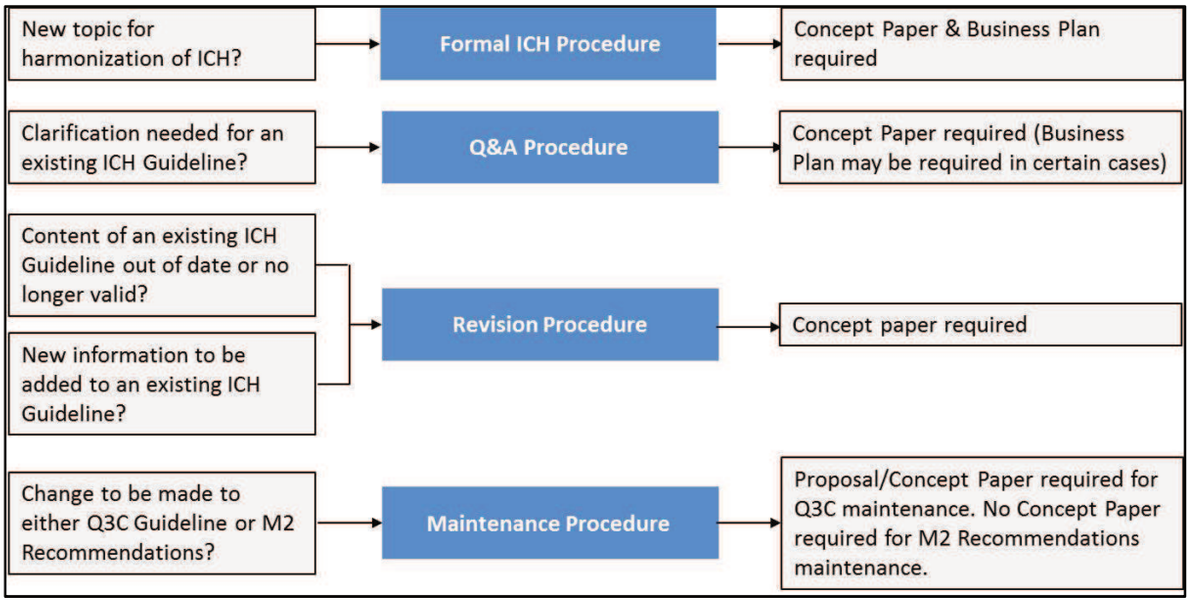
Efficacy Guidelines: This section of the ICH guidelines are concerned with the design, conduct, safety and reporting of clinical trials. The efficacy guidelines also include novel types of medicines derived produced by way of biotechnological processes and the utilisation of pharmacogenetics/genomics methodology to produce better targeted medicines.

Safety Guidelines: These guidelines have been composed to refrain from the risk such as carcinogenicity, genotoxicity and reprotoxicity.

Multidisciplinary Guidelines: These guidelines are concerned with those issues which do not appear in the quality and efficacy guidelines section. The multidisciplinary guidelines comprises the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

Source: ICH Official Website

Exhibit 4: Process of Harmonisation



Source: ICH Official Website

Key Trends in Global Pharmaceutical Sector

PIC/S

Pharmaceutical Inspection Cooperation Scheme (PIC/S) is an informal collaboration among member economies spearheaded by the EU seeking to improve the standards of manufacturing requirements amongst its members. Going further, the EU has agreed Mutual Recognition Agreements on GMP with several third countries (Australia, Canada, Japan, New Zealand and Switzerland). Currently, there are 51 regulatory bodies worldwide inclusive of the US FDA, MHRA (Medicines and Healthcare products Regulatory Agency; the UK) and PDMA (Pharmaceuticals and Medical Devices Agency; Japan) which are members of the PIC/S. This arrangement between the countries as well as the inspection agencies has the primary objective of promoting the application of good manufacturing practices. These efforts are directed at bringing about harmonisation in the health regulatory standards and procedures such that common standards can be maintained in the GMP sphere. This also facilitates opportunities for training to be imparted to the inspectors. Furthermore, this agreement aims to achieve cooperation and networking between various international and competent authorities for mutual benefits and understanding. This membership grants various benefits such as a decline in the duplication of inspections, leading to a fall in expenditure involved and also a boost to exports. The PIC/S members can avail this advantage by importing medicines from the manufacturing facilities of the other members, circumventing the chances of duplication of inspections, and enhancing the convenience of the exporters.

India is not currently a member, although PIC/S has identified India as one of the 'key players' in terms of the pharmaceutical industry. The main conditions for membership are to have a law on medicinal products, a GMP Guide equivalent to that of PIC/S, a GMP inspectorate that fulfils PIC/S quality system requirements, and experienced GMP inspectors. PIC/S entails membership candidates to bring their GMP systems up to international standards and the process of membership can be accomplished in two to three years. According to a few pharmaceutical firms, the act of India joining this membership will increase the visibility of India in the global market. It is further viewed that if India becomes a member of PIC/S, the quality and capacity of the regulatory system in India will also improve and be aligned with the global standards. Approximately two thirds of the pharmaceutical products exported from India are being supplied to the PIC/S member countries. Thus, becoming a member of this association will lead to augmentation of exports. However, the medium and small sized pharmaceutical players, particularly those supplying to the domestic markets do not find this a favourable arrangement. This move will entail them to upgrade according to the global standards, incurring an expenditure of approximately Rs. 5 crore to Rs. 20 crore per unit, which may not be a viable option for them.

BEPS

On 5th October 2015, the Organisation for Economic Co-operation and Development (OECD) released the final action plan in relation to Base Erosion and Profit Shifting [BEPS]. BEPS refers to the complex structuring done by multinational businesses to artificially shift reduced profits to low tax countries and pay little or no corporate tax. As a member of the G20 and an active participant in the BEPS project, India is committed to the BEPS project outcome and its implementation. The project is anticipated to impact the industry significantly. Impact on Indian pharmaceutical industry is, however, subject to the proposed Indian tax law and positions adopted by India in the multilateral instruments or bilateral tax treaties. Some of the key areas where the project is anticipated to impact are: on the status of Permanent Establishment (PE), tax treaties, intellectual property (IP), financial transactions and interest deductions on hybrid instruments, transfer pricing, contract research and manufacturing arrangements, and indirect taxes.

Substandard and Falsified (SF) Medical Products

The pharmaceutical industry is adversely impacted by the existence of substandard and falsified (SF) medical products which is an unacceptable risk to public health. There have been instances of these medicines

in various regions of the world including in vaccines and diagnostics. Falsified medicinal products might not contain any active ingredient, an inappropriate active ingredient or the incorrect quantity of a particular active ingredient. Some falsified medicinal products are known to contain corn starch, potato starch or chalk. They are toxic in nature, and might also be fatal. They are often designed to appear identical to the genuine product and may not cause an obvious adverse reaction, however they often will fail to properly treat the disease or condition for which they were intended, and can lead to serious health consequences including death.

WHO is working with stakeholders to minimize the risks from SF medical products by collecting data and transferring knowledge and good practices to various nations. During 2013, WHO launched the Global Surveillance and Monitoring System to encourage countries to report incidents of substandard and falsified medical products in a structured and systematic format, to help develop a more accurate and validated assessment of the problem. The system:

- Provides technical support in emergencies, links incidents between countries and regions, and issues WHO medical product alerts; and
- Gathers a validated body of evidence to more accurately demonstrate the scope, scale and harm caused by substandard and falsified medical products and identify the vulnerabilities, weaknesses and trends.

As of November 2017, WHO had issued 20 global medical product alerts and numerous regional warnings, and had provided technical support in over 100 cases. It has engaged in training a global network of over 550 regulatory staff in 141 Member States to report substandard and falsified medical products to the WHO Global Surveillance and Monitoring System[5].

Taxation Reforms

The United States

The United States has revealed a major overhaul of its tax law towards the end of the year 2017. A fall in the corporate tax rate to 21% from the previous 35%, would increase the competitiveness of US companies. Under the provision of this new tax law, multinationals are expected to pay tax on the previously untaxed accumulated offshore earnings, which will be levied at 15.5% on cash and equivalents and at 8% on the non-cash earnings. This will act as an incentive for various organisations to direct their overseas cash back to the United States. This might lead to the generation of extra revenue and funds for research; nevertheless, domestic expansion measures will be attempted very cautiously by firms. This can be attributed to the reasoning that there exists no certainty related to the permanence of US tax reforms; certain capital allocation proceedings which have long term characteristics might be impacted negatively. It can be noted that two provisions can have a substantial impact on the worldwide operations in increasing the tax burden imposed by the United States:

- Those US multinationals which have low taxed earnings offshore will be burdened for paying an additional US tax on those earnings.
- A new alternative minimum tax, called the Base Erosion and Anti-Abuse Tax, could negatively impact US subsidiaries of foreign based companies as well as US-based multinationals who procure certain goods or services from their foreign parents or affiliates[6].

The European Union

The regulatory variations in the European Union will have an effect on the pharmaceutical players selling their produce in the European Economic Area (EEA) region. The impact of the UK leaving the European

[5]WHO
[6]2018 Global Life Sciences Outlook; Deloitte

Union is anticipated to result in significant changes in the pharmaceutical landscape globally. There are several implications that have been indicated in the fields of supply chains, regulations, clinical trials as well as tax compliance. It has been proposed that the regulatory changes will be directed towards bringing about an increase in investment for boosting innovation subsequent to BREXIT. The establishment of a new regulatory, health technology assessment and commercial framework has been recommended. It has been anticipated that the UK would not be constrained by stringent tax regulations. This signifies that the UK will have the advantage of adopting a favourable tax regime, which would drive a rise in innovative operations and escalate new investments[7].

Developments in African Healthcare Regulations

The regulatory environment in Africa has undergone significant changes over the last few years. The availability of efficient and superior quality medicines at affordable prices has been considered a challenge for majority of the African countries. The lack of a robust regulatory framework leads to these complications with the National Medicines Regulatory Authorities (NMRA), at times, being unable to provide timely quality drugs and pharmaceutical products. According to the WHO, there are 54 regulatory authorities for medical products in Africa, with varying degrees of capacity among them. Many are under-resourced, leading to long delays before medical products become available to the population. The registration of medicines is also complex with the requirement of submission of scientific information and the need for skilled workers in assessing and evaluating the applications.

The African Medicines Regulatory Harmonisation Programme (AMRH) has been established to ameliorate the quality and improve standards related to regulations. In collaboration with the World Health Organisation, it is designed to review the registration of a selected list of medicines and coordinate regional harmonisation systems on the continent. The AMRH, launched in 2009 with initial funds from the Bill and Melinda Gates Foundation and overseen by the World Bank, has contributed to reduce marketing authorization timelines in East African Community and the Southern African Development Community member states. The AMRH has launched regional Medicines Regulatory Harmonization projects that have proven to be instrumental in guiding NMRAs to determine priority areas of action for medicines regulatory strengthening and harmonization in Africa.

In order to address the barrier of weak regulations in African countries, the AMRH Initiative developed the African Union Model Law on medical products regulation to ensure effective regulation and promote harmonization. The objective of the Model Law is to have at least 25 AU Member States using a version of the Model Law on medical products regulation by 2020. In order to facilitate implementation of the AU Model Law, AMRH has established a continental Technical Working Group on Policy and Regulatory Reforms composed of regulators and legal experts to guide the domestication process. The Model Law endorsed by the African Union Assembly in January 2016, is at different levels of domestication and implementation by twelve African countries, viz. Ivory Coast, Burkina Faso, Seychelles, Zimbabwe, Lesotho, Namibia, Swaziland, Gambia, Tanzania, Rwanda, Burundi and Mozambique. The progress in domestication of the Model Law by these countries provides basis for improving regulatory systems. Currently, regional roadmaps for implementation of the AU Model Law have been developed and AU Member States are able to update their regulatory frameworks and enact a version of the AU Model Law that suit their country context to strengthen their national regulatory capacity[8].

[7]Brexit Monitor - The impact on Pharma & Life Sciences; PWC

[8]Ndomondo-Sigonda M. et al. Medical Research Archives, vol. 6, issue 2, February 2018 issue

3. INDIAN PHARMACEUTCIAL INDUSTRY: REGULATORY OVERVIEW

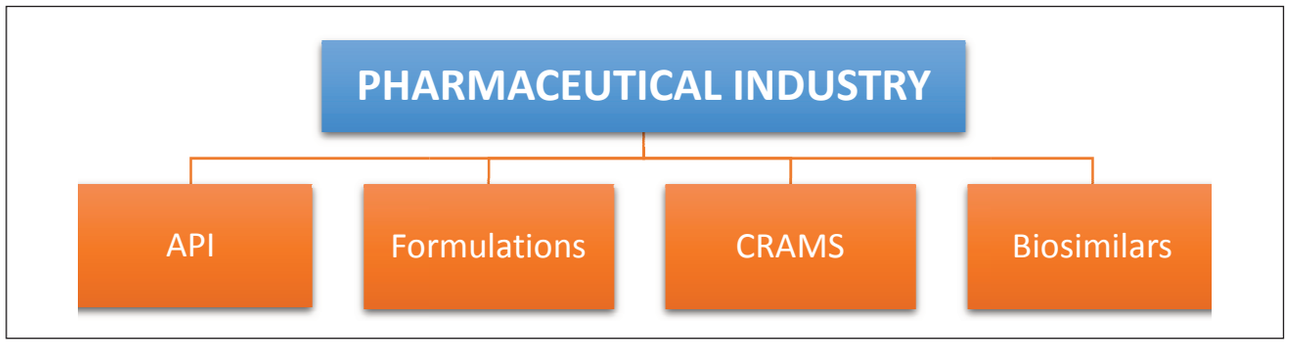
The Indian pharmaceutical industry followed the process patent structure for nearly 30 years, till the period 2005. In the period before the Amendment of the Patent Act in 2005, the generic drug producers were benefitted greatly, as they were permitted to launch the lower priced generic copies of the innovator drugs, so long as the procedure of manufacturing was not the same. The skilled and technically proficient workforce in the pharma sector rigorously undertook the reverse engineering of patented drugs. This enabled India to be recognised as the leading generic drug manufacturer and exporter globally. As per the DMF (drug master files) filings data of the year 2017, there were approximately 10,000 active manufacturing units inclusive of both foreign and domestic plants which were registered with the US-FDA. Of this total, nearly 3700 registered units were located in India[9]. This broad network of facilities has empowered the Indian manufacturers in meeting the regulatory standards demanded in the US and other regulated markets of the world.

India is the third largest pharmaceutical market in terms of volume and thirteenth largest in terms of value in the world. Indian pharmaceutical sector accounted for about 2.4 per cent of the global pharmaceutical industry in value terms and 10 per cent in volume terms during 2017[10]. The Indian pharmaceutical industry was valued at US$ 35.6 billion during the financial year 2017. The Indian pharmaceutical companies have manufacturing opportunities in two segments, namely the formulations and bulk drugs. The formulations component can further be divided into the domestic consumption and the exports category. The domestic segment accounted for approximately 55% of the aggregate formulations production, with exports forming the remaining share during 2017. The bulk drugs segment is also export oriented.

STRUCTURE OF INDIAN PHARMA INDUSTRY

Active Pharmaceutical Ingredients (APIs) - API is the ingredient in the drug which is biologically active and is produced in the initial phase of the drug manufacturing. This ingredient of the drug has the particular required therapeutic effect upon consumption on the human body. API is referred to as input or raw materials in the manufacturing of formulations. There are two ways in which API can be synthesized, viz. chemically as well as via biotechnological methods. Over the years, a substantial rise in the outsourcing of API to various low cost manufacturers in India by the global

Exhibit 5: Structure of the Indian Pharma Industry



[9]Crisil Research
[10]IBEF

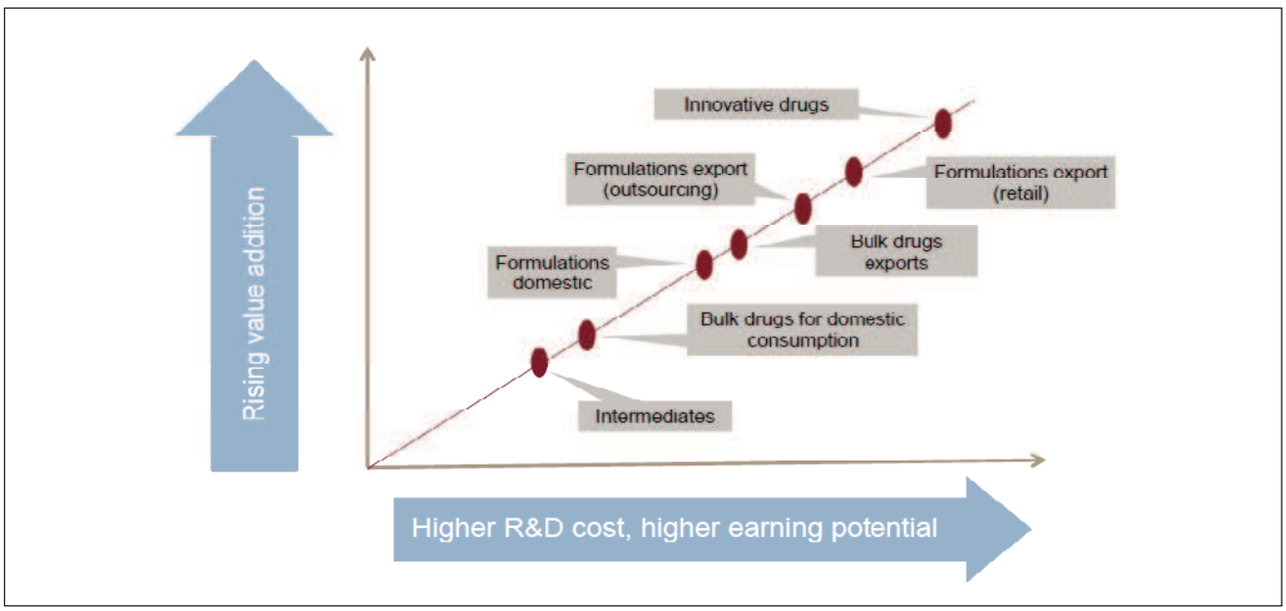
pharmaceutical companies has been observed. Regulatory ban along with stringent regulations has posed a challenge for these manufactures as there has been growing concerns regarding quality and safety in the global pharma markets.

Formulations- Formulations are the final end products in the manufacturing of drugs which can directly be consumed by the patients. These are generally in the form of tablets, capsules, injectables, gels, paste, powder and ointments. The formulations sector in India is a highly fragmented market comprising a large number of players as well as a wide product range. There are nearly 300-400 organised players and approximately 15,000 unorganised players. The market is majorly dominated by the organised players.

Contract Research and Manufacturing Services (CRAMS) - This term refers to the arrangement of outsourcing of research services as well as the task of manufacturing products to those organisations providing these services at relatively reduced cost. The pharmaceutical and biotechnology sectors are associated with these services as it involves the usage of comprehensive research and development coupled with the need for extensive manufacturing facilities. The Indian outsourcing industry has displayed huge development and advancement over the years. The positive factors which have led to this growth include favourable government policies, expansion in infrastructure base, availability of highly skilled human labour and also the increasing number of approvals accorded by the US FDA to Indian manufacturing facilities. However, with the rise in competition from other emerging outsourcing destinations such as Russia, Brazil and Taiwan, it is essential for the Indian service providers to upgrade infrastructure and skills.

Biosimilars- Biosimilars are the generic or the follow-on versions of the original biological medicines and drugs. The process of manufacturing of a biosimilar can be undertaken when the original product is being protected through patent exclusivity. However, the marketing of the biosimilar is permitted only post the expiry of the patent. These medicines are produced with the objective of producing therapeutic effects which are similar to that of the original biological medicine and produced to treat diseases similar to those cured by the innovator products. As defined by the FDA "Biosimilars are a type of biological product that are licensed (approved) by the FDA because

Exhibit 6: Indian Pharmaceutical Value Chain



Source: Crisil Research

they are similar to an already approved biological product, known as biological reference product and have been shown to have no clinically meaningful difference from the reference product." The Indian biopharmaceutical manufacturers are focusing their attention on the production of biosimilars, as compared to vaccines. The production of biosimilars is anticipated to expand owing to the rise in the share of biopharmaceuticals in the global pharma market and the favourable scenario presented by various biologics going off-patent in recent periods.

REGULATORY ENVIRONMENT

The development of pharmaceutical industry is vital for the growth of a nation, and entails the maintenance of superior quality standard, providing for the healthcare of billions of people domestically and globally. The regulations encompassing the pharmaceutical sector guarantee both the maintenance of high standards and the affordability of drugs being sold. The pharmaceutical sector is impacted by various factors such as price regulations, insurance, drug procurement by government agencies, interplay among players in the sector and service providers, patent laws, safety policies, drug regulations, rules concerning drug regulation and advertising and marketing. Since there are several elements which impact the industry, the importance of regulations increase manifold, and industry players have to take into account varied laws, policies and regulations while determining their operations.

The severity and strictness of these regulations differ from country to country. With reference to these regulations, the global pharmaceutical sector can be categorised into regulated and semi regulated markets. The regulated markets include the US, EU and Japan, with an acceptable and established framework of patent laws and proficient regulatory system for assessing drug quality. The semi-regulated markets refer to the countries which have a comparatively lesser stringent system of patent laws and regulatory system for monitoring and regulating the quality of drugs. Some of the semi-regulated markets include China, India and South Africa. There exists no single harmonised protocol for the process of drug approval among countries, and they maintain their individual regulatory framework and approval operations.

Table 6: List of Regulatory Authorities Across Key Markets

Country	Regulatory Authority
United States	US Food and Drug Administration
United Kingdom	UK Medicines and Healthcare Products Regulatory Agencies
South Africa	Medicines Control Council of South Africa
India	Food and Drug Administration
Brazil	National Health Surveillance Agency
Europe	The European Medicines Agency

Source: The Indian Pharmaceutical Industry: Changing Dynamics & Road Ahead

Pharmaceutical Regulations in India

The Indian drug regulatory system originated in 1940, with the passing of the Drugs and Cosmetics Act, to govern the production of the pharmaceutical products in India. It was in the year 1945 that the drug rules were formulated to give effect to the provisions of the Drugs and Cosmetics Act. This Act was amended on several occasions and various other regulations were established for governing the import, manufacture and sale of drugs in the country. Some of the crucial Acts and Regulations in this regard include:

- The Pharmacy Act 1948;
- The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954;
- The Narcotic Drugs and Psychotropic Substances Act 1985;
- The Medicinal and Toilet Preparations (Excise Duties) Act 1956;

- The Drugs (Prices Control) Order (DPCO) 1995 (under the Essential Commodities Act), amended in 2013 to cover specified dosages and strengths under the National List of Essential Medicines (NLEM) 2011 and modified to include medicines in NLEM-2015;
- The National Pharmaceutical Pricing Policy, 2012 (NPPP-2012);
- The Patent Act Amendment 2015 (includes amendments in the Patent Act 2002);
- The National Health Policy 2017

In India, the import, manufacture, distribution and sale of drugs is regulated by the Drugs and Cosmetics Act of 1940. The Drugs and Cosmetics Act; 1940; and the Drugs and Cosmetics Rules 1945, list down detailed provisions to mitigate the manufacture of spurious or lower quality drugs. Definitions and explanations of adulterated and misbranded drugs have been clearly elaborated so that such improprieties can evoke legal action. Over the years, various revisions and amendments have been implemented taking into considerations the transformation in economic scenarios. These regulations are in line with the guidelines specified by various international organisations such as the WHO, the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) among others. The Indian pharma industry has exhibited active participation and delivered support in the formation of the new South East Asia Regulatory Network (SEARN). Moreover, the Indian National Regulatory Authority (NRA) is a member of the Developing Country Vaccine Regulators' Network (DCVRN), an observer in ICH, and a Vice-Chair of WHO's Member State Mechanism on substandard and falsified medical products. Apart from this, various mutual agreements and memoranda of understandings have been undertaken by the Indian NRA with the NRAs of the United States, the United Kingdom, Japan, Russia and Sweden and several other countries as well[11].

Regulatory Authorities

In India, the drug regulations are segregated into the Central Drug Authorities and the State Drug Regulatory Authorities.

The Central Drugs Standard Control Organisation (CDSCO) is the apex national drug regulatory authority for carrying out the responsibilities allotted to the Central Government in accordance with the Drugs and Cosmetics Act. The functioning of the CDSCO is under the Director General of the Health Services of the Ministry of Health and Family Welfare and is headed by the Drugs Controller General of India, DCG (I). The primary objective of the CDSCO is to ensure the delivery of safe, superior quality effective drugs, cosmetics and medical devices to the public. The important functions of CDSCO include:

- Establishing policies for the implementation of the provisions underlined in the Drugs and Cosmetics Act, 1940 and the Drug Cosmetics Rules, 1945
- Providing assistance in the creation and implementation of the standards for drugs, cosmetics and medical devices
- Setting up collaboration with international organizations/bodies such as WHO, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the South Asian Association for Regional Cooperation (SAARC), the WHO Regional Office for South East Asia (SEARO), BRICS nations – Brazil, Russia, India, China and South Africa – and other counterparts
- Implementing regulatory control over the import of drugs
- Approving new drugs and clinical trials
- Coordinating with Drug Consultative Committee and Drugs Technical Advisory Board

[11]Medicines Regulations; WHO

- Approving certain licenses as Central License Approving Authority is exercised at CDSCO headquarters
- Undertaking joint inspection with the zonal offices and the state drug controllers
- Inspecting the quality of imported medicines through port offices
- Engaging in the maintenance of drug testing laboratories

The affiliated institutions under the governance of the CDSCO include the Central Drugs Laboratory in Kasauli, Himachal Pradesh and the Pharmacovigilance Programme of India at the Indian Pharmacopoeia Commission in Ghaziabad, Uttar Pradesh. The Central Government has established six zonal offices of the CDSCO, five Sub-Zonal Offices (including one created recently at Indore in Madhya Pradesh) with another being established at Guwahati in Assam, 13 port offices and eight laboratories under its control. These zonal offices work together with the State Drug Control Administration and assist them in securing uniform enforcement of the regulations and other connected legislations, on all India basis. This regulatory body is headed and supervised by the Drug Controller General of India (DGCI).

The Indian drug manufacturers and exporters are expected to adhere to the standards implemented by the DGCI as well as those imposed by the drug regulators in the importing countries. The regulations and quality standards are increasingly getting stringent due to the rise in healthcare standards and augmentation in customer expectations globally. The administration and vigilance of institutions engaged in regulation is becoming more cautious in matters related to the safety of patients and severity of compliance. The quality of the imported medicines are examined by the port offices, which undertake the testing of samples in drug laboratories.

The Central Drugs Laboratory, Kolkata is the national statutory laboratory of the Government of India for quality control of drug and cosmetics and is established under the Indian Drug and Cosmetics Act, 1940. It is the oldest quality control laboratory of the Drug Control Authorities in India and functions under the administrative control of the Director-General of Health Services in the Ministry of Health and Family Welfare.

The regulatory authority at the state level comprises the Food and Drug Administrations (FDA) at each state and certain licensing authorities set up for the Union Territories. The responsibilities assigned to the State Licensing Authorities include the following[12]:

- Licensing of manufacturing site for drugs including API and finished formulation;
- Licensing of establishment for sale or distribution of drugs;
- Approving drug testing laboratories;
- Monitoring of quality of drugs and cosmetics marketed in India;
- Investigating and prosecuting in respect of contravention of legal provision;
- Recalling substandard drugs

With reference to the Drugs and Cosmetics Act, 1940, there exists dual regulatory control, inclusive of both the Central and the State Government. The implementation and enforcement of the Act needs to be ensured by both the Central and the State Governments. Under the Act, the task of regulating the manufacturing, sale and distribution of drugs and other related products and issuing of licenses is entitled to the State Authorities, while the Central Government authorities are in charge of approving new drugs and clinical trials, listing standards for drugs, administering the quality of imported drugs as well as collaborating and co-ordinating with the State drug control organisations.

Schedule M to the Drugs and Cosmetics Rules, 1945; prescribes good manufacturing practices and the obligatory requisites with respect to premises,

[12]Medicines Regulations; WHO

plant and equipment that should be maintained by the manufacturers of drugs or as a precondition in setting up a new manufacturing unit. These directions are mandatory prerequisites to be considered for quality control in the manufacture of drugs and pharmaceuticals. With a view to evolve with the rapid advancements in technology, each licensee is expected to upgrade these practices with the usage of pertinent premises, sanitation, storage of raw materials, procedures, documentation and methodology. This primarily fosters the harmonization of drugs production in line with the international standards and guidelines as specified by WHO.

The National Pharmaceutical Pricing Authority (NPPA) is an organisation of the Government of India, which had been established to fix or revise the prices of controlled bulk drugs and formulations and to regulate the prices and availability of medicines in the country, under the Drugs (Prices Control) Order, 1995. NPPA fixes the prices of bulk and formulations of drugs within the NLEM (National List of Essential Medicines) in the coverage of Essential Commodities Act. Apart from this, the institution also engages in recovering amounts overcharged by the manufacturers for the controlled drugs from the consumers. Moreover, the prices of decontrolled drugs are also monitored to ensure that they are affordable. The list of drugs under price control is regularly updated by way of addition and barring, depending on established guidelines.

The Department of Pharmaceuticals was established in the year 2008, under the Ministry of Chemicals and Fertilizers, aimed at generating enhanced emphasis for the development of the pharmaceutical industry. While the MoHFW focuses its concentration on the broader frame of reference of public health, the potential centre of attention for the Department of Pharmaceuticals is the industrial policy. The Department undertakes promotion of research in areas related to the pharmaceutical sector, development of infrastructure, manpower and skills, education and training for technical guidance, promote private-public-partnerships, resolve issues concerned with pricing and availability of drugs, protection of IPRs, and collaboration with other ministries. Until the drugs and pharmaceuticals have not been specifically allocated to any other department, they fall under the ambit of the Department of Pharmaceuticals. Apart from this, other Government organisations and Ministries which contribute in the regulation procedures of this sector include[13]:

- Ministry of Environment and Forests
- Ministry of Commerce and Industry
- Ministry of Science and Technology
- Ministry of Corporate Affairs

Regulatory Functions

Supervising Clinical Trials

Clinical trials involving the participation of human subjects need to follow the ethical and quality standards established by Good Clinical Practices (GCP). The adherence to these standards acts as a guarantee that the safety of the subjects involved in the clinical trials has been assured, consistent with the principles enshrined in the Declaration of Helsinki, and ensures that clinical trial data are credible[14]. The GCP guidelines set up in India are formulated by an expert committee formed by CDSCO in collaboration with clinical experts, and endorsed by the Drug Technical Advisory Board (DTAB). By way of compliance with these guidelines, it is ensured that clinical trial is being carried out in a uniform manner throughout the country and produce data for the purpose of registering new drugs. It is the responsibility of the CDSCO to analyse and assess applications for clinical trials, accept or reject them, investigate sites for clinical trials, monitor the activities of the ethics committee and determine the amount of compensation to be offered on the occasion of an adverse event while carrying out a clinical trial. The approvals for conducting of clinical

[13]Regulatory framework and challenges in Indian Pharmaceutical Sector CUTS C-CIER
[14]Medicines Regulations; WHO

Exhibit 7: Regulatory Environment for Health Products in India

Ministry of Health and Family Welfare	Ministry of Chemicals and Fertilizers	Ministry of Commerce	Ministry of Science and Technology	Ministry of Environment
Directorate General of Health Services (DGHS) Indian Council of Medical Research (ICMR)	Department of Pharma-ceuticals	Patent Office	Department of Biotechnology (DBT)	Environmental clearance for manufacturing
Central Drugs Standard Control Organization (CDSCO) headed by Drug Controller General of India, DCGI (I) **+ Statutory Committees** **+ Advisory Committees** **+ State Licensing Authorities**	National Pharmaceutical Pricing Authority (NPPA): Drugs (Prices Control) Order (DPCO) 2013	Controller General of Patents	Council of Scientific and Industrial Research (CSIR) Laboratories	

Statutory Committees: Drugs Consultative Committee (DCC) provides advice on technical matters and establishing rules, and Drugs Technical Advisory Board (DTAB) helps in securing uniform implementation of Drugs and Cosmetics rules throughout India.
Advisory Committees: Subject Expert Committees (SEC) drawn from relevant panels of experts advice on approvals of clinical trials, drugs and medical devices. New Drug Advisory Committee (NDAC) headed by Secretary, Department of Health Research, and Investigational New Drugs Committee (INDC) headed by Director General of ICMR, provide recommendations on approval of clinical trials. The Indian Council of Medical Research (ICMR) provides assistance in evaluation of Phase I clinical trials. Three-tier system for examination of clinical trials includes NDAC/INDC / Technical Committee (TC) under chairmanship of DGHS / Apex Committee which is headed by under the chairmanship of Secretary, Ministry of Health and Family Welfare.
For biologicals: Department of Biotechnology (DBT) supports Drug Controller General of India (DCG (I)) in identifying, formulating, implementing and monitoring of various activities related to biotechnology e.g. through Division of Biologicals and the Cellular Biology-Based Therapeutic Drug Evaluation Committee (CBBTDEC).
For medical devices (except investigational ones): Medical Devices Advisory Committee (MDAC) advises Drug Controller General of India (DCG (I)) on review and approval of products and clinical trials.
Source: Medicines Regulation, Regulatory systems in India; WHO

trials are granted by the Drugs Controller General of India. The necessary requirements and guidelines for attempting clinic trials are elaborated in Schedule Y of the Drugs and Cosmetics Act. Applicants who intend to conduct clinical trials are supposed to submit an application to the DGCI, animal pharmacology and toxicity data, animal toxicology and clinical data (if available), the trial protocol, and information about the regulatory status of the product in other countries. Furthermore, the applicants are necessitated to point out expected or unexpected serious adverse reaction (SUSAR) of the product, if happened in other countries. The Institutional Ethics Committee (IEC) are entitled with the task of evaluating and supervising clinical trials and ensuring that they adhere to the ethical guidelines. The safety report as well as the informed consent document should be reviewed by the IECs.

The Indian Council of Medical Research (ICMR)'s 2006 Ethical Guidelines for Biomedical Research on Human Participants have been accepted as the standard operating manual by IECs in India. A proposed update to these guidelines was finalized for public comment at regional and national consultation meetings jointly organized by ICMR and the WHO Country Office for India in 2016. ICMR also maintains the Clinical Trials Registry of India (CTRI), a primary registry under the WHO International Standards for Clinical Trial Registries (ICTRP)[15].

[15]Medicines Regulations; WHO

Various initiatives have been undertaken for advancing the safety features of clinical trials in India. There have been additions in the requirements that need to be fulfilled while carrying out the informed consent process. Moreover, audio-visual recording has been made obligatory for enlightening vulnerable subjects regarding the international best practice. In India, a three tier system for evaluation of scrutiny of the proposals of clinical trials has been established. This three tier system includes the New Drugs Subject Expert Committee (SEC)/ Investigational New Drugs Committee (INDC), supervised by the Chairmanship of Directorate General Health Services and Apex Committee under the chairmanship of Secretary Health. The precondition of registration of Ethics Committee with the licensing authority was made necessary from the year 2011. Furthermore, the term injury has been defined rationally, and elaborate procedures have been listed for calculation of the compensation amount, based on a formula, to be given to a subject, on the event of an injury or death happening while undertaking clinical trial. There has also been a reduction in the amount of time taken for the evaluation of clinical trial applications, through the commencement of online submission process and extension of Subject Expert Committee Panels. The regulatory provisions with respect to clinical trials under the purview of the Drugs and Cosmetics Rules, 1945 are perpetually being amended and improved for the betterment of the industry.

Registration Functions

The registration and marketing authorization of pharmaceuticals and drugs in India include a wide variety of procedures. An amendment of the Drugs and Cosmetics Rules, now includes the necessary requirement of bioavailability/bioequivalence studies, prior to licensing, for oral formulations of drugs belonging to the Biopharmaceuticals Classification System (BCS) Class II and IV. The total amount of time taken in achieving regulatory approvals has declined substantially in the recent years. This positive development has been possible as the Subject Experts Committee is obligated to convey their recommendations related to the approvals of clinical trials as well as marketing authorization within a span of five working days.

Table 7: Timelines for Registration & Marketing Authorization Functions

Type of Application	Target Timeline (days)
Clinical Trial	180
Marketing Authorization	180
Registration Certificate for Import	270
Form 28-D (Manufacturing License)	60
Form 29 Non-Objection Certificate (NOC)	60
Import License (Form 10)	45
Test License(Form 11)	45
Export NOC for Biological Samples	45
Post Approval Change (Major)	180
Post Approval Change (Minor)	90

Source: Medicines Regulations; WHO

Regulatory Inspections

Taking into account the safety of consumers, it is essential for the pharmaceutical products to be produced in accordance with the requirements specified by the GMP regulations. A majority of the GMP regulations in India has been listed down under the Schedule M of the Drugs and Cosmetics Act, 1940. Schedule M elaborates requirements for pharmaceutical products, medical devices as well as vaccines. It mentions specifications related to the standard of infrastructural premises, safety of environment, operational control and maintenance of quality. Schedule M has been amended several times to harmonize it in accordance with the international standards like WHO-GMP and the US FDA guidelines.

The officials undertaking the GMP inspection of manufacturing units include inspectors from CDSCO, and State Drug Control Office along with product experts from Central Drug Laboratory. These inspections are usually carried out for a period of

2-5 days, depending on the quantity of products being manufactured in the unit, the complexity of products as well as the size of the unit. Inspections can be conducted on several occasions, for various reasons such as pre-approval inspection of the site for grant, regular annual inspection, inspection for evaluation of post-approval changes and risk-based inspection. Inspections are also conducted for issuance of a Certificate of Pharmaceutical Product (CPP), when exports of pharmaceutical products are to be done.

In case of non-compliance of the GMP requirements, the subjective regulatory measures are listed in Rule 85 of the Drugs and Cosmetics Rules. This section includes regulatory letters which necessitate measures to compensate for deficiencies, cancelling of licenses and legal action against the producer.

Regulation of Imported Products

The quality and standards of imported medicines are regulated by CDSCO. The CDSCO officials are allotted the task of registration of manufacturing sites located overseas, and overseeing the quality of drug formulations and bulk drugs. The quality tests are further conducted in the port offices, by testing of samples.

Licensing of Premises

As per the regulations of the Drugs and Cosmetics Act, the accountability of the supervision related to the manufacture, sale and distribution of pharmaceutical products majorly lies with the state authorities. The approval of licenses of certain special segment of products is done by the DGCI (I). These products comprises biological products including vaccines, blood and blood products, IV fluids and notified medical devices. Provisions under Rule 68-A facilitate the grant or renewal of licenses by the Central License Approving Authority[16].

Regulation of Promotional Materials

The advertisement of spurious medicines can be harmful for the safety of the public and there exist measures to control this. The spread of inaccurate or false claims or advertisements are regularly monitored through random checks and inspections, and if found guilty, is punished under general law and the Drugs and Magic Remedies Act, 1955[17].

Drug Regulations Development

Drug Price Control Orders

Prior to the year 1962, the drug industry did not observe any control on prices. However, the Government initiated the first drug price control on the pharmaceutical sector through the Drug (Display of Prices) Order 1962 and Drug (Control of Prices) Order 1963. Over the years, various amendments have been exercised on this regulation, which has resulted in variations in the proportion of control on prices as well as the essence of price control. The amendments which had a significant impact on the Indian Pharmaceutical industry were those introduced in the following years; viz. 1970, 1979, 1995 and 2013 respectively.

The DPCO is an order issued by the Government under Section 3 of the Essential Commodities Act, 1955, entitling the fixation and regulation of prices of essential bulk drugs and their formulations. The order consists of list of bulk drugs selected for fixation of prices, methodology for fixation and revision of prices, techniques for implementation and several other guidelines and directions.

The DPCO in the year 1970, was aimed at emphasising on the affordability of drugs, and ensuring the convenient availability of pharmaceuticals for the citizens. Moreover, an upper cap was executed on the pre-tax profit to be obtained by the pharmaceutical companies. This regulation significantly constrained the profit generation of the pharmaceutical sector.

The Control Order for the year 1979 included nearly 350 bulk drugs and approximately 4000 formulations within the purview of the regulation, implying that

[16]Medicines Regulations; WHO
[17]Medicines Regulations; WHO

about 80% of the industry was under the coverage of price control. Besides this, the order also imposed a ceiling price on the specified drugs under price control. This led to the profitability of the industry players to fall drastically and also prompted various global pharmaceutical firms supplying innovator drugs in India to quit the market.

Further amendments were made in the DPCO during the year 1995, with regards to the liberalisation and transformation in economic scenario and removal of the industrial restrictions. These amendments were based on the consideration of the market share of major companies to select drugs which were to be brought under price control. During the year 1995, only 74 bulk drugs and nearly 1500 formulations were categorised for price control. This number declined further with ongoing revisions in the list at frequent intervals. The list of formulations within the coverage of price control fell down to 260, while the number of bulk drugs was unaltered at 74, by the year 2005.

The DPCO 2013, entailed that the prices of drugs that featured in the National List of Essential Medicines (NLEM) be monitored and controlled by the National Pharma Pricing Authority (NPPA). While under the DPCO (1995), 74 drugs were covered for price control, this figure rose to 348 drugs as all these appeared in the National List of Essential Medicines 2011; additionally approximately 628 formulations were also subject to price control. Prior to 2013, the pricing of drugs was fixed based on the manufacturing cost declared by drug manufacturers, while post that regime, prices were regulated through market based pricing. Undr NLEM 2015, the government has incresed the number of drugs subject to price control to over 800 formulations.

Patent Acts

As highlighted above, the pharmaceutical industry is a highly regulated sector in India. The Government implements control on the production, pricing and sales of bulk drugs and formulations with the assistance of various regulatory agencies. The principle of "Essentiality of Drugs" is rendered abundant importance, as the authorities try to ensure that essential drugs are accessible to the consumers at economical costs. The two Acts which were vital in the evolution of the Indian Pharmaceutical Industry are:

- Patent Act (1970)
- Patent (Amendment) Act, 2005

India followed a product patent regime for its inventions under the Patents and Designs Act 1911. During the year 1970, the Government introduced the Process Patent instead of the Product Patent. The major rationale behind this was to diminish the reliance on imports for bulk drugs and formulations and the establishments of an indigenous pharmaceuticals sector. This reduced the predominance of the global pharmaceuticals firms and concomitantly created an environment conducive for the progress of the domestic industry players. This Act permitted Indian companies to produce patented drugs, under the condition that the process of production was not the same as the one adopted by the innovator company. This had a major favourable impact on the Indian pharmaceutical companies, who could develop cheaper versions of branded patented drugs, without the requirement of paying a license fee to the innovator companies.

Nonetheless, the Patent Act was amended, for the purpose of adhering to the WTO'S TRIPS (Trade Related Aspects of Intellectual Property Rights) regime. Taking this development into account, the product patent was re-established and the process-patent was abolished. Consequently, the sale of generic version of drugs which were patented after the year 1995 was considered illegal. Post the amendment in the Patents Act, the pharmaceutical firms were authorized to develop cheaper generic versions of the drugs which were off-patented or the ones patented before the period 1995. The period 1970 to 2005 included capacity building for the domestic pharmaceutical industry, wherein the industry strengthened the research and development expertise. This period was marked by the advent of substantially large generic companies as well as the origin of small and medium sized companies, resulting in a fragmentation of the sector.

Box 4: National Health Policy 2017

The National Health Policy 2017 was approved by the Union Cabinet, Government of India, in the month of March 2017. This policy is the third national policy of the country; prior to this, health policies were released in the year 1983 and 2002. The National Health Policy is directed towards giving priority to the role of the government in the improvement of the health system in the country. The roadmap of the Policy includes public spending and provisioning of a public healthcare system with the objective of making it accessible and affordable for the citizens. Moreover, it emphasizes on coordination with the private sector, particularly in areas of strategic purchasing, enhancing skills, increasing awareness and creation of networks for betterment of mental health services. This Policy focuses on emerging diseases and the need to invest in preventive healthcare. It also specifies certain quantitative targets, aimed at reducing disease prevalence and improving the health status of individuals. The Policy aims at ameliorating the health surveillance system and form registries for diseases negatively impacting public health, by the year 2020.

The Policy includes the establishment of a progressively incremental assurance-based approach such that universal access can be granted to the public for receiving quality health services which are affordable. The Policy recognizes the importance of the government in performing various functions such as investment, financing, promotion of awareness, developing human capital, establishing knowledge base and regulations as well as facilitating progressive assurance for health.

The National Health Policy 2017 seeks to provide quality secondary and tertiary healthcare services through the collaboration between public hospitals and non-governmental healthcare providers to diminish the out of pocket expenditure on healthcare costs. A key component of the Policy is the proposal to increase health expenditure to 2.5% of the GDP in a time bound manner. A major proportion of the resources is anticipated to be spent on primary care followed by the secondary and tertiary care segments. The Policy proposes the facility of free drugs, free diagnostics and free emergency care services in public hospitals to provide financial protection at the secondary and tertiary care levels. It also includes school health programme measures such that hygiene is maintained in the school premises. Apart from this, the Policy suggests increased access to AYUSH remedies in public facilities and an augmentation in promotion of healthy lifestyle through the introduction of Yoga.

This Policy seeks to ensure support to the voluntary health service providers in the rural and under-served areas. It advocates expansive deployment of digital tools and also proposes the setting up of National Digital Health Authority for the regulation and development of digital health. The significance to improve the regulatory landscape and the need to regulate the usage of medical devices has also been highlighted in the Policy.

Source: PIB; Ministry of Health and Family Welfare, Government of India

Compulsory Licensing

The transformation and adoption of the product patent in the year 2005 led to the commencement of the IP framework which is followed in the regulated pharmaceutical markets of the world. Nonetheless, the amendment in the Patent Act had provisions for the grant of compulsory licenses for the production of patented medicines, contingent on the fact that it met the terms and conditions which were listed in the Act. Since the grant of a compulsory license was a component of the original TRIPS agreement, consequently the insertion of this provision in the Patent Amendment Act 2005, was not considered a non-adherence to TRIPS.

The terms and conditions for the granting of compulsory license in the manufacture of drugs which are under patent protection are as follows:

- The patented drug does not satisfy the reasonable requirements of the public
- The patented drug is not accessible to the people at affordable prices
- The patented drug is not worked in the territory of India

In the provisions of a compulsory license, three years post the introduction of the patented drug in the country, a domestic manufacturer can attempt the production of the patented drug, on which the compulsory license has been granted. In this regard, the first compulsory license granted was to Natco Pharmaceuticals permitting the production of the generic version of Bayer's patented drug named Nexavar, which primarily targets the treatment of liver and kidney cancer. Prior to its compulsory licensing, Bayers had priced the drug Nexavar at Rs. 2.8 lakh for a month's supply, while Natco promised to price it at Rs. 8800 for a month's course. Additionally, Natco had been instructed to pay approximately 6% of the sales of the generic version of the drug to Bayers, which was subsequently extended to 7%, in the form of a royalty. The grant of compulsory license can be attributed primarily to the unaffordability characteristic of the medicine. However, this measure of granting compulsory license is considered to have prompted US Trade representatives to position India in the priority watch list and the efficacy of the Indian intellectual property regime was being questioned.

Major Government Schemes and Budget Proposals

Pharmaceutical Technology Upgradation Assistance Scheme (PTUAS)

The Department of Pharmaceuticals has proposed this Scheme essentially for providing support to the medium sized enterprises in the pharmaceutical sector, which are not covered by the Credit Linked Capital Subsidy (CLSS) Scheme of MSME. The CLSS Scheme provides financial assistance to the small scale industries for meeting the WHO-GMP compliances. However, the medium sized enterprises are not considered under this scheme. This scheme is drafted particularly for extending assistance to the medium sized enterprises in being able to sustain in the highly dynamic global pharmaceutical industry and meet the substantially stringent international standards and regulations.

Drugs and Cosmetics Act Amendment

The Union Budget 2017, included a proposal for the amendment of the Drugs and Cosmetics Act, with the objective of ensuring availability of drugs at reasonable prices by way of promoting the usage of generic drugs. This amendment encourages doctors to prescribe the generic version of medicines. This will have significant effect on the domestic drug sector, and in this regard the drug manufacturers will have to market generic versions of medicines rather than brands. This measure is envisaged to adversely impact the sale of high margin branded drugs and concomitantly have an effect on the aggregate revenue of the pharmaceutical industry.

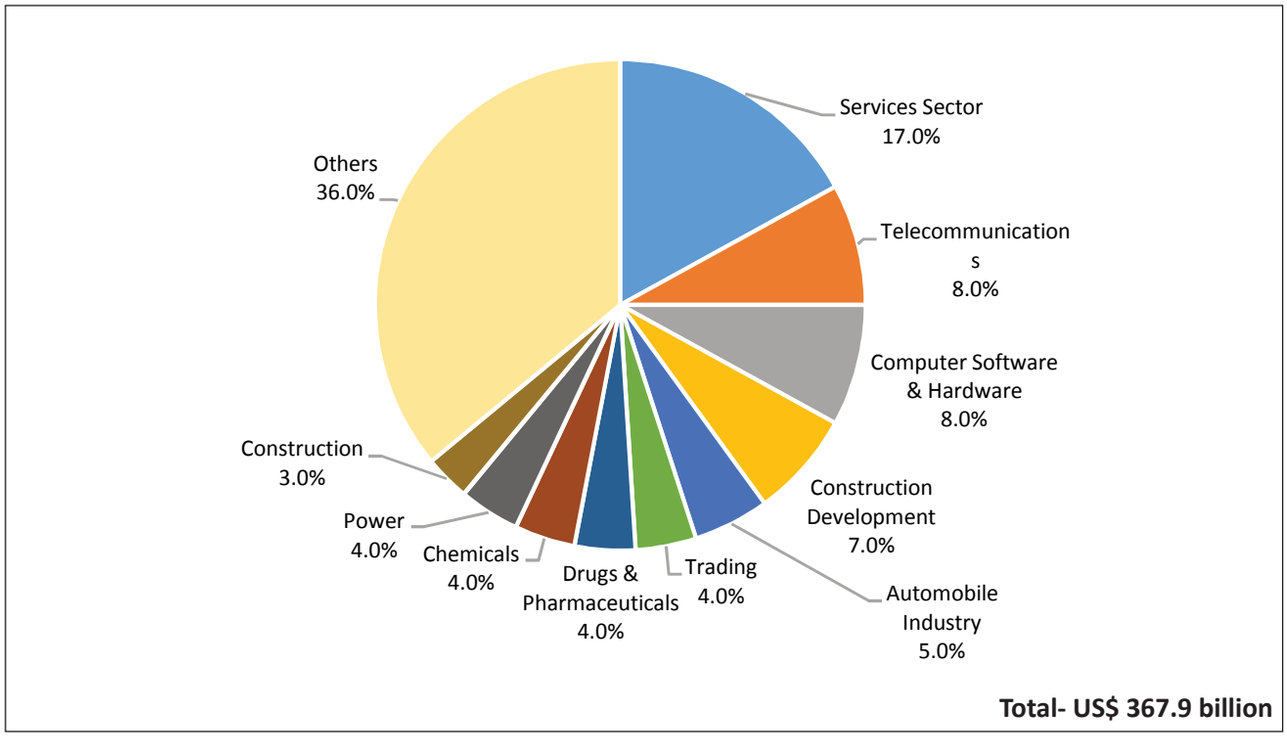
Foreign Direct Investment

During the year 2016, the FDI Policy for the pharmaceutical sector was amended. FDI in brownfield pharmaceuticals sector was permitted up to 74%, under the automatic route, and a further increase, beyond the limit of 74% necessitated prior

Government approval. This approach was envisaged to attract capital, enhance mergers and acquisitions, boost international best practices and draw updated technologies in the Indian pharmaceutical sector. For greenfield pharma investments, 100% FDI under the automatic route is allowed. In the composition of the FDI policy for the pharma sector, the Government has ascertained safeguard measures by incorporating the provision that non-complete clause will not be permitted in the event of acquisition of brownfield pharmaceutical companies by global firms. This measure facilitates Indian promoters to operate in the same line of business in new ventures. Furthermore, to confirm the availability of medicines domestically, and ensure deployment of ample amount of capital in research and development, the FDI Policy mandates a defined amount of manufacture of drugs specified in the National List of Essential Medicine drugs and a certain volume of expenditure on research and development to be retained by the investee company.

In the current scenario, with meagre production of new drugs and the expiry of patents on blockbuster drugs impending, the innovator pharmaceutical companies across the globe are anticipated to emphasize on the generic drugs to sustain growth trends. In this background, a collaboration with a prominent and proficient generic manufacturer is supposed to be amongst the most convenient entry routes to explore lucrative opportunities in the generic drug segment. With the relaxation in FDI cap in the case of the brownfield pharmaceuticals category, the domestic generic sector has been attracting the attention of global pharmaceutical companies considerably.

Exhibit 8: Cumulative FDI Inflows in India: Sector-wise (April 2000 to December 2017)

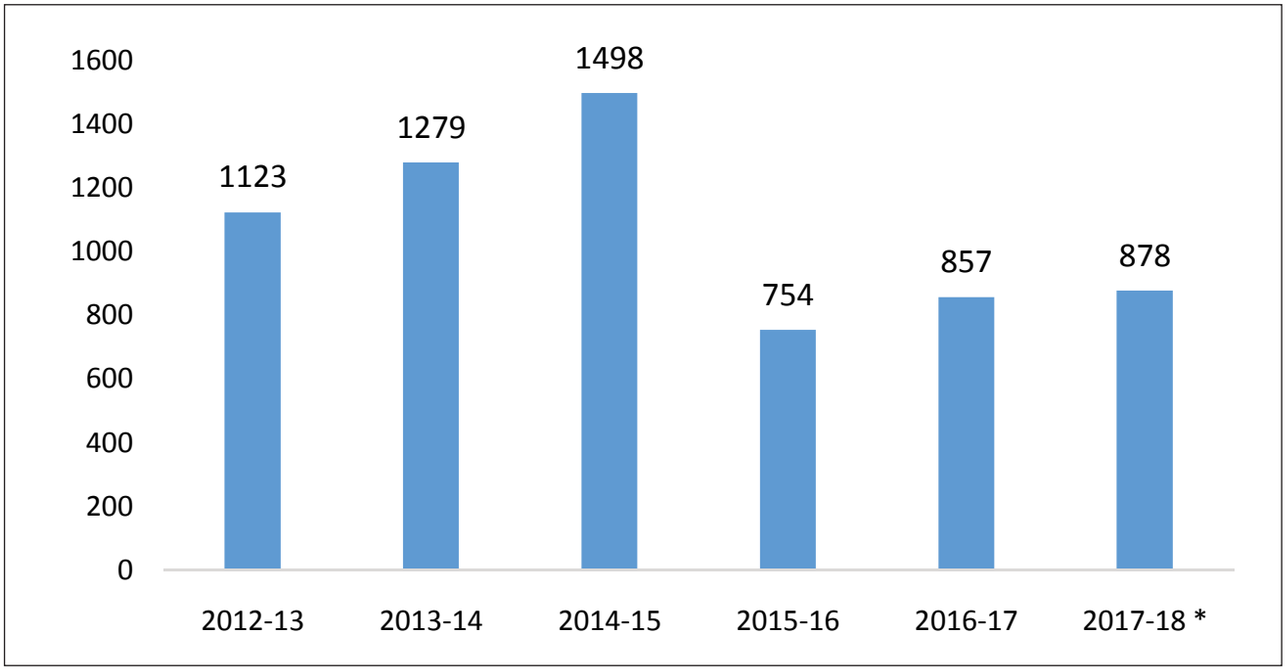


Source: DIPP

During the period April 2000 to December 2017, the cumulative FDI inflow into the Drugs and Pharmaceuticals sector stood at US$ 15.6 billion, accounting for approximately 4% of the aggregate cumulative FDI inflow for the period, making it the seventh leading recipient of foreign direct investment behind the Services Sector (17%), Telecommunications (8%), Computer Software & Hardware (8%), Construction Development (7%), Automobile (5%) and Trading Sector (4%).

The value of FDI inflow in the drugs and pharmaceutical sector during the year 2016-17 was nearly US$ 857 million, registering a year-on-year growth of 13.7%. The FDI inflows during the year 2017-18 (April- December) have been valued at US$ 878 million. The inflows peaked during the year 2014-15; however, they declined dramatically in the following year and stood at US$ 754 million. During the period 2012-13 to 2016-17, the value of FDI inflows in the pharmaceuticals sector recorded a negative CAGR of (-) 6.5%.

Exhibit 9: FDI Inflows in the Indian Pharmaceutical Sector (US$ mn)



*2017-18 Data (April- December)
Source: DIPP

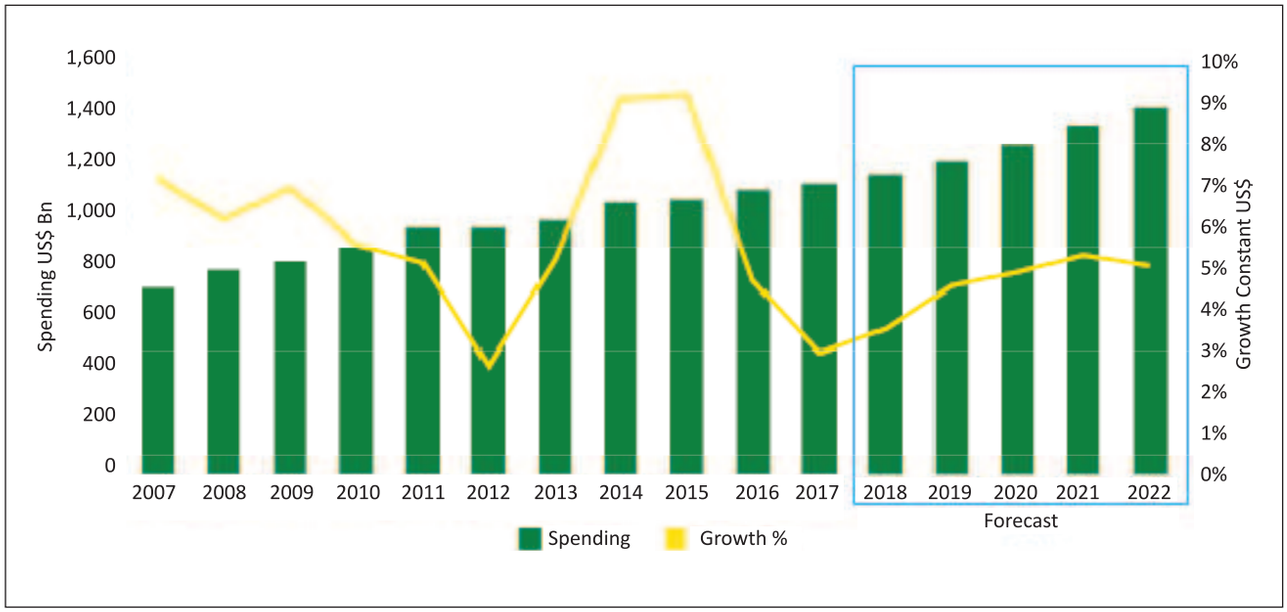
4. GLOBAL PHARMACEUTICAL MARKET: INTERNATIONAL TRADE PERSPECTIVE

WORLD PHARMACEUTICAL MARKET

The global medicine spending was estimated at US$ 1135 billion during the year 2017 , recording a CAGR of 4.6% during the period 2007 to 2017[18]. The launch of new and innovative drugs propelled the growth in the pharmaceutical market, which enabled overall growth of the regulated markets. An augmentation in the demand for generic drugs has led to rising growth momentum in the emerging markets. According to the forecast by IQVIA Institute, the worldwide spending on pharmaceutical markets is anticipated to range from US$ 1415 bn to US$ 1445 billion by 2022 (Exhibit 10).

The exhibit elaborates the share of developed and pharmerging countries in the global aggregate medicines spending. While developed regions accounted for 73% of the total in 2007, their share fell to 66% in 2017.As against this, the share of the pharmerging countries have risen considerably – from 15% to 24% during the same time frame (Exhibit 11).

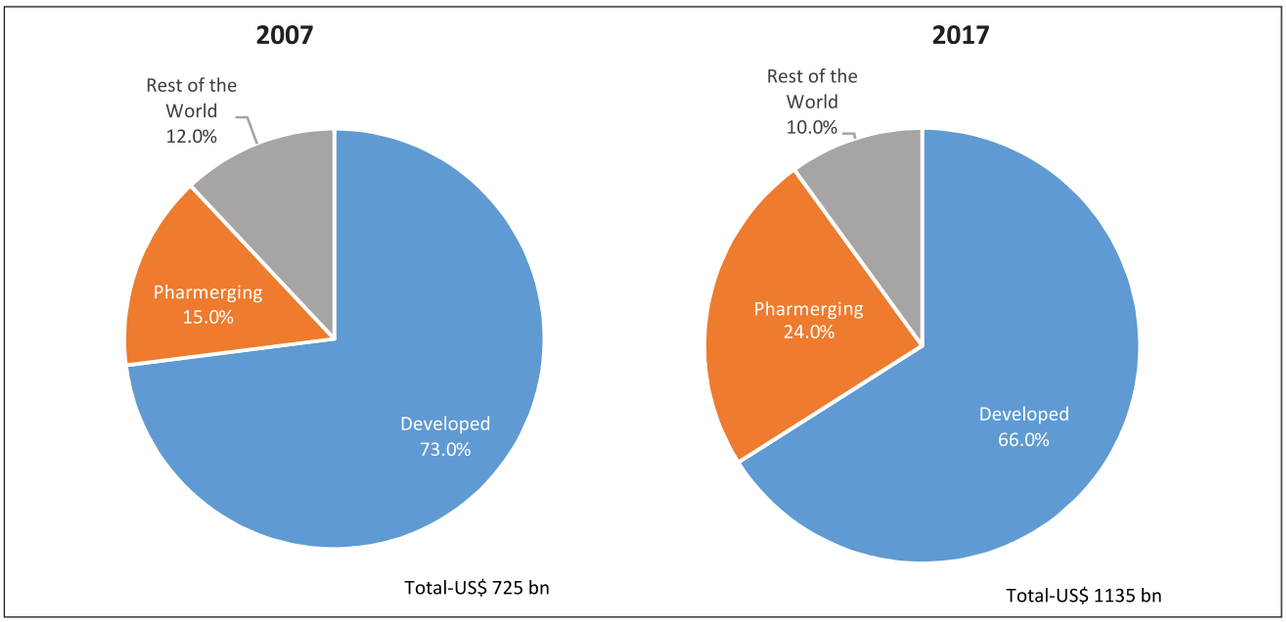
Exhibit 10: Global Medicines Spending and Growth (2007-2022)



Source: IQVIA Market Prognosis

[18]IQVIA

Exhibit 11:Region-wise Global Medicines Spending



Source: IQVIA Market Prognosis

Table 8: Region-wise Global Spending of Medicines

Region/Country	2017 Global Spending (US$ bn)	2013-17 CAGR Constant US$
Developed	**753.2**	**5.8%**
The US	466.6	7.3%
EU 5	154.4	4.4%
Germany	45.1	4.9%
France	33.1	1.3%
Italy	29.0	5.5%
The UK	25.7	6.9%
Spain	21.5	4.6%
Japan	84.8	2.0%
Canada	20.7	3.9%
S Korea	13.7	4.5%
Australia	13.1	4.7%
Pharmerging	**269.6**	**9.7%**
China	122.6	9.4%
Brazil	33.1	11.5%
India	19.3	11.0%
Russia	14.9	10.8%
Other Pharmerging Countries	79.7	8.9%
Rest of the World	**112.3**	**2.0%**
Total	**1135.1**	**6.2%**

Source: IQVIA Market Prognosis

Table 9: Leading Therapy Areas: Spending and Growth in Select Developed and Pharmerging Markets

Therapy Area	2012-17 CAGR Constant US$	2017-2022 Constant US$ CAGR
Oncology	11.8%	7–10%
Diabetes	16.9%	8–11%
Pain	5.7%	2–5%
Autoimmune	16.8%	7–10%
Respiratory	4.8%	2–5%
Antibiotics& Vaccines	3.2%	1–4%
Cardiovascular	-1.8%	(-2)–1%
HIV	11.5%	5–8%
Mental Health	-2.6%	(-2)–1%
Antivirals	25.0%	(-7) – (-4%)
Others	5.1%	3–6%

Notes: Includes 8 Developed and 6 Pharmerging countries: U.S., France, Germany, Italy, Spain, United Kingdom, Japan, Canada, China, Brazil Russia, India, Turkey, Mexico;
Source: IQVIA Market Prognosis

The US, the Europe and Japan are the dominant markets in the global pharmaceutical industry. The US market remained the single-largest market and accounted for 41.1% of the total medicines sales for the year 2017. The pharmaceutical sales in the EU 5 countries during 2017 were worth US$ 154.4 billion and accounted for nearly 13.6% of the global market. In the pharmerging markets, China with sales of the value US$ 122.6 billion was the leading country in this region, followed by Brazil and India (Table 8).

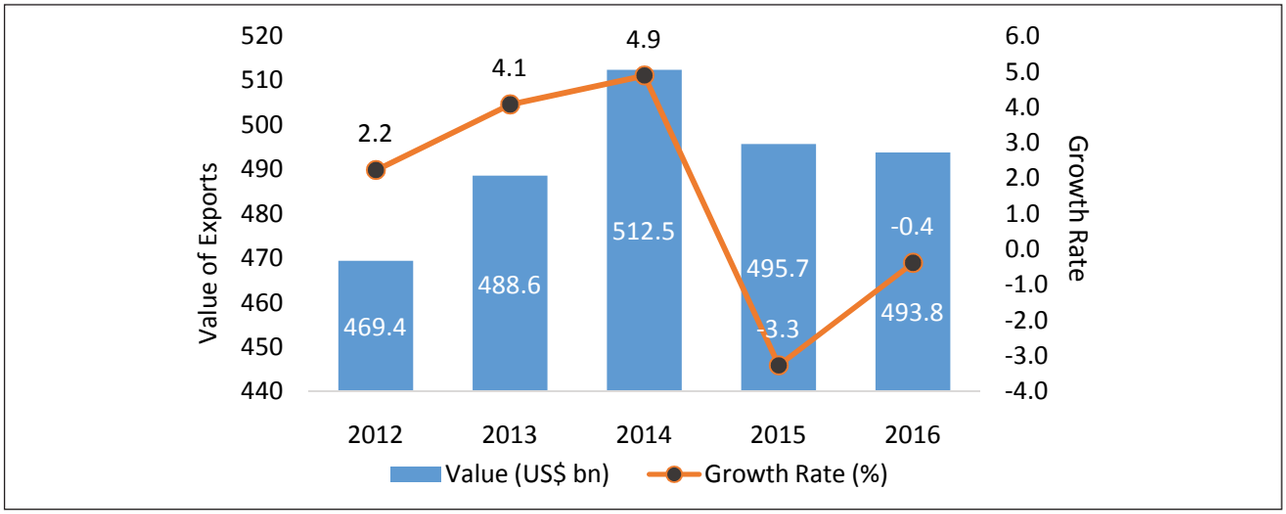
With respect to therapy categories, oncology recorded a CAGR of 11.8% during the period 2012-17 and this growth is projected to moderate to 7-10% over the 2017-22 period. Antivirals registered the largest CAGR of 25% in the five year period 2012-17, followed by Diabetes and Autoimmune categories, respectively (Table 9).

INTERNATIONAL TRADE IN PHARMACEUTICAL PRODUCTS

The global exports of pharmaceutical products were valued at US$ 493.8 billion during the year 2016, registering a year-on-year marginal decline of (-)0.4%. In the five year period between 2012 and 2016, the maximum growth was during the year 2014 at 4.9%, when the value of global exports touched US$ 512.5 billion. However, the growth rates have been negative post this period, with a decline of (-)3.3% in the year 2015. On the whole, the exports of pharmaceutical products recorded a CAGR of 1.3% during the five year period 2012 to 2016 (Exhibit 12).

Germany continued to remain the largest exporter of pharmaceutical products in the world, with the value

Exhibit 12: Global Exports of Pharmaceutical Products



Source: ITC Geneva; Exim Bank Analysis

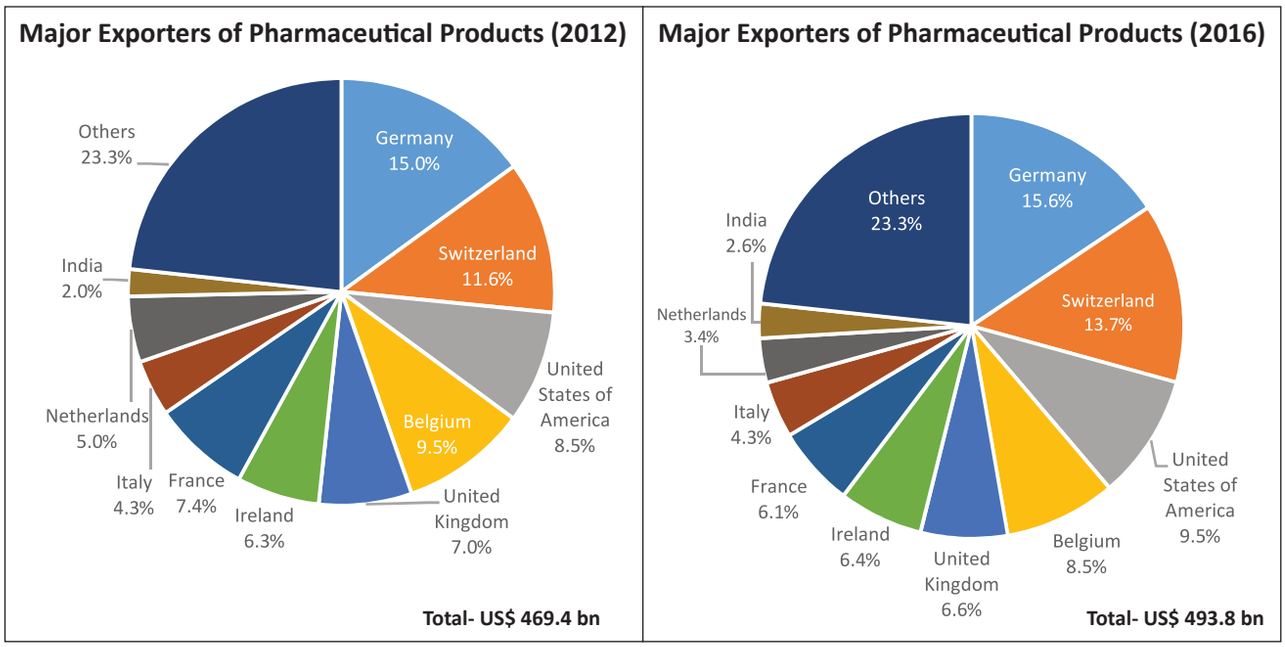
Table 10: Major Exporters of Pharmaceutical Products in the World

Exporters	2012	2013	2014	2015	2016	CAGR	Share
	US$ bn					%	
Germany	70.4	74.8	79.7	75.8	77.1	2.3	15.6
Switzerland	54.4	57.5	62.6	60.6	67.5	5.5	13.7
The USA	40.1	39.7	44.0	47.3	47.0	4.0	9.5
Belgium	44.8	50.4	49.8	43.2	42.0	-1.6	8.5
The United Kingdom	33.1	32.1	33.6	36.0	32.6	-0.4	6.6
Ireland	29.4	26.1	27.2	31.9	31.8	1.9	6.4
France	34.9	37.0	35.2	29.9	30.1	-3.6	6.1
Italy	20.0	23.6	25.3	19.8	21.2	1.5	4.3
The Netherlands	23.4	22.5	25.7	26.6	16.7	-8.2	3.4
India	9.6	11.7	11.7	12.5	13.0	8.0	2.6
World	**469.4**	**488.6**	**512.5**	**495.7**	**493.8**	**1.3**	**100.0**

Source: ITC Geneva; Exim Bank Analysis

of its exports increasing from US$ 70.4 billion in 2012 to US$ 77.1 billion in 2016 accounting for a share of 15.6% in world exports during 2016. Switzerland was the second leading exporter, with its value of exports standing at US$ 67.5 billion (13.7% share) in 2016. The US, being the third largest exporter of pharmaceuctuial products in the world, had a share of 9.5% in world exports during 2016, with its exports registering a CAGR of 4.0% during the period 2012 to 2016. The other major exporters of pharmaceutical products include Belgium, the UK, Ireland, France, Italy, the Netherlands and India. Among the top 10 exporters in the world, while four countries recorded negative CAGRs, India was the one to record the highest CAGR of 8.0% during the period 2012 to 2016, helping the country increase its share in world pharmaceutical exports from 2.0% in 2012 to 2.6% in 2016 (Table 10).

Exhibit 13: Share of Major Countries in the Exports of Pharmaceutical Products



Source: ITC Geneva; Exim Bank Analysis

Table 11: Major Importers of Pharmaceutical Products in the World

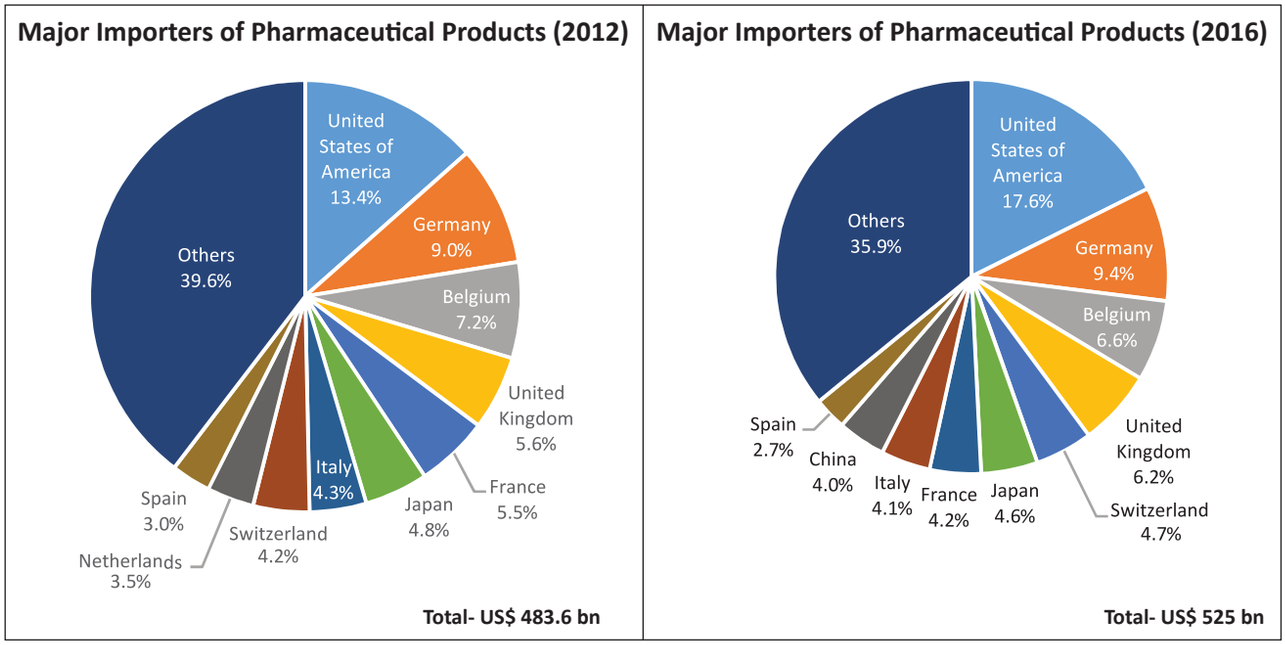
Importer	2012	2013	2014	2015	2016	CAGR	Share
	US$ bn					%	
United States of America	65.0	63.3	73.0	86.0	92.5	9.2	17.6
Germany	43.5	45.2	49.3	45.7	49.1	3.1	9.4
Belgium	34.8	41.0	39.4	36.3	34.9	0.1	6.6
United Kingdom	26.9	27.7	33.7	33.7	32.8	5.1	6.2
Switzerland	20.4	22.1	23.5	21.7	24.7	4.9	4.7
Japan	23.0	20.9	19.9	23.2	24.4	1.4	4.6
France	26.4	26.1	27.9	22.2	22.1	-4.4	4.2
Italy	20.6	21.3	21.5	20.6	21.3	0.9	4.1
China	13.0	15.1	17.8	19.2	20.8	12.4	4.0
Spain	14.3	14.5	15.2	14.8	13.9	-0.7	2.7
World	**483.6**	**501.6**	**530.4**	**516.3**	**525.0**	**2.1**	**100.0**

Source: ITC Geneva; Exim Bank Analysis

The share of the three leading exporters of pharmaceutical products have increased from the period 2012 to 2016. The share of Germany increased from 15.0% to 15.6%, that of Switzerland from 11.6% to 13.7% and of the US from 8.5% to 9.5%, during the period between 2012 and 2016. While India constituted 2.0% of the world exports in the year 2012, this increased to 2.6% in the year 2016 (Exhibit 13).

The global imports of pharmaceutical products amounted to US$ 525 billion, recording a CAGR of 2.1% during the period 2012 to 2016. The US was the

Exhibit 14: Share of Major Countries in the Imports of Pharmaceutical Products



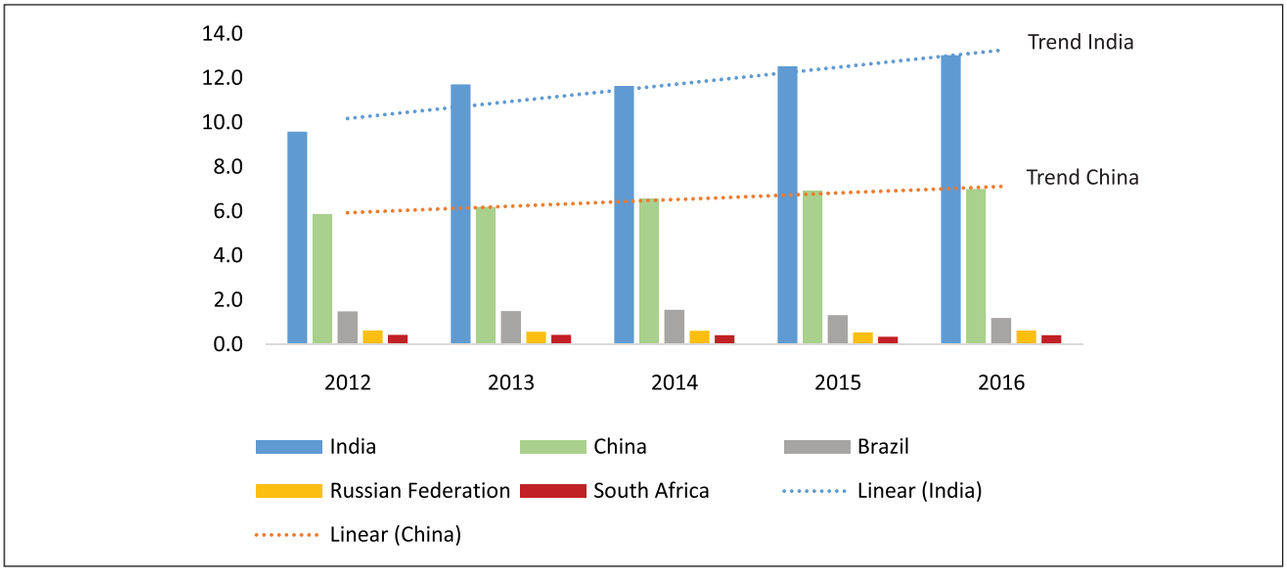
Source: ITC Geneva; Exim Bank Analysis

leading importer of pharmaceutical products in the world, with a share of 17.6% in the global imports, during the year 2016. The imports of pharmaceutical products from Germany increased from US$ 43.5 billion in 2012 to US$ 49.1 billion in 2016. Other major importers of pharmaceutical products in 2016 included Belgium, the UK, Switzerland, Japan, France, Italy, China and Spain (Table 11).

The share of the leading importer of pharmaceutical products in the world, viz. the USA increased significantly from 13.4% in the year 2012 to 17.6% in the year 2016. The share of Germany and the UK also increased during this period. Switzerland replaced France as the fifth largest importer and had a share of 4.7% in the world imports of pharmaceutical products during 2016 (Exhibit 14).

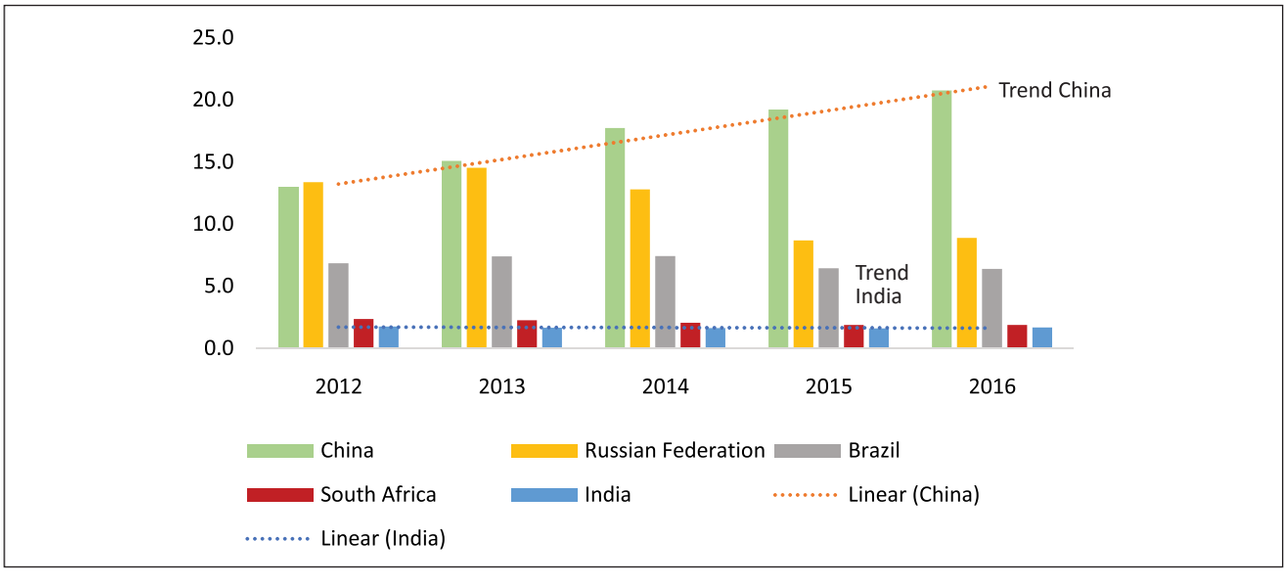
China has emerged as a significant importer of pharmaceutical products recording a CAGR of 12.4% during the 2012 to 2016 period. In 2016, Brazil, Russia, India and China (BRIC) as a bloc accounted for 4.4% of global exports and 7.5% of global imports of pharmaceutical products (Exhibit 15 & 16).

Exhibit 15: Exports of Pharmaceutical Products from BRICS (US$ bn)



Source: ITC Geneva; Exim Bank Analysis

Exhibit 16: Imports of Pharmaceutical Products by BRICS (US$ bn)



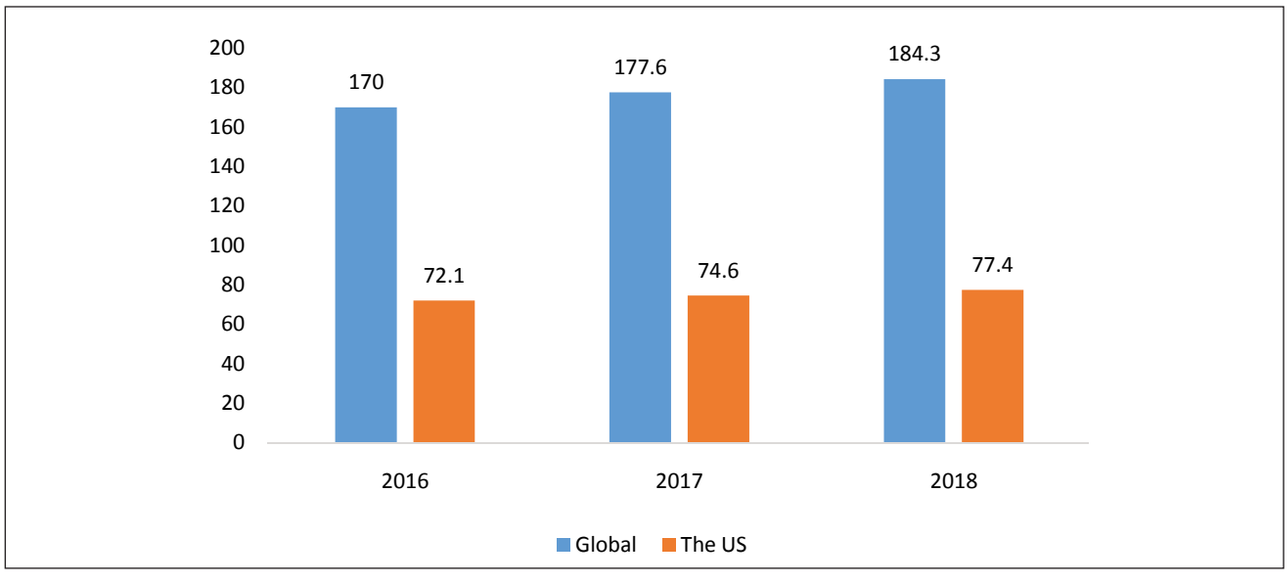
Source: ITC Geneva; Exim Bank Analysis

Developments in Global Pharmaceutical Industry

Research and Development

The research and development in the life sciences sector is focused on expenditure on pharmaceuticals, medical instruments, biotech products, agricultural products, animal testing as well as research activities. According to estimates, the combined R&D expenditure in this sector is expected to rise at the rate of 3.8% globally. The large pharma companies cumulatively invested approximately US$ 50 billion annually in research and development. A third of these companies have their headquarters and research facilities in the US. An equal share of the companies have their research facilities in Europe and approximately one-fourth have their research labs in the Asian region. Research expenditure on the pharmaceutical segment accounts for nearly 80% of the aggregate amount of R&D expenditure in the life sciences sector.

Exhibit 17: Life Sciences R& D Spending (US$ bn)



Source: Industrial Research Institute

Table 12: Life Sciences Research and Development Expenditure: Top 5 Companies

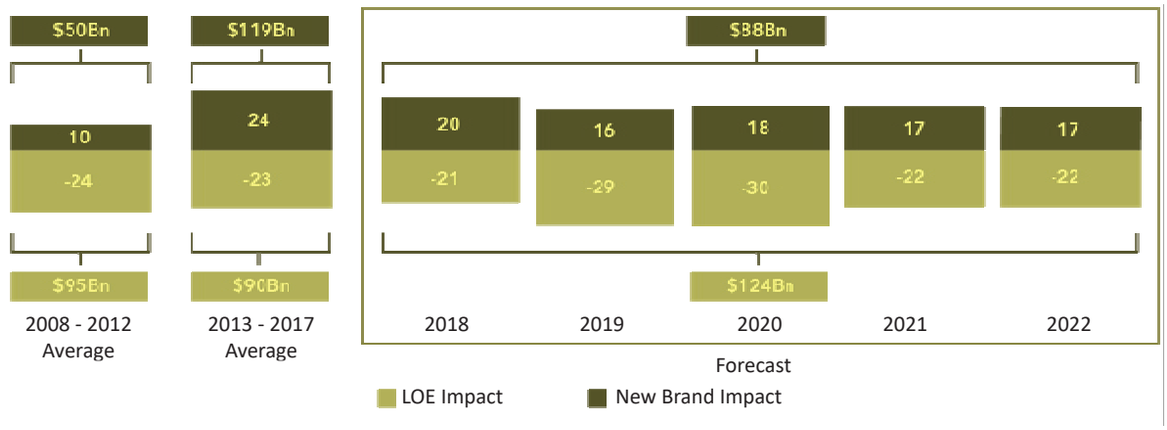
Companies	2015	2016	2017
	US$ bn		
Roche Holdings	11.35	11.542	11.769
Merck& Co.	10.124	10.155	10.187
Johnson& Johnson	9.124	9.191	9.223
Novartis	9.039	8.704	8.407
Pfizer	8.375	8.738	9.084
Total Top 5	**48.012**	**48.33**	**48.67**

Source: Industrial Research Institute

Patent Expiry

When a drug is protected by a patent, the company that holds the patent owns the exclusive rights to manufacture and market the drugs and in turn earns profit from its sales. Typically, patents in the industry are designed for a span of approximately 20 years from the date of application. However, the patents for drugs are applied considerably in advance as compared to the time by which they reach the market. Thus, the drug typically has a patent period of about 7 to 12 years after its sales commences. Once the patent has expired, other manufacturers willing to sell the generic version of the drug have to put in lesser efforts in demonstrating the safety and effectiveness. Post the expiry of the patent, the company which was engaged in the manufacture of the original drug faces substantial losses, as cheaper version of the drugs are made readily available. As per industry sources, Eli Lilly laid off nearly hundreds of sales staff after its anti-depressant drug Cymbalta went off patent by the end of 2013. Furthermore, the loss of patent of the asthma medication Singular triggered Merck's to reduce their employees by nearly 33%. As per Dickson Data, branded drugs can lose up to 90% of their sales, when generic drugs are made available in the market. According to the IQVIA Institute for Human Data Science (erstwhile IMS Institute), the impact of patent expiry in the developed market is projected at US$ 124 billion over the 2018-2022 period, 37 per cent higher than the previous five year period (2013-2017). It estimates that the peak year of impact will be 2020 when spending on brands that no longer have exclusivity will be reduced by over US$30 billion across the ten developed markets. The exhibit elaborates the forecast of the anticipated losses due to patent expiration in the developed pharmaceutical market (Exhibit 18).

Exhibit 18: Developed Markets New Brand and Brand Loss of Exclusivity Impact on Growth 2008–2022



Source: IQVIA Market Prognosis, Sep 2017; IQVIA Institute
Notes: Developed markets include: U.S., Japan, Germany, France, Italy, U.K., Spain, Canada, S. Korea, Australia; LOE- loss of exclusivity
Report: 2018 and Beyond: Outlook and Turning Points. IQVIA Institute for Human Data Science, March 2018

Blockbuster Drugs

A blockbuster drug is defined as that drug whose global sales is more than US$ 1 billion. In the year 2018, the launch of approximately 12 new drugs has been predicted, which are forecast to become blockbusters within a time frame of five years[19]. The drug Hemlibra was approved by the European Medicines Agency during the month of February 2018 and launches in the markets of Europe and Japan are predicted during this year. For this drug, the forecast sales for the period 2018 is US$ 496 million and it is expected to reach the blockbuster status by the year 2019 with anticipated sales of US$ 1.5 billion. This value is expected to rise further to US $ 4.0 billion by 2022 (Table 13).

Table 13: Expected Blockbuster Drugs (2018)

Rank	Drug	Disease	2018	2019	2020	2021	2022	Company(HQ)
			US$ mn					
1	Hemlibra	Hemophilia A with factor VIII inhibitors	496	1457	2356	3362	4002	Roche (Switzerland)
2	Biktarvy	HIV infection	896	2282	3387	4296	3716	Gilead (U.S.)
3	Ozempic	Type 2 diabetes	260	862	1576	2583	3469	Novo Nordisk (Denmark)
4	Erleada	Non-metastatic CRPC	25	500	1200	1600	2000	Johnson & Johnson (U.S.)
5	Shingrix	Shingles	242	537	879	1202	1368	GlaxoSmithKline (UK)
6	Patisiran	Hereditary TTR amyloidosis	83	373	726	1104	1212	Alnilam (U.S.)/Genzyme (US)
7	Epidiolex	Dravet syndrome and Lennox-Gastaut syndrome	19	266	645	936	1191	GW Pharmaceuticals (UK)
8	Aimovig	Migraine	115	361	685	941	1170	Amgen (U.S.)/Novartis (Switzerland)
9	Lanadelumab	Hereditary angioedema	74	350	629	902	1153	Shire (Ireland)
10	Elagolix	Endometriosis	57	268	549	896	1152	AbbVie (U.S.)
11	Steglatro	Type 2 diabetes	220	482	769	1024	1087	Pfizer (U.S.)/Merck (U.S.)
12	Sublocade	Opioid dependence	121	308	439	634	1072	Indivior (UK)

Source: Clarivate Analytics; Drugs to Watch 2018

[19]Clarivate Analytics

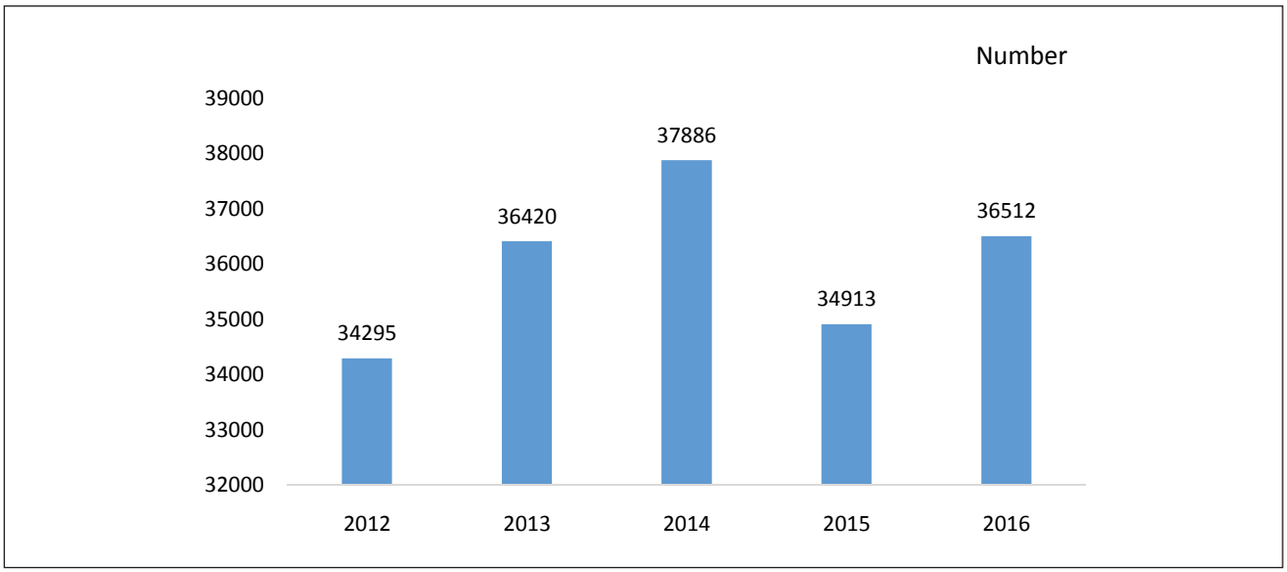
Biosimilars

The global biosimilars market is forecast to undergo considerable growth in the future. The rise in the launch of new products in the EU and the US, increase in the entry of new players and the period of patent expiries of the blockbuster biologics in the EU and the US are likely to lead to this development. The markets of China and India are anticipated to exhibit growth in the production of these products. The global biosimilar market was estimated at US$ 3.5 billion during the year 2017 and is expected to record an impressive CAGR of 43.9% during the period 2018 to 2023[20]. North America accounted for approximately 30% of the aggregate market share of biosimilars in the year 2017. In the past, the blockbuster biologics of various pharma companies such as Remicade, Rituxan, Herceptin, Enbrel, Lantus, and others have expired. The patent expiration of various other biological drugs such as Erbitux, Avastin, Orencia, and others are anticipated, facilitating the strong development of the biosimilar market in future.

Global Patents Trend

The number of patents granted in the global pharmaceutical sector reached a peak in 2014 with 37,866 patents after which it witnessed a sharp decline in 2015 when number of patents granted totalled only 34,913. However, an increase in the global filing of patents for pharmaceuticals was observed during the year 2016 (Exhibit 19). China was the leading country in pharmaceutical innovation with 9268 patents granted in 2016. China was followed by the United States and Japan with 6557 and 4755 patents being granted, respectively during the same year (Table 14).

Exhibit 19: Patents Granted in the Pharmaceutical Sector



Source: WIPO

[20]Global Biosimilars Market; Modern Intelligence

Table 14: Patents Granted in the Pharmaceutical Sector: Top 10 Countries

Countries	2012	2013	2014	2015	2016
China	9856	10333	10891	10505	9268
USA	5935	6857	7257	6805	6557
Japan	4095	4292	4905	4370	4755
Republic of Korea	2047	2335	2912	2146	2557
Australia	2201	2235	2114	2013	2317
Canada	1927	2030	1757	1557	2003
Russian Federation	1581	1446	1391	1632	1255
Mexico	3	3		3	909
Ukraine	390	404	371	406	376
Serbia	150	145	176	223	260
World	**34295**	**36420**	**37886**	**34913**	**36512**

Source: Data Generated from WIPO IP Statistics Data Centre, March 2018.

Affordable Care Act

The Affordable Care Act (also known as Obamacare) was one of the major developments in the US healthcare system and it basically referred to two legislations – the Patient Protection and Affordable Care Act, and the Health Care and Education Reconciliation Act. The Act expanded coverage for the poorest, held insurance companies accountable, lowered healthcare costs and enhanced the quality of healthcare in US. The individual mandate in the Patient Protection and Affordable Care Act has been repealed, by reducing the individual responsibility payment under Section 5000A to zero for individuals who do not purchase health insurance that qualifies as minimum essential coverage, beginning in the year 2019[21]. Further reforms are anticipated which will be aimed at reducing and limiting the federal Medicaid spending, including the ACA Medicaid expansion and repeal the ACA taxes and fees. In this scenario, the healthcare providing organisations are likely to experience uncertainty, and an increase in the uninsured rate might exert cost pressure on the industry. It is anticipated that a decline in the Medicaid expansion and the introduction of a block grant system could decline federal spending on the program by up to US$ 800 billion, in a time frame of 10 years. Moreover, owing to the curtailing of federal funds, the state lawmakers will have to decide whether to employ increased state money to compensate for the funding gap, restrict the eligibility requirements or to opt for a synergy of the two alternatives[22].

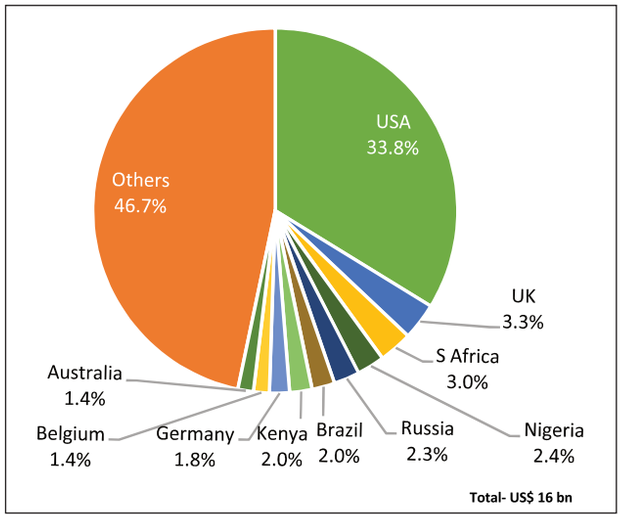
[21]Tax Reform- KPMG Report on New Tax Law
[22]PWC

5. INDIA'S TRADE IN PHARMACEUTICAL PRODUCTS: AN ANALYSIS

BULK DRUG AND DRUG FORMULATIONS

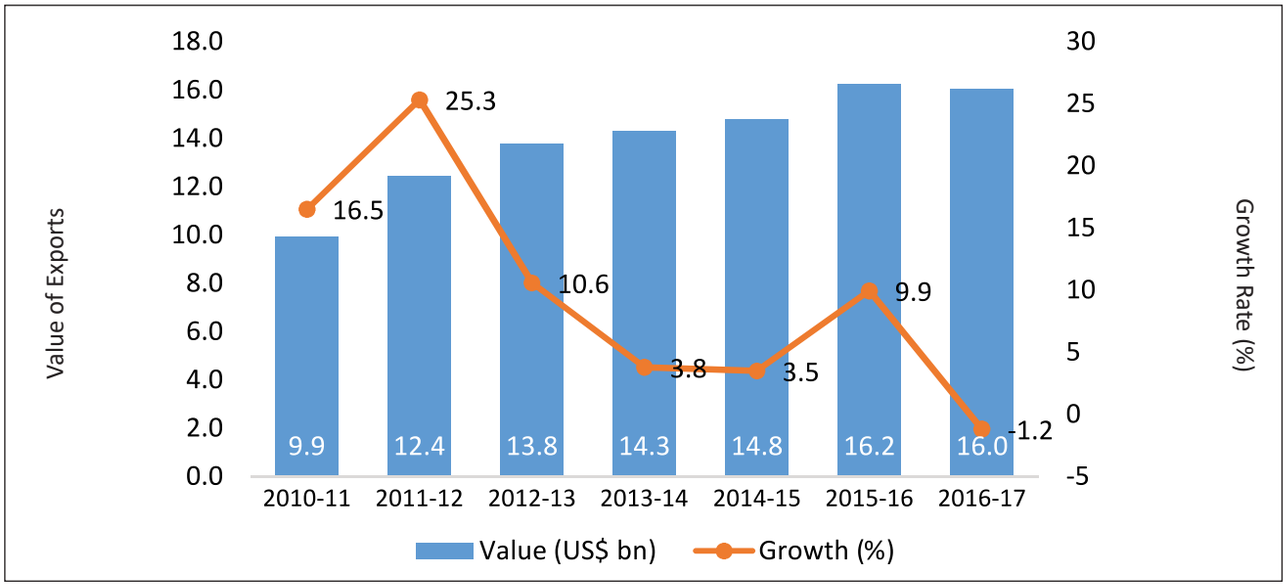
India's exports of pharmaceutical products, including drug formulations and biologicals were valued at US$ 16 billion during the year 2016-17, recording a year-on-year decline of nearly 1.2%[23]. During the seven year period 2010-11 to 2016-17, a negative growth rate in export of these products was observed for the first time during the year 2016-17. The growth rate peaked during the period 2011-12, at 25.3%. Post this period, a decline in growth rates was witnessed up until 2014-15 after which it increased to 9.9% in 2015-16, as the value of exports stood at US$ 16.2 billion. However, in 2016-17, the growth actually entered the negative domain, declining by (-) 1.2% (Exhibit 21).

Exhibit 20: India's Major Export Destinations of Bulk Drug and Drug Formulations (2016-17)



Source: DGCIS ; Exim Bank Analysis

Exhibit 21: India's Exports of Bulk Drug and Drug Formulations



Source: DGCIS ; Exim Bank Analysis

[23]The export figure is different from the one given in the previous chapter owing to (a) data source being different; (b) the data analysis carried out in the previous chapter being related to only HS code 30 (pharmaceutical products), while the analysis in this Chapter includes a few other HS codes to include bulk drugs; and (c) the reference period, which in this case is financial year unlike the last chapter where the period referred to is a calendar year

The US was the leading export destination of bulk drugs and drug formulations, occupying a share of 33.8% in the aggregate exports during the period 2016-17. The exports to UK, the second largest export destination for pharmaceutical products was valued at US$ 525.1 million during the same period. Other major export destinations were South Africa, Nigeria, Russia, Brazil, Kenya, Germany, Belgium and Australia with shares of 3.0%, 2.4%, 2.3%, 2.0%, 2.0%, 1.8%, 1.4% and 1.4% respectively (Exhibit 20).

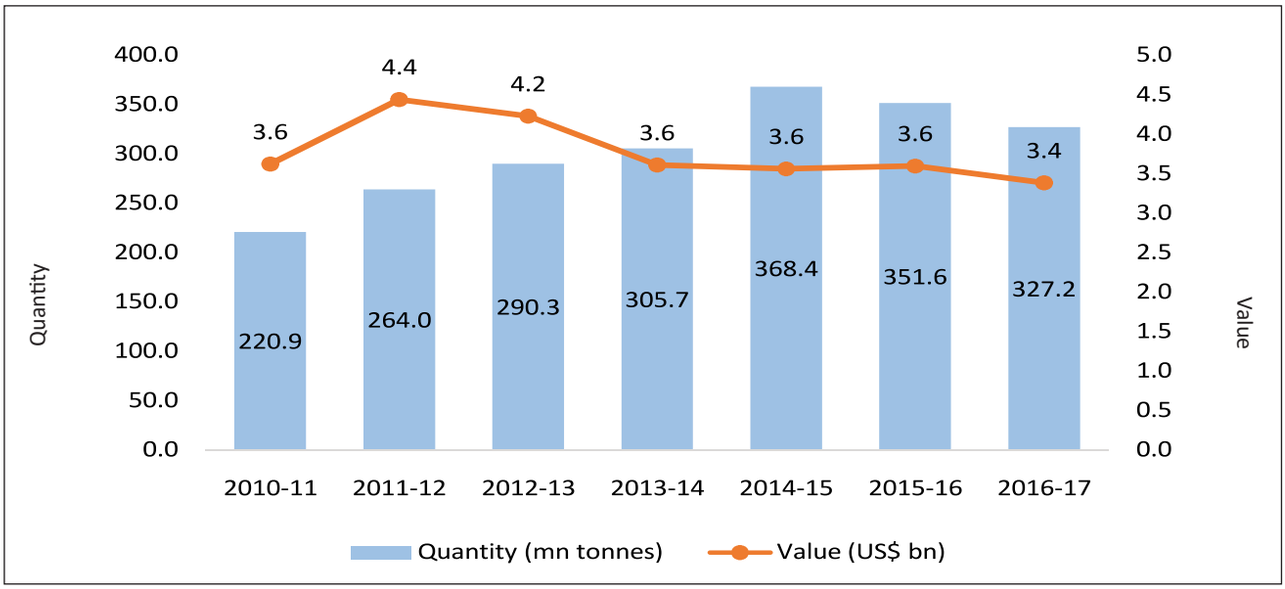
Bulk Drugs, Drug Intermediaries

Exports Analysis

The volume of exports of bulk drugs recorded a CAGR of 6.8% as the quantity of exports increased from 220.9 million tonnes in 2010-11 to 327.2 million tonnes in 2016-17. However, in terms of value, the growth has remained anaemic during this period with exports actually declining from US$ 3.6 billion in 2010-11 to US$ 3.4 billion in 2016-17. This indicates that the per unit price realisation in the export market for bulk drugs and intermediaries has witnessed a decline over the period under consideration (Exhibit 22).

Although US remained the largest export destination of bulk drugs from India, the value of exports to this country recorded a negative CAGR of (-)7.2% during the period 2010-11 to 2016-17. Consequently, the share of US in the aggregate bulk exports from India declined from 15.7% to 10.7% during this period. Germany continued to be the second largest export destination with the value of exports standing at US$ 144.7 million in 2016-17, although its share declined from 5.2% to 4.3% during this period. Brazil replaced Turkey as the third largest importer of bulk drugs from India, with its share increasing from 3.6% in 2010-11 to 3.8% in 2016-17. Japan, which did not feature among the top 10 export destination of bulk drugs in 2010-11, emerged as the fourth largest importer from India during 2016-17, accounting for 3.4% share in India's exports. The rank of Mexico as an export destination also improved from 10th to 5th, managing a share of 3.3% in the total exports of bulk drugs from India. The rank of Turkey in bulk drug exports fell from the 3rd to the 6th as its share diminished from 3.8% to 3.3% during this period. Other major export destination of bulk drugs during 2016-17 were Bangladesh, China, Egypt and Belgium

Exhibit 22: India's Quantity and Value of Bulk Drugs Exports



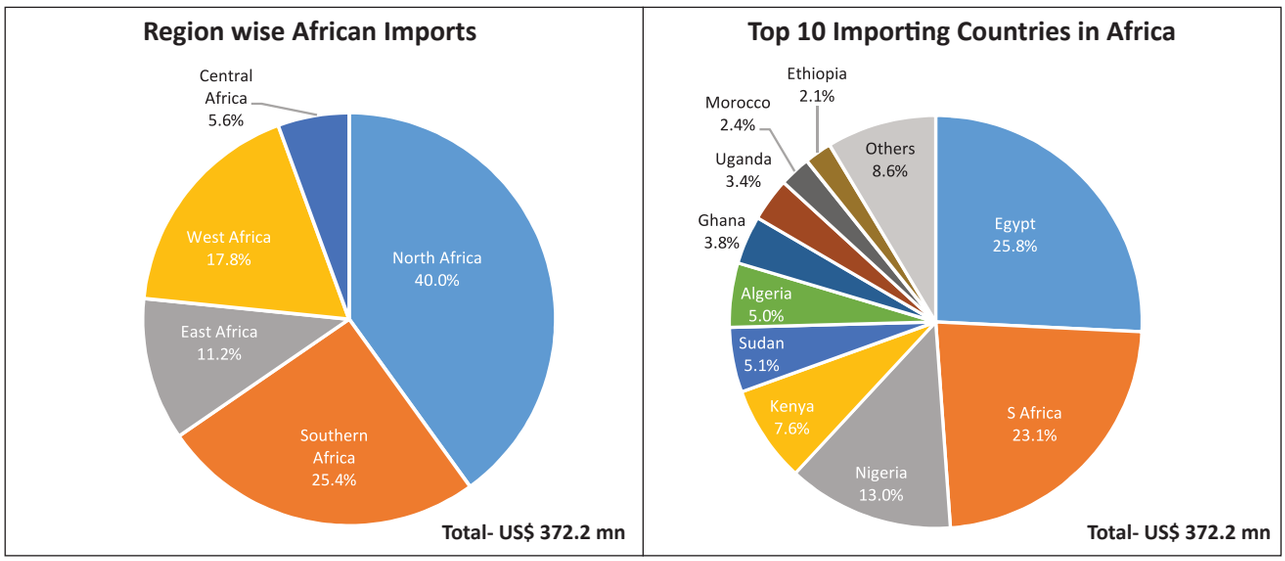
Source: DGCIS ; Exim Bank Analysis

Table 15: India's Major Export Destinations of Bulk Drugs

2010-11			2016-17		
Export Destinations	**Value (US$ mn)**	**Share (%)**	**Export Destinations**	**Value (US$ mn)**	**Share (%)**
USA	567.2	15.7	USA	361.1	10.7
Germany	187.2	5.2	Germany	144.7	4.3
Turkey	136.4	3.8	Brazil	127.7	3.8
Brazil	130.3	3.6	Japan	115.5	3.4
Israel	122.0	3.4	Mexico	111.7	3.3
China	115.0	3.2	Turkey	111.0	3.3
Italy	112.2	3.1	Bangladesh	110.2	3.3
Spain	106.4	2.9	China	103.9	3.1
UK	97.7	2.7	Egypt	95.9	2.8
Mexico	96.0	2.6	Belgium	91.6	2.7
World	**3623.4**	**100.0**	**World**	**3383.5**	**100.0**

Source: DGCIS ; Exim Bank Analysis

Exhibit 23: India's Bulk Drugs Exports to Africa (2016-17)



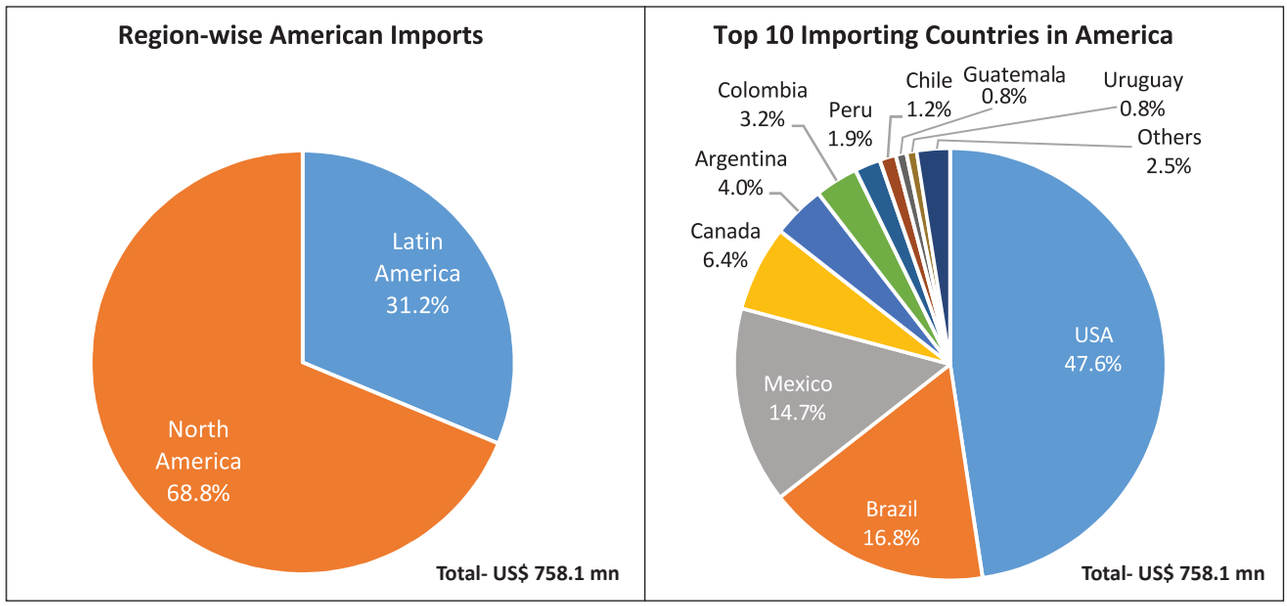
Source: DGCIS ; Exim Bank Analysis

with shares of 3.3%, 3.1%, 2.8% and 2.7% respectively (Table 15).

Africa

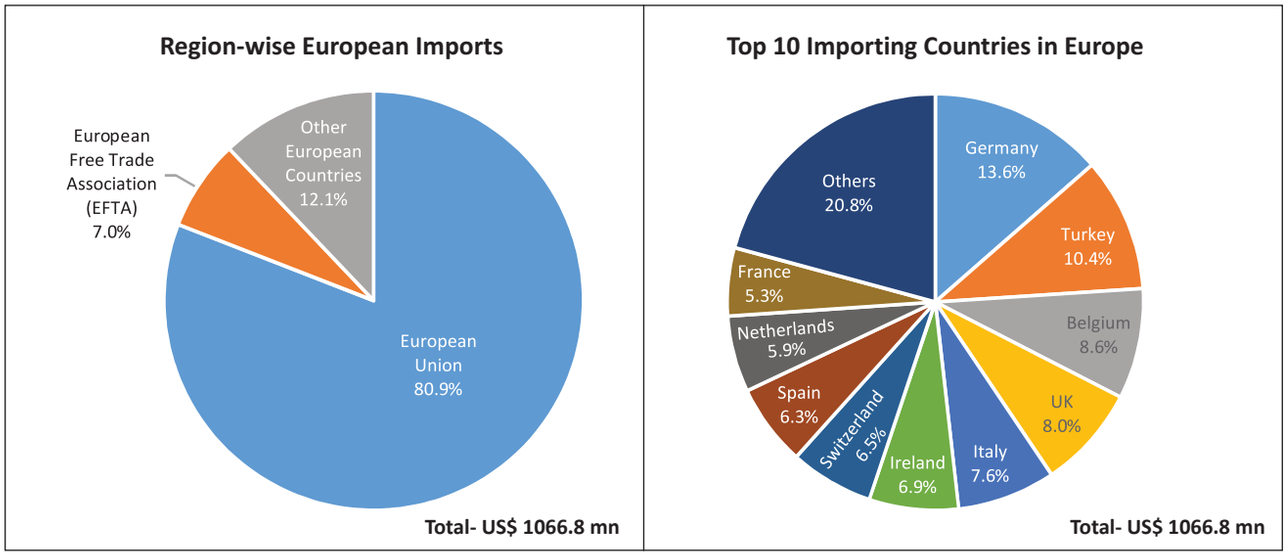
The exports of bulk drugs to the African region was valued at US$ 372.2 million during the year 2016-17. The North African region accounted for the majority of imports of Indian bulk drugs, with a share of nearly 40%, this was followed by Southern Africa (25.4%), West African (17.8%), East African (11.2%) and Central African region (5.6%). Among the African countries, Egypt was the largest importer, with its value of imports being US$ 95.9 million. South Africa was the second largest African importer, with a share of 23.1% in the total African imports of bulk drugs from India. Other large export destinations in Africa included Nigeria, Kenya, Sudan, Algeria, Ghana, Uganda, Morocco and Ethiopia (Exhibit 23).

Exhibit 24: India's Bulk Drugs Exports to America (2016-17)



Source: DGCIS ; Exim Bank Analysis

Exhibit 25: India's Bulk Drugs Exports to Europe (2016-17)



Source: DGCIS ; Exim Bank Analysis

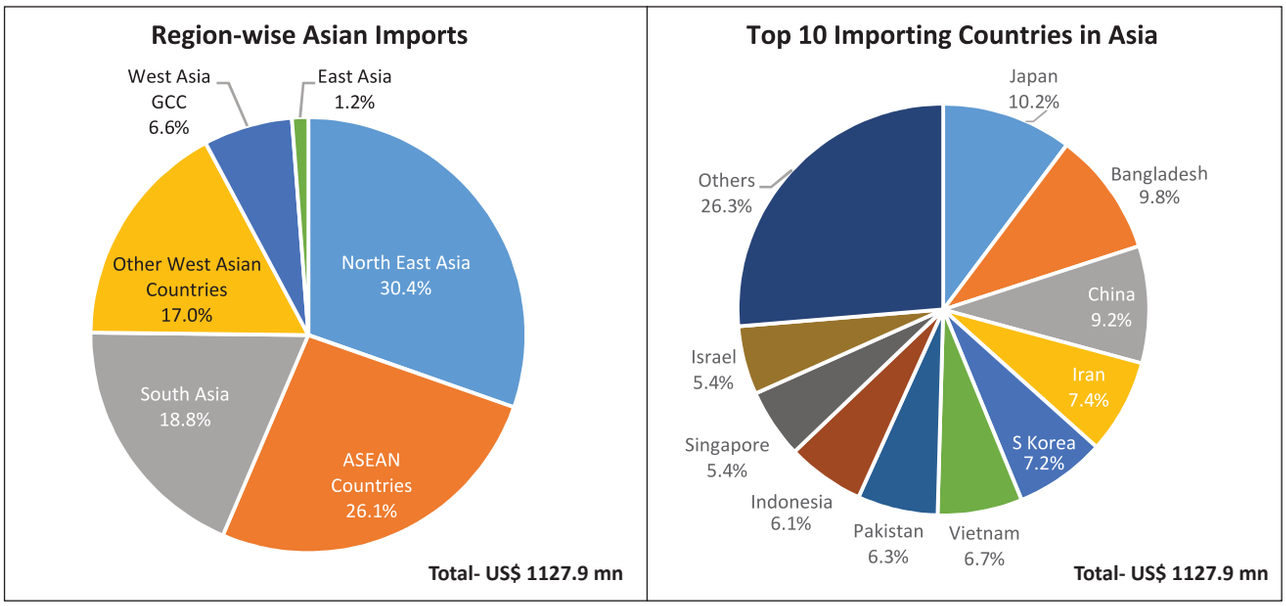
America

The value of bulk drugs exports by India to the American region was US$ 758.1 million during 2016-17, with North America accounting for 68.8% (US$ 521.3 million) and Latin America accounting for the remaining 31.2% of the total exports. In terms of country wise analysis, the USA was, by far, the leading export destination in the American region, with value of imports at US$ 361.1 million (47.6% share). Brazil, the second largest bulk drug importer in the American region had a share of 16.8%. Other major export destinations in this region were Mexico, Canada, Argentina, Colombia, Peru, Chile, Uruguay and Guatemala (Exhibit 24).

Europe

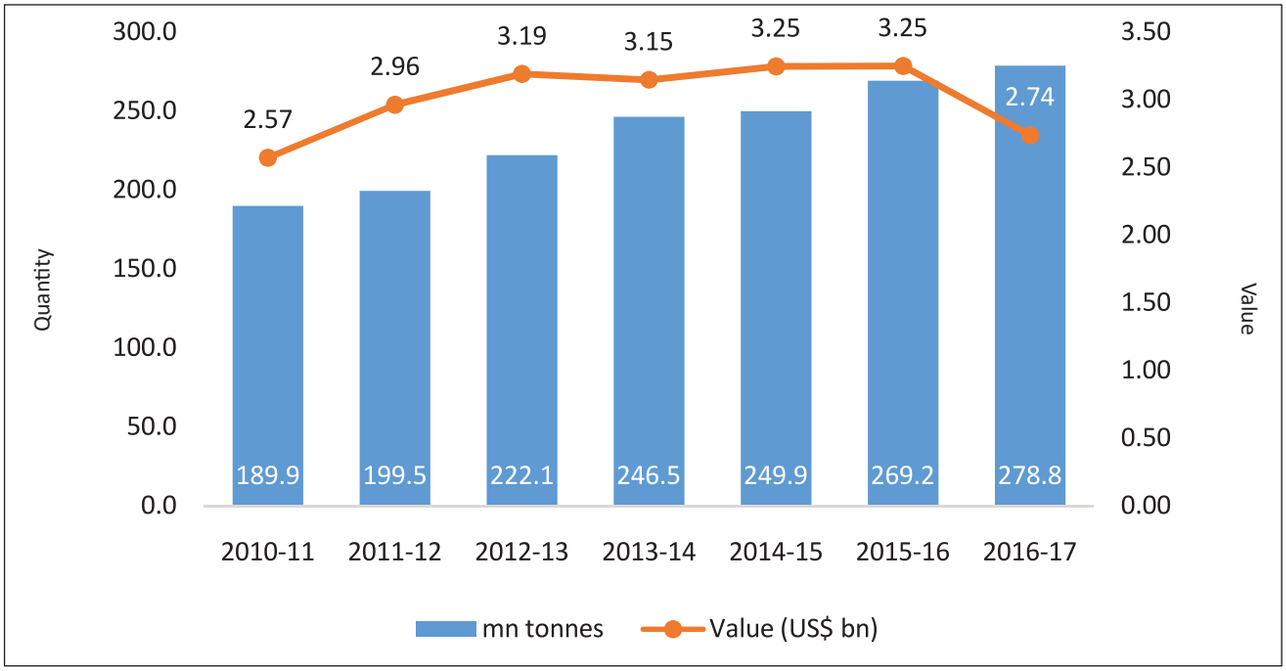
India's exports of bulk drugs to Europe amounted to US$ 1066.8 million in 2016-17. Germany was the largest importer of bulk drugs from India in the European region. India's export of bulk drugs to

Exhibit 26: India's Bulk Drugs Exports to Asia (2016-17)



Source: DGCIS ; Exim Bank Analysis

Exhibit 27: India's Imports of Bulk Drugs



Source: DGCIS ; Exim Bank Analysis

Germany were valued at US$ 144.7 million, with a share of 13.6% in the aggregate European exports. Turkey was the second largest export destination with a share of 10.4% followed by Belgium, the UK, Italy, Ireland, Switzerland, Spain, the Netherlands and France (Exhibit 25).

Asia

The export of Indian bulk drugs to Asia were valued at US$ 1127.9 million during 2016-17. Japan was the leading Asian importer of bulk drugs with its imports standing at US$ 115.5 million. Bangladesh

was the second largest export destination with a share of 9.8%, followed by China (9.2%), Iran (7.4%), South Korea (7.2%), Vietnam (6.7%), Pakistan (6.3%), Indonesia (6.1%), Singapore (5.4%) and Israel (5.4%) (Exhibit 26).

Imports Analysis

The import value of bulk drugs by India recorded a CAGR of 1.1% during the seven year period between 2010-11 and 2016-17. In the year 2016-17, the value of imports stood at US$ 2.74 billion, registering a sharp y-o-y decline of 15.7% (Exhibit 27). China was, by far, the leading import source of bulk drugs from India, accounting for a share of 66.7% in India's aggregate import of bulk drugs. The value of bulk drugs imports from China have increased at a CAGR of 1.6% during the period 2010-11 to 2016-17. Other major import sources of bulk drugs were the US, Italy, Germany, Singapore, Spain, France, Japan, South Korea and Denmark (Table 16).

Table 16: India's Major Import Sources of Bulk Drugs

2010-11		2016-17	
Import Sources	**Value (US$ mn)**	**Import Sources**	**Value (US$ mn)**
China	1660.7	China	1826.3
Germany	139.2	US	122.3
US	125.0	Italy	104.6
Japan	71.2	Germany	72.4
Spain	60.7	Singapore	63.0
Italy	53.1	Spain	58.3
South Korea	46.3	France	46.9
Belgium	42.8	Japan	45.3
France	40.1	South Korea	41.7
Denmark	35.0	Denmark	40.7
Total	**2571.8**	**Total**	**2738.5**

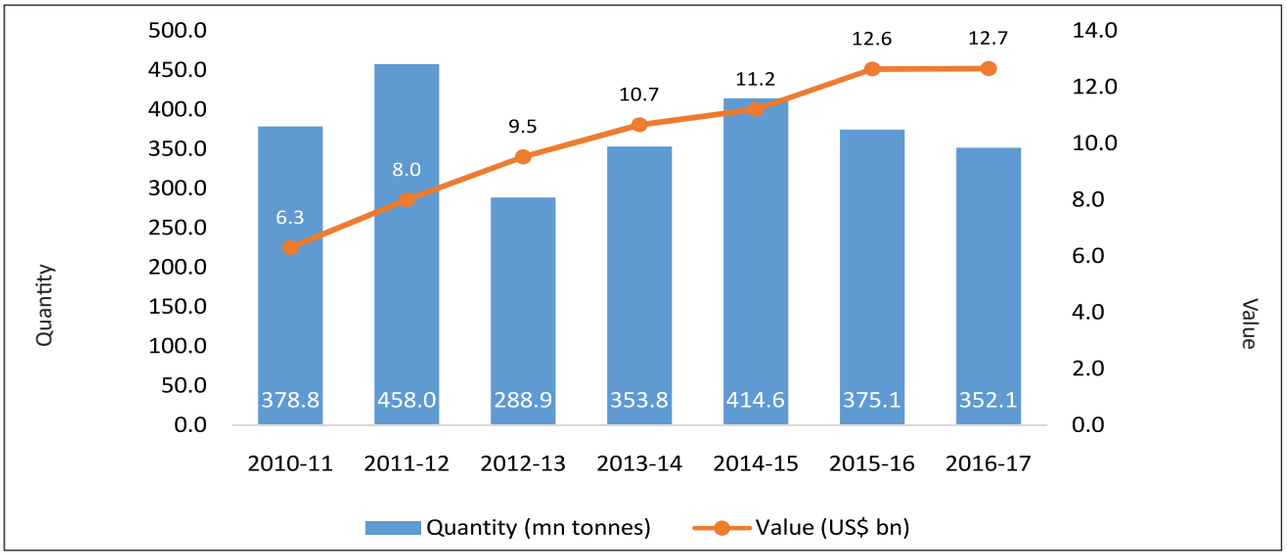
Source: DGCIS; Exim Bank Analysis

Drug Formulations

Export Analysis

Unlike bulk drugs, the exports of drug formulations have displayed a considerable growth over the years, with the value of exports more than doubling from US$ 6.3 billion in 2010-11 to US$ 12.7 billion in 2016-17, although only a marginal year-on-year growth was registered during 2016-17 at 0.1%. However, in term of volume, the quantity of drug formulations exports recorded a negative CAGR of (-)1.2% during the period 2010-11 to 2016-17, with exports declining from 378.8 million tonnes to 352.1 million tonnes during this period. As against this, the value of exports recorded a positive CAGR of 12.3% during the same period (Exhibit 28).

Exhibit 28: India's Exports of Drug Formulations



Source: DGCIS ; Exim Bank Analysis

Table 17: India's Major Export Destinations of Drug Formulations

2010-11			2016-17		
Export Destinations	**Value**	**Share**	**Export Destinations**	**Value**	**Share**
	(US$ mn)	(%)		(US$ mn)	(%)
USA	1775.8	28.2%	USA	5057.8	39.9%
Russia	399.6	6.3%	UK	439.4	3.5%
S Africa	274	4.3%	S Africa	389	3.1%
UK	272.4	4.3%	Nigeria	343.5	2.7%
Nigeria	190.3	3.0%	Russia	339.3	2.7%
Kenya	156.9	2.5%	Kenya	289.5	2.3%
Germany	133.9	2.1%	Australia	208.8	1.6%
Netherlands	129.6	2.1%	Brazil	196.5	1.6%
Ghana	116.9	1.9%	Sri Lanka	196.3	1.5%
Sri Lanka	115.5	1.8%	Tanzania	188.7	1.5%
Total	**6306.8**	**100.0%**	**Total**	**12666.4**	**100.0%**

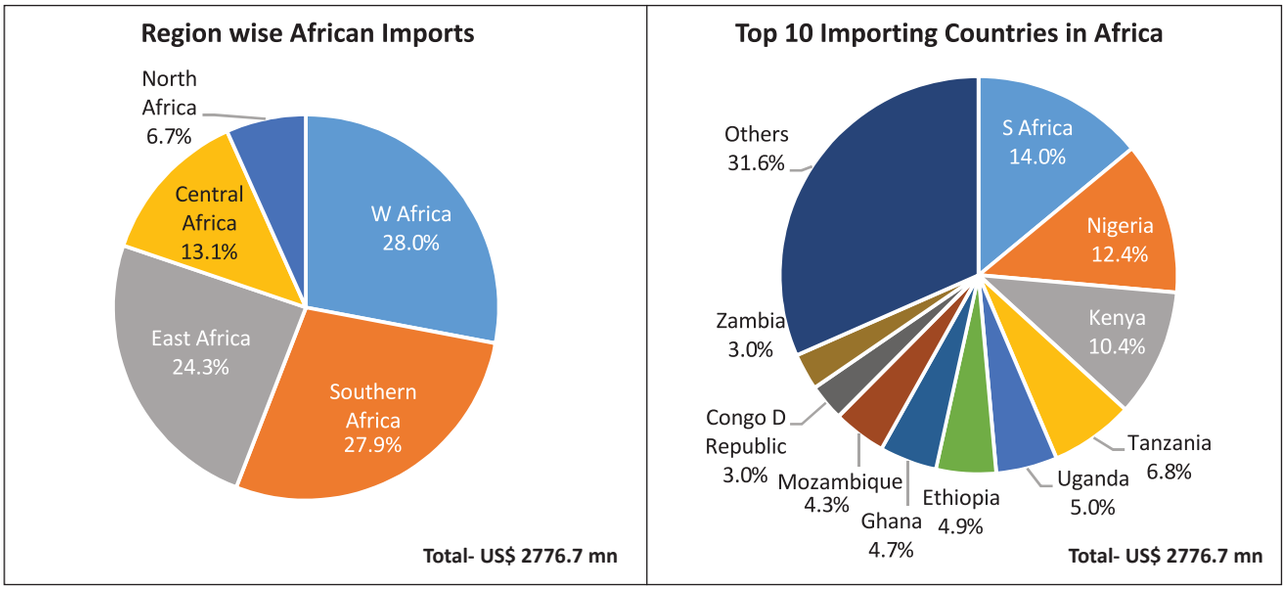
Source: DGCIS ; Exim Bank Analysis

USA continued to be the largest export destination of drug formulations from India, with its imports having augmented substantially from US$ 1775.8 million to US$ 5057.8 million in the period 2010-11 to 2016-17. Consequently, the share of US increased sharply from 28.2% to 39.9% during this period. The UK emerged as the second largest export destination in 2016-17 as compared to its fourth position in 2010-11, although its share in India's exports of drug formulations declined from 4.3% to 3.5% during this period. South Africa continued to be the third largest export destination of drug formulations, although, like the UK, its share in aggregate exports also fell, from 4.3% to 3.1% during the period under consideration. An interesting point to note is that the importance of Russia as a destination for exports of drug formulations has gone down significantly, with the country's share falling from 6.3% to 2.7% during 2010-11 to 2016-17, resulting in the rank of Russia being relegated to 5th in the latter period, from 2nd in 2010-11. The above analysis clearly shows a concentration in India's exports of drug formulations in favour of the US. This exposes the Indian drug industry to a high concentration risk wherein any policy change in the US could have a significant bearing on the exports of drug formulations from India. In order to mitigate this risk, there is a need to diversify the export destinations, especially to other leading importers of drugs and those that have shown dynamic growth in their imports (Table 17).

Africa

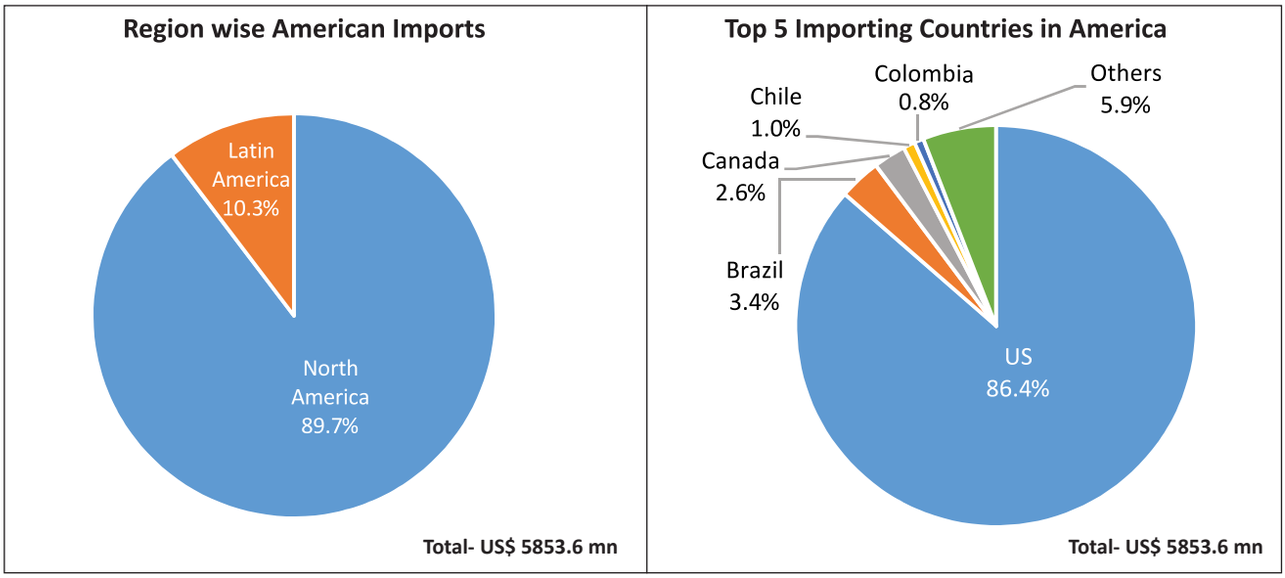
India's exports of drug formulations to Africa were valued at US$ 2.8 billion during the year 2016-17. The West African region was the leading importing region in the continent with imports from India valued US$ 776.5 million. The Southern African region accounted for the second highest share (27.9%) followed by East Africa (24.3%), Central Africa (13.1%) and North Africa (6.7%). In terms of countries, South Africa was the largest export destination for drug formulations in the African continent, with imports from India valued at US$ 389 million. Nigeria, the second largest export destination had a share of 12.4% followed by Kenya (10.4%), Tanzania (6.8%), Uganda (5.0%), Ethiopia (4.9%), Ghana (4.7%), Mozambique (4.3%), Congo D. Republic (3.0%) and Zambia (3.0%) (Exhibit 29).

Exhibit 29: India's Drug Formulations Exports to Africa (2016-17)



Source: DGCIS ; Exim Bank Analysis

Exhibit 30: India's Drug Formulations Exports to America (2016-17)



Source: DGCIS ; Exim Bank Analysis

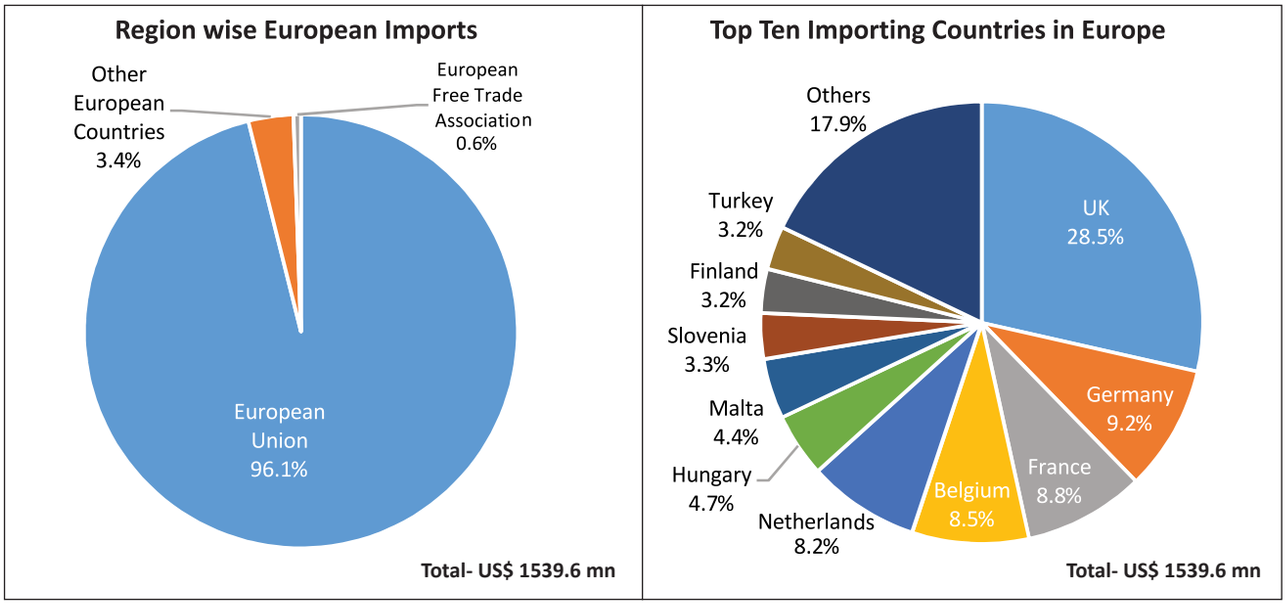
America

The North American region accounted for approximately 89.7% of the aggregate American imports of drug formulations from India, with its value of imports aggregating US$ 5248 million in 2016-17. In the American region, the US was, by far, the leading importing country, accounting for a share of 86.4% in the aggregate imports of drug formulation of the North American region from India. Brazil, the second largest importing country in this region, had imports valued at US$ 196.5 million. Other major importers of drug formulations from India in America included Canada, Chile and Colombia, with shares of 2.6%, 1.0% and 0.8% respectively (Exhibit 30).

Europe

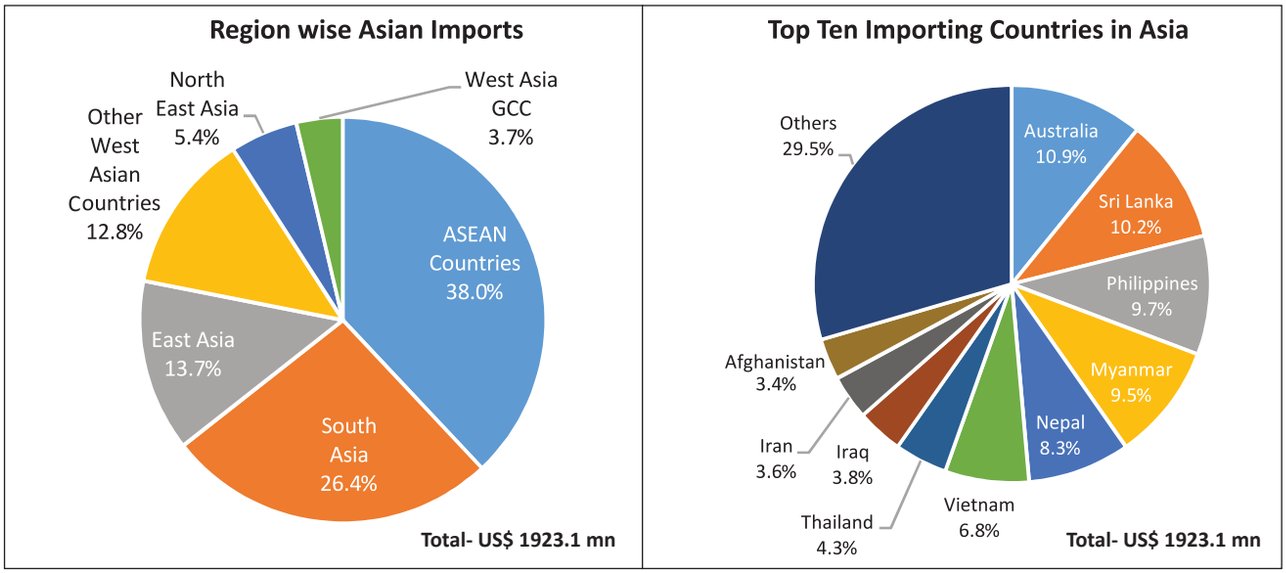
European imports of drug formulations from India in 2016-17 were valued at US$ 1539.6 million, with the

Exhibit 31: India's Drug Formulations Exports to Europe (2016-17)



Source: DGCIS ; Exim Bank Analysis

Exhibit 32: India's Drug Formulations Exports to Asia (2016-17)



Source: DGCIS ; Exim Bank Analysis

share of the European Union at 96.1%. The UK, with a share of 28.5% in the aggregate European imports, was the largest importer in this region. The value of imports of drug formulations by Germany from India stood at US$ 141.2 million, accounting for a share of 9.2%. The other major European importers of drug formulations from India included France (8.8%), Belgium (8.5%), the Netherlands (8.2%), Hungary (4.7%), Malta (4.4%), Slovenia (3.3%), Finland (3.2%) and Turkey (3.2%) (Exhibit 31).

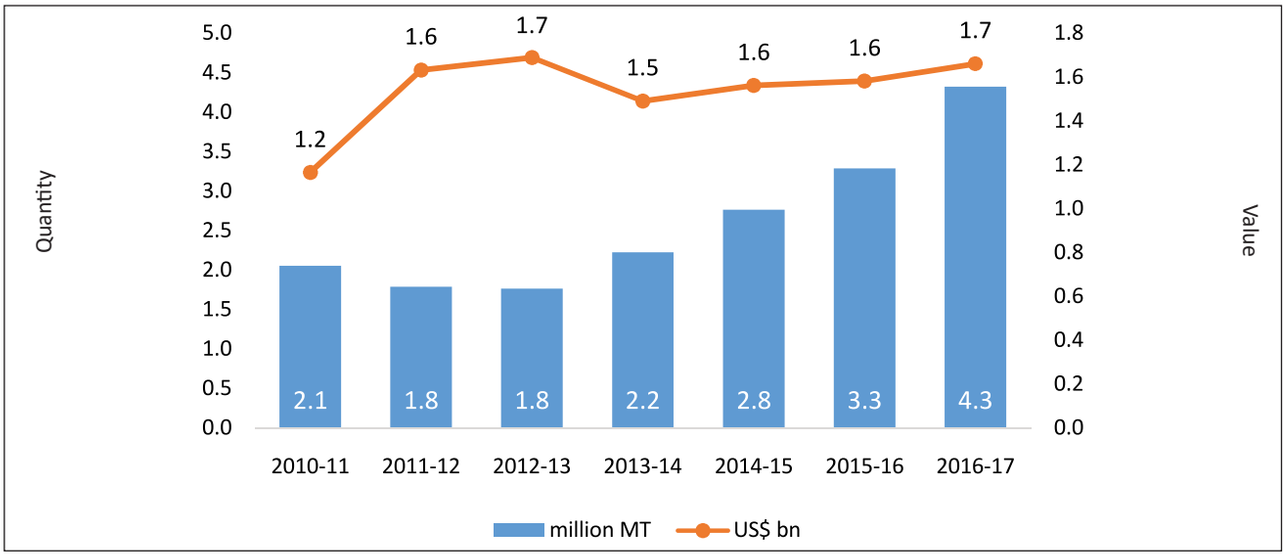
Asia

The imports of drug formulations by the Asian region stood at US$ 1923.1 million in 2016-17, with Australia being the leading import source, contributing a share of 10.9%. Other major export destinations for India for this product from the Asian region during 2016-17 included Sri Lanka (10.2%), the Philippines (9.7%), Myanmar (9.5%), Nepal (8.3%), Vietnam (6.8%), Thailand (4.3%), Iraq (3.8%), Iran (3.6%), and Afghanistan (3.4%) (Exhibit 32).

Imports Analysis

The exhibit below illustrates an increase in the quantity of drug formulations imported by India. As is evident, the volume of imports witnessed a consistent secular increase after 2012-13 and recorded a CAGR of 13.2% during the period 2010-11 to 2016-17. The value of imported drug formulations registered a CAGR of 6.1% during the same period, increasing from US$ 1.2 billion in 2010-11 to US$ 1.7 billion in 2016-17 (Exhibit 33). The US, which was the second largest import source in 2010-11, emerged as the leading import source of drug formulations for India in 2016-17, accounting for a share of 17.2% in the country's aggregate imports of the product. Germany, was the second largest supplier of this product with India's value of imports standing at US$ 232.3 million. Other major import sources of drug formulations for India during 2016-17 included France, China, Switzerland, Indonesia, Brazil, Belgium, Denmark and Italy (Table 18).

Exhibit 33: India's Imports of Drug Formulations



Source: DGCIS ; Exim Bank Analysis

Table 18: India's Major Import Sources of Drug Formulations

2010-11		2016-17	
Import Sources	**Value**	**Import Sources**	**Value**
	(US$ mn)		**(US$ mn)**
Switzerland	410.2	USA	285.9
USA	147.5	Germany	232.3
Germany	85.3	France	141.9
China	83.7	China	135.2
Italy	56.8	Switzerland	105.6
France	54.2	Indonesia	86.7
Belgium	46.7	Brazil	75.1
Denmark	42.9	Belgium	72.7
UK	37.4	Denmark	71.8
Indonesia	32.9	Italy	71.7
Total	**1165.1**	**Total**	**1662.2**

Source: DGCIS ; Exim Bank Analysis

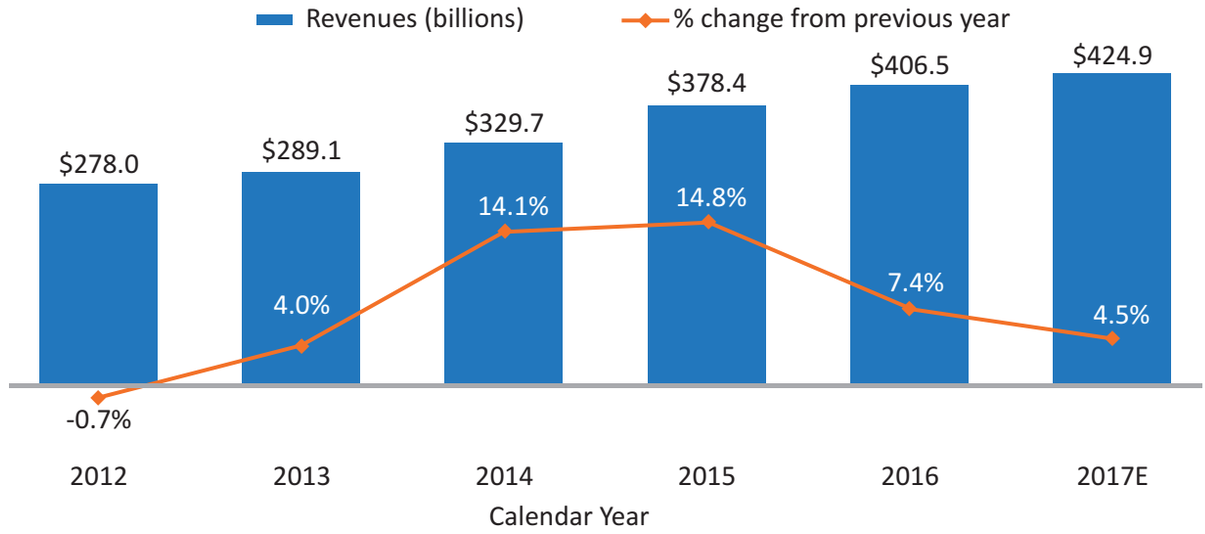
6. CHALLENGES AND STRATEGIES

PRICING PRESSURES

In the current scenario, the governments of several countries including Australia, France and Germany are laying emphasis on reducing the cost of pharmaceutical products and making it comparatively more affordable. Accordingly, there is considerable pressure on the pharmaceuctuial players to justify and substantiate the cost of their products through demonstrating innovative features and greater efficacy relative to peers. Several countries have been attempting drug price controls by way of reforms. For instance, the Government of China has made it mandatory for all the pharmaceutical procurements in government hospitals to be done through provincial centralized bidding system. Similarly, reform driven control on drug pricing by the Government is also followed in the UK, Japan and India.

At the same time, the increased rate of wholesale consolidation in the US market has led to considerable decline in the bargaining power of exporting countries, and has especially impacted the Indian players leading to pricing pressures. As per industry sources, during the year 2016, 3 players in the US pharma distribution market, viz. AmerisourceBergen Corp, Cardinal Health Inc. and McKesson Corp, together held nearly 85% of the market share. The total revenues since 2012 for these three wholesalers' is estimated to have reached US$ 424 billion in 2017, a 4.5 percent increase from the 2016 figure[24]. Over the past few years, these three companies have acquired many regional and specialty wholesalers within the United States leading to further consolidation and concentration in the distribution supply chain.

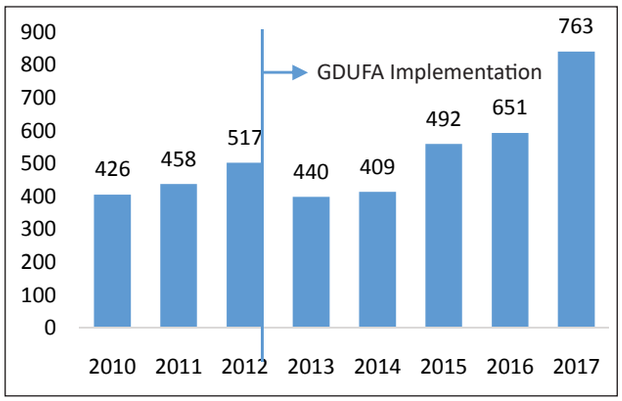
Exhibit 34: Revenues of Big Three US Pharma Wholesalers



Data include AmerisourceBergen, Cardinal Health and McKesson. Data represent calendar years. Revenue data include certain related businesses that are not reported separately. Revenue data exclude international drug distribution.
Source: Pembroke Consulting estimates

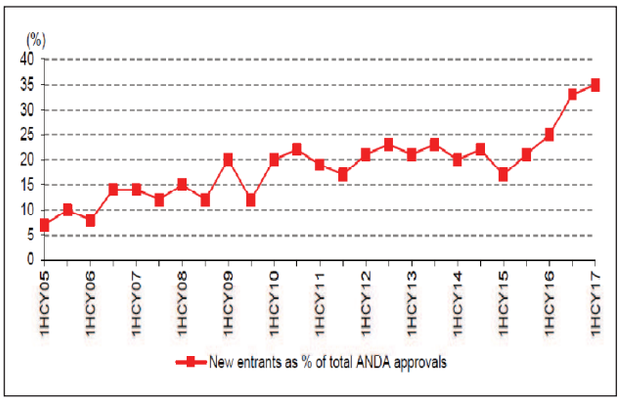
[24]Source: Drug Channels Institute

Exhibit 35: ANDA Approvals by US FDA



Source: USFDA

Exhibit 36: Approvals for New Entrants in the US



Source: USFDA

Table 19: Rise in the Number of Players per Drug in the US

Indian Player	Number of Competitors	
	2014	2016
Sun Pharma	2.5	4.5
Lupin	2.7	4.5
Dr. Reddy's	2.3	4
Cadila	2.4	3.5
Aurobindo	3.4	2.6
Torrent	3.7	7.5
Glenmark	4	4.5
Alembic	3.4	3.8

Source: USFDA

Moreover, the increase in the pace of ANDA approvals caused by the implementation of Generic Drug User Fee Amendment has led to a huge inflow of players in the US market, driving pressure on realisations. Owing to the GDUFA implementation, from the period October 2012, over 90% of the ANDA backlog has been cleared by the US FDA till the year 2017. In fact, the share of new entrants for approval of generics increased significantly from less than 20% in the first half of 2014 to 35% in the first half of 2017.

Yet another indicator is the increase in number of players per drug, which again has witnessed a sharp rise for most India generic players, at times more than doubling.

With the objective of addressing the present challenges, it is important for the pharmaceutical firms to attempt a variation in their strategy. They could focus on the development of new and innovator drugs and undertake novelty in drug delivery mechanisms. It is beneficial to target complex and chronic diseases which are high in value and have lesser competitors. The production of medicines for the treatment of rare diseases also serves as an opportunity for higher revenue. Moreover, players should try to devise ways by which replication of these new drugs and delivery mechanisms become complicated for their peers.

The pharmaceutical players could also focus on development of biosimilars which could provide new avenues of cost-effective growth, rather than restricting their attention to the generic drugs segment alone[25]. Those players who are engaged in therapeutic areas and produce high value products backed by strong research and development,

[25]Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials. But Biosimilars are not generics, and there are important differences between biosimilars and generic drugs. For example, the active ingredients of generic drugs are the same as those of brand name drugs. In addition, the manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug. By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

typically receive the highest earnings. In order to deal with the pricing pressure in the export markets, the Indian pharma firms can enter or expand their presence in the emerging markets. A comprehensive and effective expansion strategy and adoption of cost effective mechanisms will enable the pharmaceutical companies to maximize their benefits.

REGULATORY COMPLIANCE

Regulatory compliance has emerged as a critical challenge for the pharmaceutical industry, particularly in the regulated markets. Noncompliance is cost intensive, and may expose the companies to revenue losses, reputational risks, patient safety issues, criminal sanctions, and can jeopardize the future of the entire business unit. Compliance issues facing the pharmaceutical industry include government policies, drug safety, counterfeiting, information security and privacy, intellectual property protection, corruption and adulteration, and other third-party risks. Policies and regulatory frameworks of the US-FDA and EU's EMA have strong implications on the global pharmaceutical industry. While each country develops and enforces its own regulations, increasing number of countries are enhancing cross-border agency collaboration to strengthen regulatory decision making and enforcement actions. Drug safety standards, particularly those associated with quality systems implementation, data integrity, and validation of manufacturing and testing processes continue to tighten in many countries around the world.

Under such a scenario, meeting the evolving regulatory stipulations such as Current Good Manufacturing Practices (CGMPs) should be given prime importance by the pharmaceutical companies. Along with addressing the emerging legal requirements, the companies need to lay emphasis on following the policy of substantial compliance and risk management. The Indian pharma firms need to persistently evolve with the variations in the global regulatory compliances and accordingly adjust cost and resources to adhere to those standards. There are various instances of firms having to pay huge penalties for noncompliance during inspections, cases of data falsification and lack of meeting quality standards. Apart from the monetary loss, this also brings a bad reputation for the firm, driving reduction in customers and further opportunities.

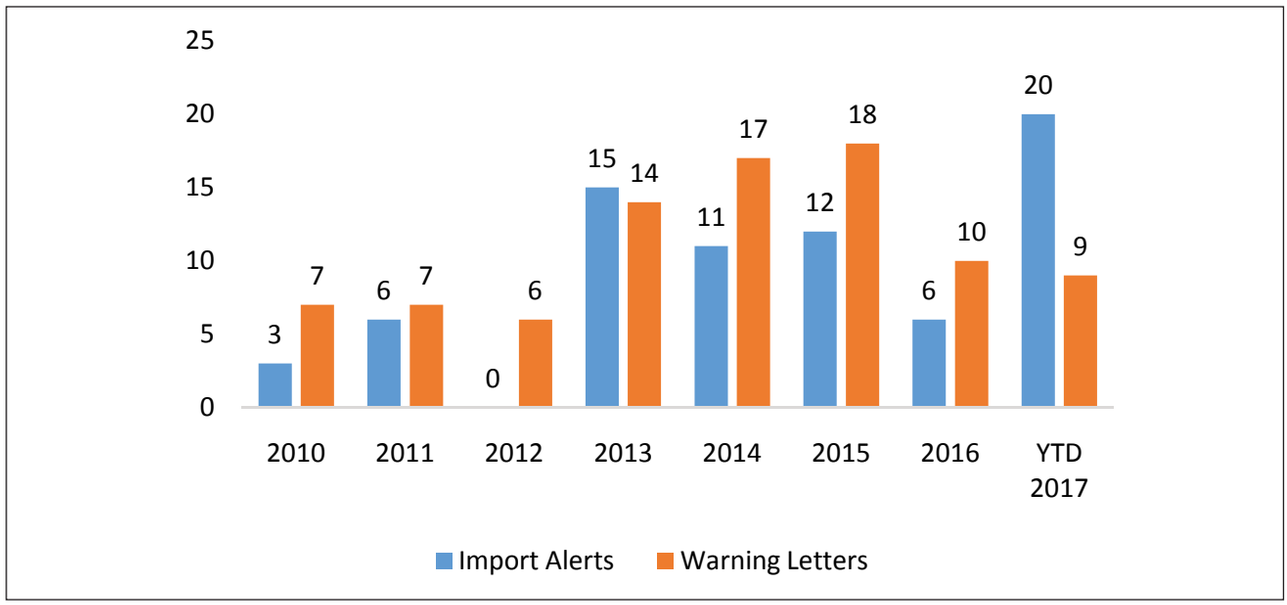
The Indian pharmaceutical players continue to face the challenge of compliance with the good manufacturing practices prescribed by the USFDA. Subsequent to receiving large number of warning letters and import alerts[26] during the period 2013 and 2014, the large sized players hired US based consultants with the objective of meeting the compliance requirements. This has resulted in them undertaking corrective measures and ensuring that the facilities are US FDA compliant. While the number of import alerts and warnings letters declined in 2016, the mid and small sized firms were still unable to meet the requirements in 2017. During the year 2017, majority of the import alerts were for the small players under the category 66-41[27].

FDA may issue a 'close-out letter' after an evaluation of the corrective actions taken by the firm in response to the warning letter has been done.

[26]Warning Letter: The manufacturing units which are engaged in the supply of drugs are frequently inspected by the FDA. At the completion of the inspection, if the investigator concludes that there exist violations of the Food Drug and Cosmetics Act, then a FDA Form 483 is issued to the management of the concerned firm. The FDA expects a response to the Form 483 observations within a period of 15 days. In the circumstance when the FDA is unsatisfied with the response furnished by the manufacturer in reply of the Form 483, then the FDA might issue a warning letter to the firm.
Import Alert: FDA Import Alert signifies that the product does not comply with FDA laws and regulations. As a result, the products will be detained at the border without physical examination, as there exist adequate evidence regarding the regulatory noncompliance of the product.

[27]Import Alert 66-41: This import alert represents the Agency's current guidance to FDA field personnel, regarding the manufacturer(s) and/or products(s) at issue. This alert is applicable when an evidence exists related to the marketing or promotion of unapproved drugs, to individuals residing in the United States. In this circumstance, the products should be considered for detention without physical examination.

Exhibit 37: Regulatory Alerts for India by US FDA



Source: USFDA

The Strategies to deal with this challenge include:

- Comprehend, Compare and Contrast Country-wise Regulatory Compliance

The pharmaceutical firms should be facilitated with an updated repository enumerating regulatory requirements notified by each country's regulatory organisation. The repository can be formulated in a manner that lists down the common requirements as well as the variations in standards, such that minimum set of regulatory adherence can be identified to address the compliance across various global agencies. In this regard, the measure of taking suggestions from local legal experts can be useful in having a clear understanding of the regulations. Such a repository should be a live one with virtually a real time updation of any regulatory changes.

- Appropriate Training to Stakeholders

For ensuring the compliance to standards, skill development of various stakeholders is crucial. Preparedness and proficiency in documentation and following statistical techniques as per regulatory requirements are also of considerable importance in this regard. The employees involved in regulations department should refer to inspection reports, annual reports as well as compliance statistics which are provided by the regulatory agencies. Moreover, participation in conference, seminars and trade shows which involve sharing of important presentations elaborating the regulatory requirements and trends on any further future development can be of great use.

- Retain Accurate and Complete Production Information

To demonstrate and justify that the manufacturing process being applied by the firm is in compliance with good manufacturing practices, it is essential for them to have a comprehensive record of their production information, which can be presented to the inspectors and auditors. It has been noted that Indian pharma firms rely on contract testing and production operations, with the intent of circumventing their engagement with the inspections held by the regulatory agencies. Nevertheless, the

regulatory authorities have pointed out that licensed manufacturer is accountable for the adherence of GMP standards for the products. Thus, the strategy of depending on contract manufacturers to avoid their accountability for data accuracy may not be appropriate. The use of interpreters during an inspection, which is also done in China, can be effective in addressing the language obstacles.

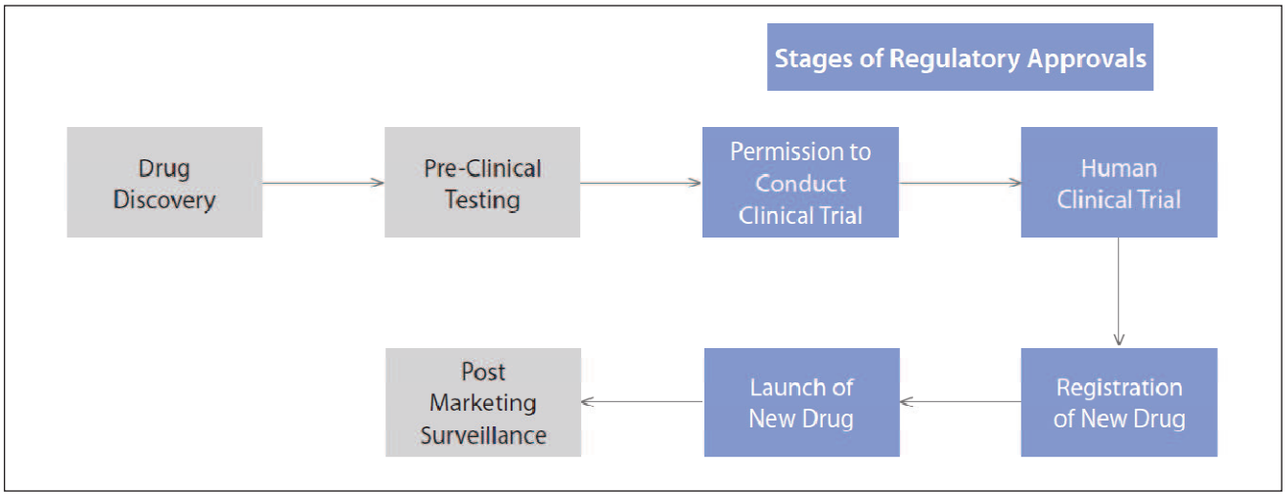
CLINICAL TRIALS

Clinical trials play an essential role in guaranteeing the safety in usage of drugs. India has been fortunate in being endowed with certain positive factors such as an extensive patient pool participants, investigators with expertise and several medical colleges which can be used as sites. The participation of India in global clinical trials rose from a mere 0.9% in the year 2008 to nearly 5% in the year 2013. Clinical trials held in India were the maximum during the year 2010, post which a fall was displayed which could be related with the global slowdown. Subsequent to this period, the major downfall in clinical trials in India can be noted in the year 2013, triggered by massive changes in Indian regulations concerned with clinical trials. India has not been successful in maintaining its performance in terms of clinical trials.

In 2013, there were certain modifications which were made to the regulatory regime of clinical trials in India. One major development in this regard was the need for the Ethics Committee to register with the Central Drug Standard Control Organisation. Some of the other reforms included the provision for examination of adverse events and procedures for compensation in case of clinical trial-related injury or death and audio-visual recording of the informed consent process. These amendments have resulted in an increase in transparency and enhanced control on the operations of the Ethics Committee (EC). However, there are various challenges which continue to impact clinical trials.

The lack of appropriate regulatory guidance on certain issues, dearth of adequate lucidity on various legal terms and the deficiency of sound communication strategy from the drug regulators have had adverse impacts. The global multinational pharma companies have become sceptical about the operations in India due to this uncertainty and lack of clarity[28].

Exhibit 38: Stages of Regulatory Approvals in Drug Development



Source: Challenges and Prospects for Clinical Trials in India, ICRIER

[28]Challenges and Prospects for Clinical Trials in India, ICRIER

Under the current regulatory framework, clinical trials can only be carried out at centres that have the appropriate facilities and are staffed with experienced investigators to carry out the trials. These institutes must also have institutional ECs that are registered with the Central Drugs Standards and Control Organization (CDSCO). Furthermore, the National Accreditation Board for Hospitals and Healthcare Providers (NABH), has set up standards that the ECs need to maintain, in order to get the accreditation to carry out trials in India. Notwithstanding this, there is a need for accreditation of clinical trial sites and principal investigators as well.

There is a skewed distribution which can be observed in terms of medical research in the country. During the year 2016, out of a total of 1083 registered EC, Maharashtra had nearly 23.9% concentration followed by Gujarat (11.5%) and Karnataka and Tamil Nadu with 10.3% each. However, the number of registered ECs in Jharkhand, Jammu and Kashmir, Sikkim and Himachal Pradesh was only 1. Moreover, there are certain states and union territories which do not have a single EC[29].

Another area of concern is that various medical colleges which are approved by the Medical Council of India to run post graduate courses do not possess registered ECs. There is a requirement of an approval from a registered EC for academic non-regulatory studies; thus there is a need for such a transformation accordingly.

The Strategies for this challenge are:

- Usage of IT Enabled Platforms:

The development of an IT enabled platform would empower the EC to scrutinise the clinical trial project at various stages all along the life cycle of the project. These initiatives have proven to be successful in various countries. In this regard, the NAHB and Forum for Ethics Review Committee (FERCI) can play a pivotal role in the progress of this plan of action. The eEC tool[30] can be further advanced and can be used for this objective. This tool which has been created by FERCI, facilitates institutions to forward their Ethics Committee Review and approval process in the CReATE platform.

- Good Clinical Practices Online Learning Module

The requisite capacity building and training on GCP by way of online mentoring through modules is being used in various developed countries including the US and the EU. The specialists from FERCI and the Indian Council of Medical Research (ICMR) can be requested to establish the modules with updated information. This coaching should be made obligatory for the existing as well as newly joined members in the Ethics Committees. Moreover, upon successful completion of the online learning course certificates of proficiency in GCP should be imparted, acting as an incentive.

- Drafting of Standard Operating Procedures

There should be the establishment of Standard Operating Procedures (SOP) for the reference of the ECs. This will facilitate the provision of a standard for the EC which can be used by them in their functioning. This SOP can also be amended in the future for betterment. National Accreditation Board for Hospitals and Healthcare Providers (NAHB) with the assistance of inputs from CDSA (Clinical Development Services Agency), FERCI and ICMR could undertake the drafting of standard operating procedures.

- Mandatory Accreditation of Ethics Committee

The NAHB and Quality Council of India in collaboration with other important stakeholders has created the draft accreditation standards for clinical trial sites, ethical committees and on the basis of which

[29]Ethics Committee in India: Past, Present and Future ; Urmila M Thatte, Padmaja A Marathe

[30]This tool enables institutions to move their Ethics Committees review and approval practices on to the CReATE Platform (IT enabled platform for facilitating Ethics Committee). Once on board, investigators can register with an institute and submit their studies/projects for Institutional Ethics Committee (IEC) approval. Once these are submitted to IEC, they will go through IEC staff verification and IEC members review and approval / rejection of project/submission.

inspectors and investigators have been mentored. The accreditation of ECs should be made obligatory. Moreover, the NAHB and Quality Council of India in collaboration with other experts should institute the formation of other accreditation bodies, to boost the accreditation mechanism for ECs.

- Establishment of Central Ethics Committee

With the objective of intensifying the scrutiny process and avoiding the differences that occur among different ECs overseeing a similar protocol, the suggestion of adopting a Central EC might seem beneficial. This measure has been advocated by the US Food and Drug Administration as well as the Human Research Protection. Depending on the regional boundaries, the various local ECs can opt for IT based tools in the translation of the informed consent form in vernacular languages.

- Monitor ECs Activities

The essential function of an ethics committee is to ensure the safety and protection of the participant volunteering for the clinical trial. An evaluation whether the ECs can be trusted and are loyal towards their primary objective is of supreme importance. In this consideration, the IRB Research Assessment's Tool (RAT) has been developed and was applied in the state of Gujarat. There should be an expansion in the employment of such tools. The composition of an EC is typically in adherence to the regulations, however the quality of project review, approval and persistent monitoring by the ECs needs an assessment.

- Improvement in Skill and Infrastructure Development

For development in this field, it is paramount that the standard of clinical research is upgraded particularly in government hospitals and institutions. There are various occasions wherein willing patients do not get the chance to participate in a clinical trial because of the poor infrastructure of the sites and unpreparedness of various investigators for their job.

- Intensify Public Awareness

The need of the hour is to boost the understanding of the public about clinical trials, their usage and the responsibility of people who participate in trials. The confidence of the people should be boosted that their participation in the clinical trial will help in the betterment of the lives of millions of other people.

Box 5: Digital R& D Transformation: Usage of Smartphones in Clinical Trials

Smartphones to Remotely Collect Neurological Measurements for a Multiple Sclerosis (MS) Trial

An app was connected to smartphone sensors (accelerometer, gyroscope, and magnetometer) to remotely monitor participants in an MS study and compare readings with in-clinic assessments. Through this app, the patients were instructed to undertake activities such as hand and wrist turning, gait and balance exercises, as well as cognitive tests to analyse their neurological activity. Moreover, data associated with the passive measurements of gait and mobility related to the patients was also collected by the app. The data from these sensors was then used to create a continuous picture of the progression of diseases. According to observations, it was revealed that results from remote patient monitoring were comparable to in-clinic assessments and, in some cases, were even more sensitive.

Smartphone Apps used to Measure Endpoints that matter to Rheumatoid Arthritis Patients

The feasibility of using mobile devices in collecting data concerned with rheumatoid arthritis patients, was tested by a biopharma company. This involved the development of an app which collected data from surveys and smartphone sensors. While in the morning, a patient answers questions, regarding length of joint stiffness and other metrics, simultaneously the phone's accelerometer records data from wrist motion exercises. As per the study, the raw accelerometer data could be converted into a score and was found to be more accurate as compared to the motion-scoring exercises conducted in a physician's office.

Source: Digital R&D Transforming the Future of Clinical Development; Dawn Anderson, Jonathan Fox, Natasha Elsner

DATA INTEGRITY

The Indian pharmaceutical industry has been experiencing a surge in the inspections undertaken by the global regulatory organisations. The importance given by these bodies to data integrity is increasing manifold. The lack of being able to fulfil this requirement has mandated the pharma companies to come out with novel strategies to strengthen their data integrity. It cannot be denied that it is essential for the pharmaceutical players to attempt assessment of the status of their data integrity and bring it in conformity to the standards demanded by international regulatory organisations.

With the objective of guaranteeing the safety of drugs, regulatory bodies such as the US FDA have laid down certain standards, namely the Good Manufacturing Practices. The organisations which comply with the GMP illustrate efficient manufacturing and monitoring procedures. However, to display this it is required that it is substantiated with appropriate data to effectively ensure traceability of the manufacturing process. In the pharmaceutical industry, data integrity is a crucial component and the organisation should be able to proficiently exhibit the integrity of data on the occasion of a regulatory audit. This segment becomes paramount as data is the basis on which the manufacturer of the drug is able to illustrate various details regarding the safety and quality of the drug.

Title 21 CFR Part 11 lays down the US FDA regulations related to the electronic records and electronic signatures, with reference to maintaining records and submitting information to the FDA. EU GMP Annex 11 applies to all forms of computerised systems used as part of GMP regulated activities. A computerised system is defined as a set of software and hardware components which together fulfil certain functionalities. In case of a computerised system replacing a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process[31].

If the concerned organisation is unable to comply with the regulatory investigation related to data integrity, it can lead to withdrawal of the drug from various markets and widespread loss of prestige. The various ways in which data integrity is compromised includes falsification of data, inappropriate recording of activities, representing already existing data as new, and deleting the data. The breach of data integrity can lead to consequences of warning letters and import alerts apart from other kind of penalties. On the occasion of import alerts, the US FDA has been suggesting that the Indian pharmaceutical companies should opt for involving third party auditors and consultants to undertake assessment of the data integrity and help them resolve the issues[32].

The Causes of data integrity issues are:

Dearth of Skilled Manpower: The lack of requisite workforce and the burden of enormous work pressure causes the recording of partially complete and incorrect data. One of the leading causes which results in data integrity breach is the dearth of skilled employees, particularly in the lower and middle sections of the organisation, and their incompetency in comprehending the FDA regulations and requirements. The dearth of requisite number of qualified workforce in the regulatory agencies of the country has added to the woes. While India has various drug manufacturing facilities, the number of inspectors are not proportionately available.

Preference of Quantity over Quality: The pressure of meeting targets and deadlines might be the reason for giving lesser than due importance to the recording of data. It is crucial on the part of the management to alert their employees about the significance of marinating accurate data. There are occasions when the employees are not taught the details related to GMP.

[31]European Commission Health and Consumers Directorate-General Public Health and Risk Assessment Pharmaceuticals
[32]Analysing the State of Data Integrity Compliance in the Indian Pharmaceutical Industry, EY

Table 20: Implications of Violating GMPs

Business Loss	Issuance of warning letters can lead to product recalls or import alerts, as well as a fall in the stock prices of listed companies
Reputational Damage	List of companies violating guidelines are posted on a regulator's website, making the information publicly available, which can be further picked up by the media, thereby tarnishing the company's reputation
Regulatory Influence	Additional inspections can be carried by other regulatory bodies or customers tarnishing the company's reputation
Competitive Disadvantage	Competitors can leverage this opportunity to enhance their market share
Diversion to Remediation and Increase in Attrition Rate	Diversion of management and employees' attention from their daily activities, to focus on Corrective Action and Preventive Actions. The lengthy remediation process tends to cost time, money and often loss of talent

Source: Analysing the State of Data Integrity Compliance in the Indian Pharmaceutical Industry, EY

Lack of Effective Training: As per industry sources, it has been reported that the trainings organised by companies are at times futile owing to language barriers. If the employees are unable to comprehend the knowledge imparted during training due to accent, the purpose of the training sessions gets defeated.

Inefficiency in Guidelines and Regulations: During the year 2013, the Ministry of Health and Family Welfare notified the Electronic Health Record Standards for India, with a further notification in the year 2016. In spite of the listing down of data protection guidelines, the decisions related to security requirements and selection of appropriate technology for the purpose of data protection is left to be decided by the organisations. The practice of maintaining digital record of the patients is rarely followed by hospitals in India[33].

The Strategies are as follows:

- Undertaking Audit Trails: There should be provisions to attempt computerised audit trails, which keep an account of the date and time along with the sequencing of events. Moreover, if any modifications are made to the records, then a note should be maintained regarding the prior entries, substantiating the rationale behind the changes. This method can be of great importance especially when there is a requirement to frequently create, modify or delete regulated records[34]. Internal as well as external examination of the data integrity sessions should be arranged to determine the loopholes and fix them accordingly. As a preventive measure, companies having a suitable past achievement record with the global regulatory bodies, should continue to access their data integrity for continuance of commitment.
- Ensuring Computer Security: To safeguard the integrity of data, ensuring the security of computer systems is indispensable. The responsibility of attempting any alterations in any segment of the computer system should be allotted to authorised personnel such that the records are safe. The periodic review of information should be organised regularly and backups should be maintained. Unauthorised access of the computer should be denied.
- Skill Development Sessions: The junior as well as mid-level staff should be imparted trainings in which the importance of data integrity and the FDA requirements should be highlighted. Certain technical procedures can be taught to enable them to achieve their task.

[33]Vision 2025 Unlocking India's Potential for Leadership in Pharmaceutical Innovation; PWC
[34]Strategy to Avoid Data Integrity Issues in Pharmaceutical Industry; The Pharma Innovation; Jain Sanjay Kumar

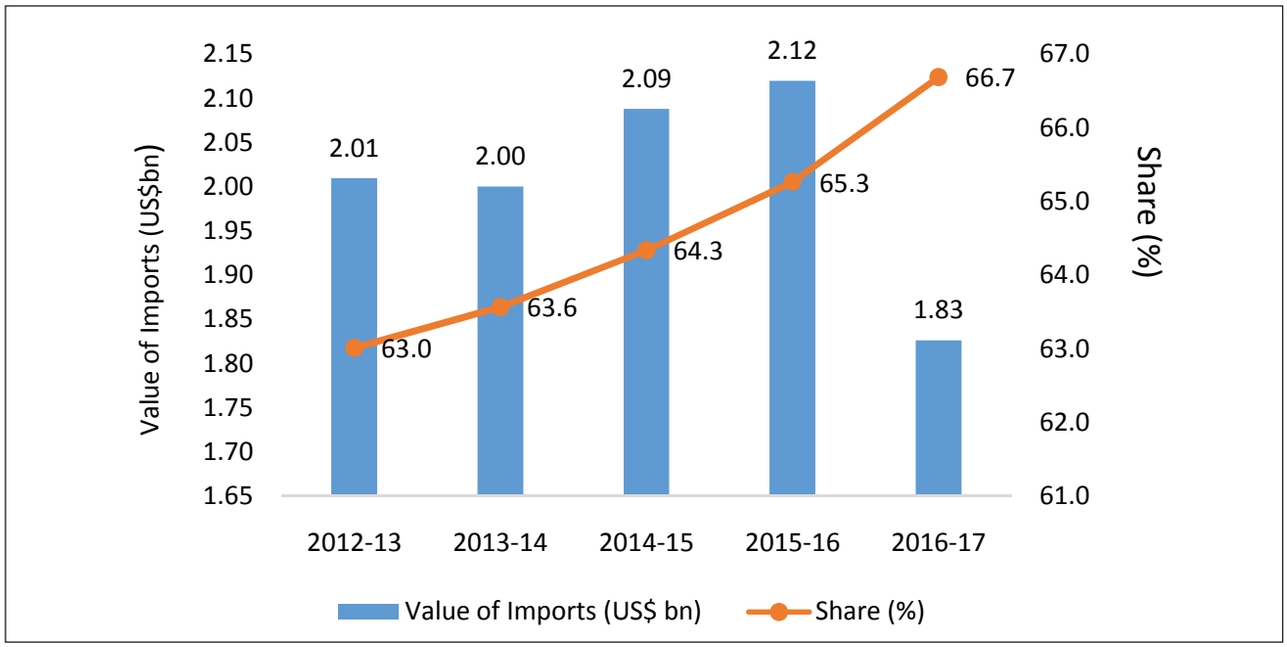
- Harmonization of Standards: An important strategy being adopted by countries across the globe is developing and transforming their domestic regulatory regime, with a view to put them in line with the global regulations. The regulations prescribed by major markets such as the US, the EU and Japan, are the important regulations dominating the global pharma industry. The attempt of aligning the domestic regulations with these global ones will make the task of data integrity more convenient and easy.

- Learnings from Other Countries: The Data Protection Acts which are implemented in other advanced countries can be referred to, such as the Health Insurance Portability and Accountability Act of 1996 in the United States. The Act in the UK, Clinical Practice Research Data Link (CPRD) has proven to be very constructive in observational data and research. Moreover, the exercise of central bodies to certify the electronic health record products should also be introduced. The implementation and operation can be in the nature of Certification Commission for Health Information Technology (CCHIT) which in the United States, approves the electronic health record products[35].

EXCESSIVE DEPENDENCE ON CHINA FOR DRUG IMPORTS

India is heavily dependent on China for bulk drug intermediates and APIs with the country accounting for nearly two-third of India's imports of such products. An over dependence on bulk drugs, active pharmaceutical ingredients and other raw materials from China, could have an unfavourable impact on the Indian pharmaceutical industry. Any discontinuance of supply could trigger a major loss for the pharma players. India has emerged as a key exporter of generic drug to various markets across the world. In order to maintain its manufacturing targets, India imports considerable quantities of bulk drugs and APIs from China. According to industry sources, the lower prices offered by Chinese suppliers has been one of the major reasons for the augmentation in imports. Owing to the price controls placed in India, the Indian manufacturers are unable to compete with their Chinese counterparts, who offer reduced prices.

Exhibit 39: Value and Share of India's Imports of Bulk Drugs and Intermediates from China



Source: DGCIS; Exim Bank Analysis

[35]Vision 2025 Unlocking India's Potential for Leadership in Pharmaceutical Innovation; PWC

Table 21: Major Import Sources of Bulk Drugs and Intermediates for India (2016-17)

Import Sources	Quantity	Value	Share
	Million KG	US$ mn	%
China	169.2	1826.3	66.7
The US	12.6	122.3	4.5
Italy	5.0	104.6	3.8
Germany	4.0	72.4	2.6
Singapore	19.0	63.0	2.3
Spain	3.5	58.3	2.1
France	5.1	46.9	1.7
Japan	7.3	45.3	1.7
South Korea	12.8	41.7	1.5
Denmark	0.0	40.7	1.5
Total	**278.8**	**2738.5**	**100.0**

Source: DGCIS; Exim Bank Analysis

During the year 2016-17, China had a share of 66.7% in the aggregate bulk drug imports by India, valued at US$ 1.83 billion. In terms of quantity of imports, China contributed nearly 60.7% of the total bulk drug imports. China was followed by the US, Italy and Germany, which have minute share in the aggregate imports (Table 21). An analysis of the five year period 2012-13 to 2016-17 reveals that China has continued to dominate the Indian imports of bulk drugs and intermediaries. The share of China has risen from 63% in the period 2012-13 to 66.7% in the period 2016-17.

The imports from China include metformin, analgestics, paracetamol, ranitidine, vitamin C and its intermediaries. Chemical synthesis based APIs or intermediaries such as paracetamol, metaformin, ibuprofen and quinolones are also imported[36]. The problem of immense reliance on China for various bulk drugs and raw materials needs to be tackled effectively, as any slight variation in their policies or relations with India, can result in a considerable downturn for the industry.

With respect to this issue, it is imperative for the Government and the industry body to strengthen the domestic active pharmaceuctuial ingredients market such that the need for imports can be circumvented. While the Indian pharmaceutical industry has evolved as a successful generic drug and formulations manufacture, the Chinese market's competitive advantage lies in the ability to provide low cost raw materials. The creation of a scenario by

Table 22: Global Innovation Index of Some Select Economies

	Global Innovation Index 2017		Human Capital and Research		Research and Development (R&D)		Researchers		Gross Expenditure on R&D (GERD)	
	(Rank)	(Score)	(Rank)	(Score)	(Rank)	(Score)	(Rank)	(Score)	(Rank)	(Score)
Brazil	69	33.1	50	35.9	29	37.2	55	8.3	32	26.9
China	22	52.5	25	49.2	17	58.5	45	14.1	17	48.5
India	**60**	**35.5**	**64**	**32.3**	**32**	**35.9**	**81**	**1.8**	**43**	**19.1**
South Korea	11	57.7	2	66.2	1	88.2	3	85.8	2	98.4
Russia	45	38.8	23	50	25	41.5	29	37.8	34	26.1
South Africa	57	35.8	60	32.8	39	27.1	65	5.2	48	16.6
UK	5	60.9	6	63.3	10	69.5	18	54.1	21	39.5
USA	4	61.4	13	57.2	4	78.8	20	51.2	10	65

Source: Global Innovation Index 2017

[36]Indian Pharmaceutical Industry : Challenges and Prospects; Exim Bank

Table 23: Global Competitiveness Index: R&D Innovation

Country	Capacity for Innovation		Quality of Scientific Research institutions		Company Spending on R&D		University – Industry Collaboration on R&D		Availability of Scientists and Engineers		PCT patents Granted/ million Population		Overall Innovation	
	Score	Rank	Score	Rank	Score	Rank	Score	Rank	Score	Rank	Score	Rank	Score	Rank
USA	6.0	2	6.0	5	5.9	2	5.7	2	5.7	2	176.5	10	5.8	2
UK	5.5	11	6.3	2	5.1	14	5.4	6	4.9	17	99.1	18	5.1	12
South Korea	4.7	35	4.8	32	4.4	28	4.4	27	4.5	38	249.5	5	4.8	18
India	**4.5**	**42**	**4.7**	**35**	**4.5**	**23**	**4.4**	**26**	**4.6**	**32**	**1.7**	**63**	**4.1**	**29**
China	4.5	44	4.6	36	4.6	21	4.4	28	4.7	29	17.7	30	4.1	28
South Africa	4.9	30	4.4	42	4.3	32	4.4	29	3.5	100	5.8	49	3.8	39
Russia	4.2	65	4.4	41	3.5	54	3.9	42	4.3	50	7.8	46	3.5	49
Brazil	4.1	73	3.7	77	3.4	62	3.4	70	3.6	90	3.4	53	3.2	85

Source: Global Competitiveness Report 2017-18, World Economic Forum.
Note: PCT- Patent Cooperation Treaty.

policy makers in the country which is conducive for boosting the domestic API market can be beneficial. Greater incentives for encouraging investments and financial support for achieving a robust domestic API industry is the key solution[37].

The modest cost of production and the grant of subsidy in China have been important instruments which have led to the development of the API segment in China. Moreover, the low-priced import fee in India, has also encouraged the imports. With the motive of restricting the Chinese imports, the policy makers can undertake the strategy of increasing import fee. Nevertheless, the most important measure in this regard would be to improve the domestic manufacturing base and also to diversify their import sources. An increase in the investment in research and development as well as infrastructural facilities will be constructive in this direction. The establishment of mega parks for active pharmaceutical ingredients will boost the domestic sector. The regulatory procedures in the country should also be simplified and made transparent for the ease of the API Manufacturers. The Government could consider incentivising formulation producers who select domestically produced APIs by taking them out of the purview of price control. This could incentivize them to rely on the indigenously produced raw materials whilst improving their bottom-line.

[37]Pharmabiz

RESEARCH AND DEVELOPMENT

India's gross expenditure on R&D has been low at just around 1 per cent of GDP. India currently ranks 60th out of 127 on the Global Innovation Index (GII) 2017, though this ranking has improved from 66th in 2016. Among the BRICS countries, only South Africa is behind India in R & D expenditure ranking (Table 22).

As per the Global Competitiveness Report 2017-18, India's capacity for innovation has been lower than that of many countries like the USA, the UK, South Korea, but better than China. In terms of University–Industry collaboration on R&D, India ranks better than all other BRICS countries and in terms of availability of scientists and engineers, it ranks better than other BRICS countries except China. However, in terms of patents applications per million population, India significantly lags behind other BRICS countries and in terms of company spending on R&D, India ranks marginally below China (Table 23).

There is extensive scope to initiate an increase in scientific research particularly in the healthcare and pharmaceutical sector. A vast majority of updated medical equipments and devices, diagnostics as well as examination and inspection tools are imported by

India, with Indian patients getting an access much later than their availability in the advanced countries.

An industry report undertaken during 2016, assessed the impact that public investment, intellectual property rights and drug pricing policies have on global life sciences innovation, taking into consideration 56 countries. In this assessment India secured the lowest position. This can be principally attributed to weak IP protections and dearth of biologics data exclusivity protection. Apart from this, the relatively less investment in healthcare related research and the stringent regulation on prices of pharmaceuticals which limit the revenue, have also been highlighted[38].

ABSENCE OF SINGULAR LEAD AGENCY TO OVERSEE PHARMACEUTICAL INNOVATION

In the present scenario, there exist no single authority for the construction and performance surveillance of public pharmaceutical research centres. The National Institute of Pharmaceutical Education and Research (NIPER) and various other public sector undertakings are under the purview of the Department of Pharmaceuticals, while the biotech parks are overseen by the Department of Biotechnology. Moreover, approximately 20 centres are affiliated to the Council of Scientific and Industrial Research (CSIR), and 32 research centres are governed by Indian Council of Medical Research

Table 24: Comparison of Indian Biotech Parks with that of Other Countries

Country	Innovation Score Card Rank	State of Cluster Development	No.of Employees	Total Companies	Academic Institutions
The USA	1	5	20,000 to 50,000	Minimum 100 companies to more than 1000 companies (Including major multinationals)	Development of clusters around major universities and research centres for e.g. Harvard, University of Massachusetts, Boston University and MIT in the Boston cluster, University of California around San Diego, University of San Francisco around San Francisco Cluster
The UK	9	10	1500 to 7700	Approx. 100	Built around major universities like Oxford, Cambridge while the cluster in London has collaboration with 28 Universities
Singapore	5	12	Approx. 4000	40 Corporate Research labs	
South Korea	23	31		30 to 300	Approx. 10
Japan	16	8	1500-7000	Approx.300	Kobe Biomedical cluster built around RIKEN which is Japan's largest research institution
India	51	27	500-1500	Less than 20 in most cases	No Specific Guidance to develop around centres of academic excellence

Source: Vision 2025 Unlocking India's Potential for Leadership in Pharmaceutical Innovation; PWC

[38]How National Policies Impact Global Biopharma Innovation: A Worldwide Ranking; ITIF April 2016

(ICMR). The absence of an apex institute to promote innovation is an important issue which needs to be tackled, as multiplicity of regulatory bodies adds to an increase in complications. In the case of Singapore, the lead public sector agency, the Agency for Science, Technology and Research is responsible for inducing economic oriented research to bolster scientific innovation and technologies[39].

INFRASTRUCTURAL ISSUES

Indian pharmaceutical industry also faces the challenge of inadequate infrastructural support such as lack of animal breeding facilities and good laboratory practices (GLP). Moreover, the deficiency of skilled laboratory technicians to supervise and administer the activities and decipher the information from tests has also been unfavourable. As per data, in the National Centre for Biological Sciences, there exist nearly 71 registered animal breeders, 36 GLP certified test facilities under the ambit of the National GLP Program and a single GLP certified protein categorisation lab.

There is dearth of appropriate clinical infrastructure which is caused by the shortage of experienced and qualified staff to get engaged in clinical trials. This is further exacerbated by the non-availability of a suitable curriculum, course work and training in this field. The lack of understanding of the personnel in efficient carrying out of clinical trials has been observed. Moreover, a large number of proficient scientist and doctors in India migrate to various other countries in search for better opportunities. In this regard, the success story of Korea can be underscored, with respect to superior clinical trial infrastructure. The Korea National Enterprise for Clinical Trial (KONECT) provides upgraded clinical trial services in three segments

- Fifteen regional clinical trial centres are supervised by the Clinical Trial Centre

Table 25: India's Rank in Global Competitvness Index (2017-18)

Secondary Education Enrolment Rate			Tertiary Education Enrolment Rate		
Country	**Rank**	**Value**	**Country**	**Rank**	**Value**
Belgium	1	166.8	Greece	1	113.9
Finland	2	149.5	Turkey	2	94.7
Sweden	3	140.5	South Korea	3	93.2
Australia	4	137.6	Singapore	4	92.2
The Netherlands	5	135.5	Australia	5	90.3
India	**97**	**74**	**India**	**88**	**26.9**
Quality of Education System			**Extent of Staff Training**		
Country	**Rank**	**Value**	**Country**	**Rank**	**Value**
Switzerland	1	6.2	Switzerland	1	5.7
Singapore	2	5.8	United States	2	5.5
Finland	3	5.8	Norway	3	5.4
United States	4	5.6	Luxembourg	4	5.4
Qatar	5	5.6	Singapore	5	5.4
India	**26**	**4.6**	**India**	**34**	**4.5**

Source: Global Competitvness Report (2017-18)

[39]Vision 2025 Unlocking India's Potential for Leadership in Pharmaceutical Innovation; PWC

- The staff engaged in the process are mentored and trained by the Clinical Trial Training Academy
- A special dedicated fund namely the Clinical Trial Technology Development Fund is granted by the Korean Ministry of Health and Welfare to ease innovation in this direction

Moreover, collaborations between KONECT and several privately run contract research organisations have enabled significant developments in the innovation fields. India should replicate this model to ameliorate the clinical trial infrastructure and promote productive and pertinent course structure in colleges and organisation to improve the skills of personnel and staff. The curriculum in medical colleges and research institutes should be modified to specialise in clinical trial and research including bioethics and regulatory science. There should be an increase in the allotment of funds for the construction of greater animal breeding facilities and an augmentation in the number of GLP certified public labs will be beneficial[40].

TALENT POOL REQUIREMENT

The performance of the research and innovation in the pharmaceutical sector is substantially contingent upon the talent pool in the country. It is mandatory to add on to the qualified professionals having domain knowledge. Along with such efforts, it is also important to constantly update the skills of the workforce such that they are able to adjust to the constantly changing demands of the global market. There is a mismatch between the supply and demand of skilled professionals which needs to be taken care of in order to restore India's competence in the pharmaceutical sector.

The Global Competitiveness Index (GCI) Report states that quality of higher education and training is crucial for economies to move up the value chain and go beyond simple processes and products. The index measures secondary and tertiary education enrolment rates as well as the quality of education as evaluated by the business leaders. The extent of on-job training is also taken into account as it is beneficial in upgrading the skill of employees. According to the GCI Report 2017-18, India scores relatively low and ranks 97th among 137 countries in gross enrolment for secondary education, and ranks 88th in gross enrolment for tertiary education. India also scored relatively low in availability of specialized training (Table 25).

One of the major trends noted is the dearth of doctoral candidates as well as graduates and post graduates in the field of science, technology, engineering and mathematics. Moreover, retention of the skilled workforce also intensifies the issue, as a vast majority of them migrate to the US and the UK. India's pharmaceutical industry is impacted by the lack of both quantity and quality of talent pool. Moreover, there are also cases of the education curriculum and system not being oriented towards the requirements of the industry.

Furthermore, the current research and development in the pharmaceutical industry in India is aimed at therapeutic diseases with a global orientation such as diabetes, cardiovascular diseases and those affecting the nervous system. Unfortunately, the diseases which are prevalent in the Indian context such as malaria and tuberculosis are not given adequate significance. There is an urgent need to promote innovative research in this domain.

Some of the Strategies include:

- There should be a rise in the funding program facilitating an augmentation in the amount of grants and scholarships as well as stipends being provided to the researchers in this field. A rise in scholarships for researchers and graduate and post graduate students will favourably impact pharmaceutical research.
- There should be enhanced provisions for transfers and internships, wherein the scientist and researchers enrolled in an university can have the experience of working in labs and the research

[40]Vision 2025 Unlocking India's Potential for Leadership in Pharmaceutical Innovation; PWC

and development department of pharmaceuticals firms, and even in other international research organisations. This will give them an exposure and experience in the area of pharmaceutical innovation. A separate entity or organisation should be established for the function of facilitating collaboration and association between the following stakeholders, namely the scientists and research organisations on the one hand and the industry bodies on the other.

- The collaboration of research organisations and universities with globally renowned organisations can improve the quality of research. The technology transfer, discussion and learnings from proficient experts internationally, and engaging in joint development and research programs will support Indian research.
- Putting in efforts towards improving the quality of education being imparted in the National Institute of Pharmaceutical Education and Research (NIPERs) will lead to remarkable developments in the drug development process.
- With the objective of retaining the talent pool in the country, it is essential to adopt the establishment of an encouraging and favourable scenario in the country with the delivery of sufficient and suitable salaries and incentives.

INTELLECTUAL PROPERTY RIGHTS

The protection of intellectual property acts a driver to encourage the pharmaceutical companies to undertake extensively expensive and superior quality research for innovation and developments in the field of medicines. With the possession of a patent, the inventor and innovator of the drug has the right over the invention and no other player is allowed to copy and see it for a particular defined period of time. The IPR structure in India has exhibited significant development post the event of India's IPR regime being in line with the TRIPS. However, there are various complications which still exist.

A vast majority of these patent activities are undertaken by the considerably large sized pharmaceutical firms including multinational corporations. Another trend noted is that the applications are expansively focussed on novelty in the method or procedure of production, and not on the product itself. The products related to applications are concerned with intermediaries and formulations with maximum contribution in modified-release dosage forms. The smaller companies are comparatively insignificant in terms of their research and development as well as innovation endeavours, which can be attributed to the dearth of technological backing due to insufficient funds. Thus, the Indian pharmaceutical SME firms do not engage in the IP activity. It is crucial for the SME units to build associations and collaborations with the research wings of public as well as large sized private organisations and focus on R&D and innovation.

It is very important to motivate and encourage Indian pharmaceutical firms to undertake an innovative approach concentrating on new drug discoveries, novel dosage forms along with new applications of already existing drugs. Measures such as reducing the expenditure involved in filing and the maintenance of patents and also providing assistance in the cost involved in litigation and associated legal formalities can be helpful.

DATA EXCLUSIVITY ISSUE

Data exclusivity refers to the protection of data which is engendered in the process of clinical trial of drugs and submitted to regulators for marketing approval. The details of this is listed in paragraph 3 of Article 39 of the TRIPs Agreement. The pharmaceutical players invest considerable time and resources to guarantee the safety and effectiveness of the drug in the process of clinical trial. This measure prevents the generic drug companies to utilize that confidential data and produce generic version of the drugs. So, various governments facilitate the pharma companies who have undertaken clinical trial, with Data Exclusivity

period, which typically ranges between five to eight years. Thus, data exclusivity is a representative of a compromise between the innovator drug producing companies and the generic drug producing companies, by which the innovator companies are granted a period of exclusivity. Nevertheless, once the exclusive period expires, the generic drug companies can use the data for their drug approval.

In India the Drugs and Cosmetics Act, 1940 (section 122E) includes provisions to provide data exclusivity for a 'new drug' for an aggregate period of 4 years up to the date of approval. A "new drug" is not defined as a patented drug but simply a drug which has not been used in the country to any significant extent. Like the United States, the Indian law requires an applicant for a new drug to engage in extensive testing and clinical trials. But this requirement may be waived for purposes of "public interest" or if the new drug has been approved and marketed for several years in other countries. Such a requirement is a standard norm to avoid duplication of trials in different jurisdictions which can result in increasing the cost and delaying the introduction of the drug in the market[41].

In the United States, the FDA approval of a drug is linked to the patent protection. Thus, on the occasion of a generic drug company application (ANDA), the application will be processed only on the condition that there is no valid patent on the same. This methodology of patent linkage creates hurdles in the entry of generic drug players in the market. This arrangement is beneficial for those countries who have companies which are majorly innovator drug producers. However, it can be unfavourable for countries like India, which typically have generic drug producing companies. In India, the marketing of a drug is not associated with its patent status. The advanced countries triggered by the demands of their pharmaceutical lobbies have been putting pressure on developing countries like India to observe data exclusivity, to continue their monopoly and prevent the generic companies to expand their market.

The application of DE implementation in all countries regardless of their socio-economic capabilities and manufacturing competencies is not a viable strategy. Taking into account, the economic incentives of originator companies and simultaneously giving priority to making affordable medicines accessible to the public, alternative approaches can be considered. These include preferential pricing, tax benefits and special benefits from originator companies for patients of least developed countries.

TECHNOLOGY TRANSFER

There are various important discoveries related to drugs which are initiated in the academic sphere, and for the development of the pharmaceutical industry it is vital to have a collaboration between academia and the industry. The transfer of technology between these two entities are essential and there should be adequate partnerships and arrangements to facilitate the same. In India, the earnings from technology transfer and the academia patenting rates are comparatively less. The Government of India has commenced the promotion and encouragement for commercialisation of intellectual property from the public research organisations; however, there are no acclaimed guidelines for the same.

The Bayh Dole Act which was enacted in the year 1980, has played a key role in enhancing the patenting activities in the universities established in the United States. This Act empowers universities as well as non-profit research institutions to own patent and commercialize inventions which have been undertaken under the ambit of funded research programs in the institutions. This measure has prompted various organisations to engage in extensive transfer of technology from the lab to the industry. Similar initiatives have been attempted by other countries as well. The Technology Transfer

[41]The Significance of the Data Exclusivity and Its Impact on Generic Drugs ; School of Law Texas A&M University

Promotion Act and the Technology Transfer and Commercialisation Promotion Act, has been successful in provision of support to the universities to boost the technology transfer. Japan's Industry Revitalisation Law also has a similar objective.

In addition, it is important to attract foreign investments in the pharmaceutical sector, especially in greenfield ventures. During the period April 2000 to December 2017, the cumulative FDI inflow into the Drugs and Pharmaceuticals sector stood at US$ 15.6 billion. However, a majority of investments have been made in the brownfield projects. The FDI Policy allows 100 per cent FDI through automatic route in greenfield pharmaceuticals and 74 per cent in brownfield FDI through automatic route and beyond 74 per cent through Government approval. FDI in brownfield projects, under both automatic and government approval routes, is further subject to compliance of conditions like the production level of National List of Essential Medicines drugs, R&D expenditure, transfer of technology. Indian pharma companies could leverage the FDI policy by having in-house R&D with forgen investment. To encourage FDI in R&D into India, the Government could consider a fixed minimum per cent of FDI into the pharmaceutical sector mandated for R&D investments. This will make India a global leader in pharma R&D and further strengthen its position in the pharmaceutical space.

Persistent rise in the demand for pharmaceutical products globally, is anticipated to boost Indian pharmaceutical players in the future. There are various factors facilitating the growth of the Indian pharma sector including rise in the ageing population and the proliferation of chronic diseases worldwide. Furthermore, governments in several developed economies are exercising curb on healthcare expenditure and extending their dependence on lesser priced alternatives, expanding opportunities for Indian pharma companies. The pharmaceutical industry is expected to grow at CAGR of around 7% during the period 2018- 2023. This growth can be attributed to the expected new launches by the large pharma players particularly in the generics segment. Moreover, the pricing pressure in the US market is predicted to diminish from the year 2019 onwards. Going forward, with appropriate strategies coupled with an enabling policy and regulatory environment, the Indian pharmaceutical industry has the potential to become a US$ 100 billion market with substantial export orientation by the year 2025.

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