



International Journal of Pharmacy and Analytical Research (IJPAR)

IJPAR | Vol.12 | Issue 4 | Oct - Dec -2023

www.ijpar.com

ISSN: 2320-2831

DOI : <https://doi.org/10.61096/ijpar.v12.iss4.2023.549-556>

Research



Regulatory issues for export and import of pharmaceuticals and biological products in India, Brazil, Switzerland

Eeramoni Prasanna Laxmi*, Dr. S. A. Sreenivas

Department of Regulatory Affairs, Sree Dattha Institute of Pharmacy, Nagarjuna Sagar Road Sheriguda, Ibrahimpatnam Rangareddy - 501510.

*Author for Correspondence: Eeramoni Prasanna Laxmi

Email: Prasanna863977@gmail.com

	Abstract
Published on: 17 Oct 2023	<p>This article mainly focuses on the drug import and export from India, Brazil, Switzerland. Now a day's foreign pharmaceutical companies have a better legal foundation for releasing new drugs. The medical regulatory system has become more complicated, and new drugs can take a year or more to be approved for marketing. Ever-changing laws and regulations are driving demand for regulatory affairs professionals to provide the current needs of industries for the global competition and who can help pharmaceutical companies to effectively bring their medical products to the countries. In today's competitive scenario, the reduction of the time taken to launch the product is imperative and hence vital for company's success. Biological products produced by biotechnological methods from living organisms are a diverse category derived. With the advent of new biotechnology techniques, the development of biological products has become safer and more consistent. A regulatory framework controls the manufacture, development, and use of biologics in clinical practice. Regulations are sets of standards and norms that manufacturers must follow to ensure maximum public protection from the developed products. Biological product regulation involves the overall management system to secure high levels of safety and quality of biological products.</p>
Published by: DrSriram Publications	
2023 All rights reserved.  Creative Commons Attribution 4.0 International License.	
	Keywords: pharmaceuticals, drugs

INTRODUCTION

Biological products, as defined by the World Health Organization (WHO)¹ are medicines obtained from microorganisms, blood or other living tissues whose manufacturing procedures may include one or more of the following elements: growth of microorganism, strains in different types of substrate, use of eukaryotic cells, biological substances extracted from tissues, including human, animal and plant tissues, and also products obtained by recombinant DNA or hybridoma technology, and the propagation of microorganisms in embryos or animals, among others.² In its most recent definitions, the WHO includes the following medicines as biological products: vaccines, allergens antigens, hormones, cytokines, enzymes, derivatives of human blood and plasma, immunological sera,

monoclonal immuno-globulins, antibodies, fermentation products (including products made by recombinant DNA technology) and reagents employed for in vitro diagnosis. Medicines of biological origin constitute one of the largest sectors of growth of the pharmaceutical industry, and their regulation presents major challenges. Some of these challenges are related to the inherently variable nature of the source materials and the manufacturing methods used [4e6]. Likewise, there is a need for analytical methods, mostly bioassays, for facilitating the characterization of biological products. The use of these methods involves additional special efforts in their standardization and implementation. Unlike conventional medicines which are produced using technologies able to provide a high degree of homogeneity and manufacturing consistency, the manufacture of biological products involves processes that are difficult to reproduce, and the use of natural sources, such as cell cultures or the extraction of materials from live organisms which tend to generate heterogeneous products in the absence of strict manufacturing controls. Thus, one of the main challenges in the manufacture of these products is to achieve consistency in their production. Therefore, the manufacture of biological products implies the need for a comprehensive system of quality management which covers all staffs and stages in the production, to ensure the quality, safety and effectiveness of the final product. The development of such products requires the participation of regulatory agencies in a role different from that which they usually play in relation to conventional medicines. The development of such specialized production methods requires a very specialized process control which rests mainly on the manufacturer. Likewise, provision of evidence of specific quality control in the finished product becomes very complex and sophisticated, and may even have to be tailored for each particular product, which can diminish the value of prescriptive laboratory tests. That is why the assessment of compliance of Good Manufacturing Practices (GMP), the demonstration of effectiveness in clinical trials, and the post-marketing surveillance, become fundamental pillars for the product's approval by regulatory agency. At present, there are multiple reference documents issued by WHO, as technical report series which are product specific, training manuals, guidelines and other general documents, which provide guidance and direction to the regulators, manufacturers and users of biological medicines. While many of these documents are oriented toward production and control of vaccines as part of the category of biological products, there are also documents aimed at production and control of biotechnological products made by recombinant DNA technology [6e9]. Likewise there are reference preparations available, such as cytokines/growth factors, endocrine substances and recombinant coagulation factors [12]. Despite current availability of multiple reference documents issued by the WHO [6e11], European Commission of Medicines (EMA) [13e24], and by the International Conference on Harmonization (ICH) [25e28], related to biotechnological and biological products, there is no consensus among these reference institutions for the countries of the Region, on some important definitions used, and the mechanisms for the regulation of biotechnological products. As an example, we can cite that the WHO uses the name therapeutic biological medicines, while the EMA and the ICH use the names biological medicinal products containing biotechnology-derived proteins and biological/ biotechnological products, respectively, for referring to the same type of biological product.³

Biotechnology has brought a considerable input into the development of human healthcare. About 25 years ago biological products used for treating diseases were mostly obtained by extraction from human or animal tissue. For example, insulin extracted from cattle or pigs has been used to treat diabetic patients for decades before recombinant human insulin was introduced⁴. The use of biotechnological products such as recombinant proteins overcomes the problems of extracting sufficient amounts from natural sources as well as possible intolerances to animal proteins. Furthermore, concerns regarding contaminants such as the bovine spongiform encephalopathy, commonly known as mad cow disease, increased the demand for recombinant products in order to replace available extracted products.⁴ Another important example of biotechnological products are monoclonal antibodies. Due to their selective binding to unique antigens they are widely used for protein purification but also for therapeutic purposes.⁴

Biotechnology has evolved a broad variety of divergent medicinal products including hormones and blood factors as well as vaccines and monoclonal antibodies for chronic, acute and rare diseases, such as some cancers, especially breast cancer, hepatitis C, chronic renal failure, haemophilia, diabetes, growth deficiency, multiple sclerosis, rheumatoid arthritis and Crohn's disease.⁵ Within the pharmaceutical market the biopharmaceutical sector is significantly growing. In 2007 biologics accounted for 94 billion US\$ representing around 15% of all sales within the pharmaceutical sector.⁵ At least 500 potential biopharmaceuticals are currently being evaluated in clinical trials. Vaccines and monoclonal antibody-based products represent the two largest product categories.

Thus, biotechnology has been recognised as a key technology of the 21st century in many sectors and human health can be regarded as one of the main application areas.⁶ The European Commission adopted in 2002 a strategy containing a 30 point action plan in which the European

member states were requested to foster innovation of biotechnology in the pharmaceutical sector. Similarly, a focus was set on better regulation and risk communication.⁶

Emerging fields of biotechnology are therapies based on gene therapy, somatic cell therapy or tissue engineering.⁷ Such innovative therapeutics are summarised under the term advanced therapy medicinal products (ATMP). ATMPs offer new opportunities for treatment of rare or previously untreated diseases or early detection of dysfunctions of the human body or others, e.g. skin replacement products.⁷

In 2007 a regulation for ATMPs has been adopted to overcome the lack of a clear and coherent legal framework and to boost research in this field.⁸ The intention was to harmonise the regulation of these therapies and to adapt technical specificities to ATMP products. The regulation involves a classification procedure to facilitate the classification of these products. This is important for the companies when the classification of the case is ambiguous as the application of ATMP requires a lot more data regarding quality and safety compared to other biological products.⁸

Aim and objectives

This article mainly focus on regulatory issues for export and import of pharmaceuticals and biological products. Exports and imports are important for the development and growth of national economies because not all countries have the resources and skills required to produce certain goods and services.

Why is import and export important?

Exporting and importing helps grow national economies and expands the global market. Every country is endowed with certain advantages in resources and skills. For example, some countries are rich in natural resources, such as fossil fuels, timber, fertile soil or precious metals and minerals, while other countries have shortages of many of these resources. Additionally, some countries have highly developed infrastructures, educational systems and capital markets that permit them to engage in complex manufacturing and technological innovations, while many countries do not.

Imports are important for businesses and individual consumers. Countries like Ellen's often need to import goods that are either not readily available domestically or are available cheaper overseas. Individual consumers also benefit from the locally produced products with imported components as well as other products that are imported into the country. Oftentimes, imported products provide a better price or more choices to consumers, which helps increase their standard of living.

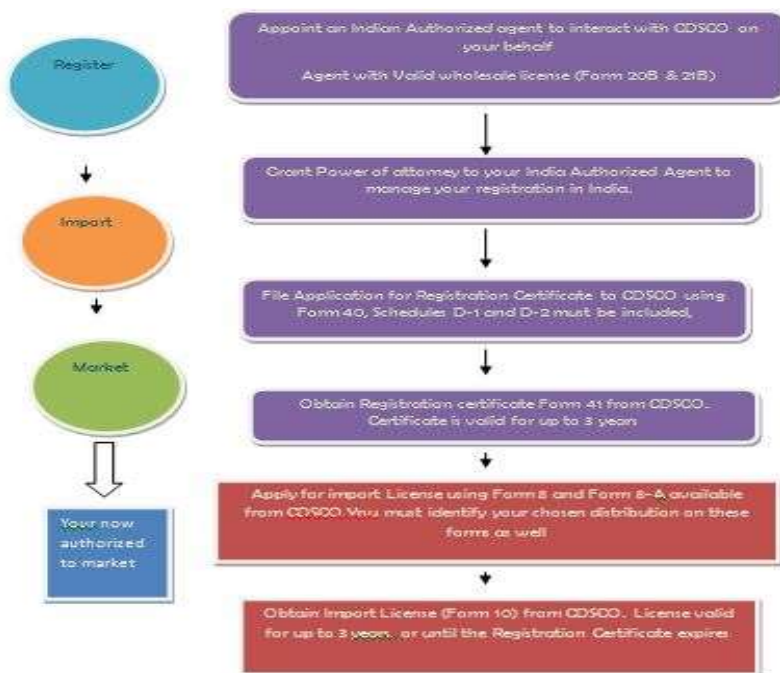


Fig 1: Import of Drugs

Countries want to be net exporters rather than net importers. Importing is not necessarily a bad thing because it gives us access to important resources and products not otherwise available or at a cheaper cost. However, just like eating too much candy, it can have bad consequences. If you import more than you export, more money is leaving the country than is coming in through export sales.

On the other hand, the more a country exports, the more domestic economic activity is occurring. More exports means more production, jobs and revenue. If a country is a net exporter, its gross domestic product increases, which is the total value of the finished goods and services it produces in a given period of time. In other words, net exports increase the wealth of a country.⁹

All around the globe, People are in need of medicines; some of the medicines are manufactured and available to them locally. For the remaining percentage the drug has to be imported from other countries. This emphasizes the trade of the drugs from one place of the world to another. Such a trade must be regulated in either way, both ethical and business oriented. Some of the organisations which regulate Pharma Business are World Trade Organisation (WTO), International Trade Organisation (ITO), and World Health Organisation (WHO). Apart from this, every country has its own laws and legislations for the purpose¹⁰.

India occupies a third largest position in the world in the field of Pharmaceutical industry. These industries are regulated by the Ministry of Health & Family Welfare and Ministry of Chemical & Fertilizers. Despite of its position in Pharmaceutical market and its growing economy, a well sophisticated Research and Development is not affordable due to various reasons. To overcome this pitfall, India opens up its pharmaceutical market to MNC's and it encourages the trading of the drug in and out of the country. Most of the drugs for the Indian market are imported from the European Union followed by North America and Asia. India has a special policy for the purpose of Import and Export called as "EXIM" policy. This policy gives way to quantitative as well as qualitative improvements in the field of Research and Development activities.

The Central Drugs Standard Control Organisation (CDSCO) regulates the import and export of the drugs in the country, through 11 Port offices located in different parts of the country. CDSCO regulates the manufacture, sale, import, export, and clinical research of drugs in India by the following rules and acts.

Drugs and Cosmetics act, 1940 and Rules, 1945.

Pharmacy act, 1948

Drugs and Magic Remedies act, 1954.

Medicinal and Toilet Preparation act, 1956.

Narcotic and Psychotropic Substances act, 1985.

The Drugs (Prices Control) order, 1995.

The CDSCO also work through state authorities. While, the central authorities are responsible for approval of new drugs, clinical trials in the country; laying down the standards for the drugs control over the quality of imported drugs coordination of the state drug control organisations; the state authorities regulates manufacture, sale and distribution of drugs, licensing drug testing laboratories, approving drug formulations for manufacture, carrying out pre and post licensing inspections, for the drugs manufactured and marketed in the respective states^{10,11,12}

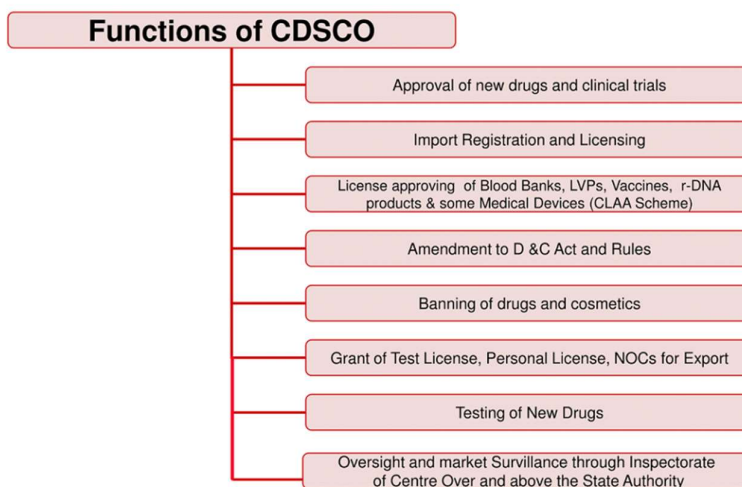


Fig 2: Functions of CDSCO

The new patent regime has ushered in the era of product patents for the pharmaceutical sector, in line with the obligations under the World Trade Organization (WTO) and Trade- Related Aspects of Intellectual Property Rights (TRIPS) Agreement. As a result, the Indian pharmaceutical industry has become self-reliant in several areas and has developed a sounder and technologically advanced R&D segment.

The industry offers several opportunities for investments and trade owing to the following advantageous features:

Self-reliance displayed by the production of 70% of bulk drugs and almost the entire requirement of formulations within the country;

Low cost of production and R & D of quality bulk drugs and formulations

Strong scientific, innovative and technical manpower

Increasing balance of trade in pharma sector.

Efficient and cost effective source for producing generic drugs, especially the drugs going off patent in the next five years.

Excellent center for clinical trials in view of the diversity in population.

Fast growing biotech industry which has great potential in the international market.

Procedure for Import and Registration of Drugs

Form and Manner of Application

Import License

An application for an import License shall be made to the licensing authority in Form 8 for drugs excluding Schedule X, and in Form 8-A for Schedule X drugs; either by the Manufacturer or by the Manufacturer's agent in India who is having the wholesale license for sale or distribution of drugs and shall be accompanied by a License fee of one thousand rupees for a single drug and one hundred rupees for each additional drug and by an undertaking in Form 9 duly signed by or on behalf of the manufacturer.

Any application for import licence in Form 8 or 8-A, which shall be accompanied by a copy of Registration Certificate issued in Form 41 under Rule 27-A; in the case of emergencies the issue of Import License by the central government in Form 10 or 10-A without issuance of Registration Certificate under Rule 27-A, for reasons to be recorded in writing.

A fee of two hundred and fifty rupees shall be paid for a duplicate copy of licence, if the original is defaced, damaged or lost.

Registration Certificate

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

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

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

(ii). A fee of one thousand US dollars shall be paid along with the application in Form 40 for the registration of a single drug meant for import into and use in India and an additional fee at the rate of one thousand US dollars for each additional drug.

The fees shall be paid through a Chalan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110 001 or any other branch or branches of Bank of Baroda, or any other bank, as notified, from time to time, by the Central Government, to be credited under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104- Fees and Fines"; in the case of any direct payment of fees by a manufacturer in the country of origin, the fees shall be paid through Electronic Clearance System (ECS) from any bank in the country of origin to the Bank of Baroda, etc. The applicant shall be liable for the payment of a fee of five thousand US dollars for expenditure as may be required for inspection or visit of the manufacturing premises or drugs, by the licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority under rule^{13,14}.

The applicant shall be liable for the payment of testing fee directly to a testing laboratory approved by the Central Government in India or abroad, as may be required for examination, tests and analysis of drug. A fee of three hundred US dollars shall be paid for a duplicate copy of the Registration Certificate, if the original is defaced, damaged or No Registration Certificate shall be required under these rules in respect of an inactive bulk substance to be used for a drug formulation, with or without Pharmacopoeial conformity¹².

Licenses for of drugs manufactured by a single Applicant

Import

A single application may be made, and a single License may be issued, in respect of the import of more than one drug or class of drugs manufactured by the same manufacturer. (Provided that the drugs or classes of drugs are manufactured at one factory or more than one factory functioning conjointly as a single manufacturing unit: Provided further that if a single manufacturer has two or more factories situated in different places manufacturing the same or different drugs a separate License shall be required in respect of drugs manufactured by each such factory.).

Registration Certificate

A single application may be made, and a single Registration Certificate in Form 41 may be issued in respect of the import of more than one drug or class of drugs, manufactured by the same manufacturer.

Specified before a license in form 10 or form 10-a is granted:

A License in Form 10 or in Form 10-A shall be granted by the licensing authority having regard to-

The premises, where the imported substances will be stocke

The occupation, trade or business ordinarily carried out by the applicant:

That the applicant has not complied with the provisions of the Act or these rules, or

That by reasons of- His conviction under Narcotic Drugs and Psychotropic Substances Act and Previous suspension or cancellation of the License granted to him.

Any person who is aggrieved by the order passed by the licensing authority 4.

Grant

Import License

On receipt of an application for an import License in the form and manner prescribed in Rule 24, the licensing authority shall on being satisfied, that, if granted, the conditions of the License will be observed, issue an import License in Form 10 or Form 10-A, as the case may be.

A License, unless, it is sooner suspended or cancelled, shall be valid for a period of three years from date of its issue and for a fresh license is made three months before the expiry.

Registration Certificate:

On receipt of an application for Registration Certificate in the Form and manner specified in rule 24-A, the licensing authority shall, on being satisfied that, if granted, the conditions of the Registration Certificate will be observed, issue a Registration Certificate in Form-

If the applicant does not receive the Registration Certificate within the period as specified in provision to sub rule (1), he may appeal to the Central Government.

A Registration Certificate, unless, it is sooner suspended or cancelled, shall be valid for a period of three years from the date of its issue and for a fresh Registration Certificate is made nine months before the expiry of the existing certifica

Suspension and cancellation

Both the Import License and Registration Certificate will be suspended or Cancelled, if the manufacturer or licensee fails to comply with any of the conditions, the licensing authority may after giving the manufacturer or licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel it for such period as it thinks fit either wholly or in respect of some of the substances to which it relates. The drugs in the schedule C and C1 are prohibited for import into the country after the expiry of potency of the drug product. If the drug is banned in the country of origin then it is prohibited from importing into the country except for the purpose of Examination, test or Analysis¹⁶. Imported Drugs: Drug shall be packed and labelled in conformity with the rules parts IX and X and also Schedule F (1), in the case of drugs for Veterinary use is Part XII.

Packing of Patent or Proprietary Medicine

Patent or proprietary medicines shall be imported in bulk containers, applicant need to get permission from the licensing authority at least three months prior to the date of import and the validity will be twelve months from the date of issue.

CONCLUSION

The process of Import & Export of Drugs in any country including India is a lengthy process involving the various reviewing and registration processes; as a result lot of inputs are required to achieve the core objective of supply of medicine to the public. The various regulatory requirements, licensing of product and different kinds

of application forms that are required to taken into considerations for the biologic product manufacturing, import, marketing and sales.

ATMPs comprise therapeutic products based on nucleic acids, cells and tissues believed to have a major impact on human health. In principal, the classification in these groups is necessary and including products with similar risk potential. However, the classification shows weaknesses because it is limited to products with certain therapeutic aspects and a specific set of active substances. Unfortunately, other biological medicinal products having similar function or effect mechanisms in the human body are not included. Additionally, including products of further new technologies with similar risk potential such as transgenic animals would have been useful. A classification of ATMPs in low and high risk groups may be considered. A major advantage of this new Regulation of ATMPs is that the classification procedure will be performed by a central committee leading to harmonised decisions regarding the classification.

The rules are very clear prescribing the procedure to be adopted in this regard however; it is a tedious task to follow the procedures systematically and to meet the requirements. Latest amendments are given by the CDSCO according to the current Laws and Trading strategies for the approval for Import/Export in India. "Approval Process for Import and Export of Drugs in India" gives an outlook on the entire process of getting a Drug Imported/Exported in India. The procedure and requirements vary considerably depending on the status of the Drug Applied.

Brazilian Regulation on Imported Goods and Products for Sanitary Surveillance, mainly for pharmaceutical products and food, adopting definitions, categories of imports, registration of the import license, among others. According to the Technical Regulation on Imported Goods and Products for Sanitary Surveillance, imported products subject to sanitary surveillance intended for trade, industry or direct consumption, shall have ANVISA's consent for importation.

Even though it is one of the largest pharmaceutical markets, it has its challenges. For example, exporting of drugs to Brazil is a difficult task as it takes over couple of years for registration and further inhibition is that all communication should be done in their native language which is Portuguese.

Swissmedic is the national authorisation and supervisory authority for drugs and medical products. The agency ensures that only high-quality, safe and effective medical products are available in Switzerland.

The requirements for any drug to be approved for Import/Export as a New Drug for the first time are more stringent & informative than the requirements for an already approved Drug which are considerably relaxed.

Exports and imports are important for the development and growth of national economies because not all countries have the resources and skills required to produce certain goods and services. Nevertheless, countries impose trade barriers, such as tariffs and import quotas, in order to protect their domestic industries.

ACKNOWLEDGEMENT

The Authors are thankful to Sura Labs, Dilshuknagar, Hyderabad for providing the necessary facilities for the research work.

REFERENCES

1. World Health Organization. Training manual: licensing, lot release, laboratory access; 2001.
2. World Health Organization. Annex 1: good manufacturing practices for biological products. Geneva: WHO; 1992. Technical Report Series: 822
3. World Health Organization [Homepage]. Geneva: The Organization; 2008 [cited on February 10th 2008]. Biologicals, Available from <http://who.int/biologicals/areseen>
4. Walsh G. Biopharmaceuticals, Biochemistry and Biotechnology. John Wiley and Sons Ltd. **Second Edition**, 551 pages (2003).
5. Walsh G. Pharmaceutical benchmarks 2010. *Nat Biotechnol.* **28**, 917-924 (2010).
6. The Commission of the European Communities. Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions on the mid term review of the Strategy on Life Sciences and Biotechnology. <http://ec.europa.eu>. Doc.-Ref.: COM(2007) 175 final, **10.04.2007**, p. 1-12 (2007).
7. Schneider, C.K. and Celis, P. Opinion: Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Discov.* **9**, 195-201 (2010).
8. Jekerle V. et al. Legal basis of the Advanced Therapies Regulation. *Bundesgesundheitsbl.* **53**, 4-8 (2009).
9. K. Dubey, Rajesh Kumar and Pramila Tripathi, Global promotion of herbal medicine: India's opportunity - *Current Science*, 2004, 86(1)
10. World Health Organization (2012) Depression. http://www.who.int/mental_health/management/depression/en/

11. Economic Times (2014) Documentation. http://articles.economictimes.indiatimes.com/2014-05-06/news/49661672_1_toansa-usfda-indian-drug-makers
12. Hollister LE and Csernansky JG: Clinical Pharmacology of Psychotherapeutic Drugs. Churchill Livingstone, New York, Third Edition 1990.
13. Vijay Malik, Law Relating Drugs & Cosmetics Act 1940 and rules 1945 24th Edition, 2014.
14. Central Drugs Standard Control Organization (2014) Import & Registration Division <http://www.cdscsco.nic.in/forms/ShowSearchResult.aspx?Search=import>
15. Drugs and Cosmetic Act (2012) Import of New drug <http://www.cdscsco.nic.in/forms/ShowSearchResult.aspx?Search=clinical%20trials>
16. Sumit Kumar, Rishabh Panwar and Upendra Singh, Regulatory Affairs in the Pharmacy Curriculum, International Journal of Research and Development in Pharmacy and Life Sciences, 2013, 2(6): 690-698
17. Uma Vasireddy, G. Krishna Mohan, M. Lakshmi Narasu and P. V. Appaji, Impact of India's formulation and bulk drug registrations with U.S. FDA on its exports: A stochastic analysis - Scholars Research Library, Der Pharmacia Lettre, 2011, 3 (4):84-100
18. Ravi Kiran and Sunita Mishra, Research and Development, Exports and Patenting in the Indian Pharmaceutical Industry: a Post TRIPS Analysis, Eurasian Journal of Business and Economics 2011, 4 (7): 53-67.
19. Shamnad Basheer and Mrinalini Kochupillai, 'Exhausting' Patent Rights in India: Parallel Imports and TRIPS Compliance, Journal of Intellectual Property Rights, 2008, 13, September 2008:486-497. 22.
20. Pulok K. Mukherjee and Atul Wahile - Integrated approaches towards drug development from Ayurveda and other Indian system of medicines – Journal of Ethnopharmacology, 2006, 103(1): 25-35.