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REGULATORY REQUIREMENTS FOR THE DRUG APPROVAL PROCESS IN US, EUROPE AND INDIA

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ABSTRACT

The discussion seeks to review drug product registration and various aspects of gaining approval from the United states food & drug administration (USFDA), European medicines agency (EMA) and Central drug standard control organization (CDSCO) for a new drug in order to obtain a marketing authorisation in United States, Europe, India and their successful role in enhancing the standards set by them. Then the specific regulatory agency must approve all new / generic drug products can be put on to the market. Through regulation, all new drugs should be proved safe and effective before they can be licensed by the relevant marketing regulatory organization. USFDA is the regulatory body responsible for food and drug product safety enforcement in the US. EMA is the governing agency responsible for food and drug product safety legislation in Europe. CDSCO is the regulatory body responsible for food and drug product safety legislation in INDIA. Drug approval process in USFDA involves submitting of an Investigational New Drug Application, followed by submission of New Drug Application. The EU provides four different processes for the approval of drugs that is centralized procedure, decentralized procedure, national procedure, and mutual recognition procedure. In INDIA the approval process is under the control of CDSCO, has its own procedure for approval of drug product in India. The applications regarding the new drug, they were reviewed by agency officials and then the safety and efficacy of the drug should be reviewed by the particular agency further the drug is approved.

INTRODUCTION

At present, various countries need to comply with the various regulatory requirements for the authorization of new drugs. A single regulatory approach is almost a challenging task for gaining a MAA (Marketing Authorisation Application) to be applied to different countries. Thus, in order to establish an appropriate regulatory strategy, one should have the knowledge about the identical and comprehensive regulatory necessities for MAA of each and every nation. Approval procedure of drug consists of two parts. First part is for the clinical trials and second part is for the approval of drug for marketing. Before drug approval there should be several steps need to be followed by the regulatory bodies. In the first step the non-clinical drug studies are

conducted to confirm the safety and efficacy of the drug. In the next step an application should be submitted for the conduction of clinical trials to regulatory body of the concerned country. Then further step should describe about the clinical trials. The clinical trials were conducted in four stages, i.e. stage 1 to stage 4 studies. These studies are conducted to confirm the safety and efficacy of drugs. Then the applicant should apply the application to the competent authorities for marketing the drug. The regulatory authority should review the application and should give the approval for marketing the drug. The approval should be given only if the drug product has been found to be safe and effective with the desired effect compared to the adverse effect.[i] Basic drug regulation can be illustrated in Figure1

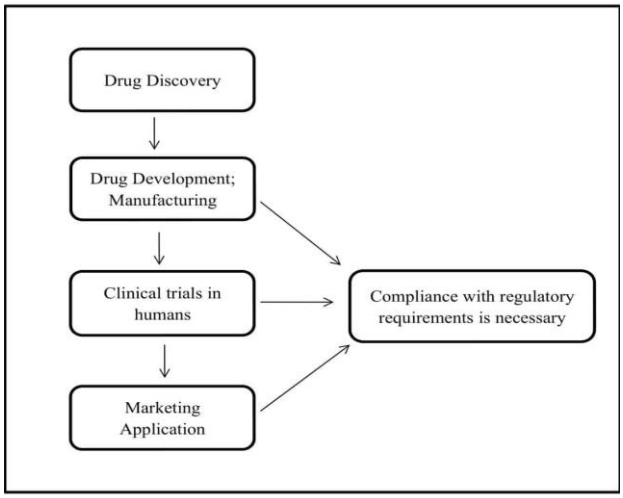

Figure 1: Basic Drug Regulation

1. The approval process of drug in United States: U.S. probably has the most stringent standards for approving new drugs in the world. Many of them considered that the drug approval process in the United States is most demanded in the world. The FDA (Food and Drug Administration) is in charge of the protection and promotion of public health. Like the general process of drug approval, the FDA should follow two stages for giving approval for new drug: (a) Clinical trials (b) New drug application (NDA) approval. The new drug approval procedure by FDA can be started only after the application for IND has been submitted.[ii]

a) Investigational New Drug application (IND) : An application that was submitted to FDA to initiate clinical trials in human beings, if the preclinical trial report shows that the drug was safe.The company or institution, referred to as the sponsor, they are responsible for submitting an IND application. The application should give a preclinical evidence of high quality to support testing the drugs in human beings. Nearly 85 percent of drugs undergo trials before the approval of IND application. Meeting should be organized by FDA; it is a pre-IND meeting. This meeting should be organized to discuss the various issues that occur during the clinical trials:

- The design of the study, which is helpful to conduct clinical studies.
- Protocol should be designed for conducting the study.
- Manufacture and control of drug.

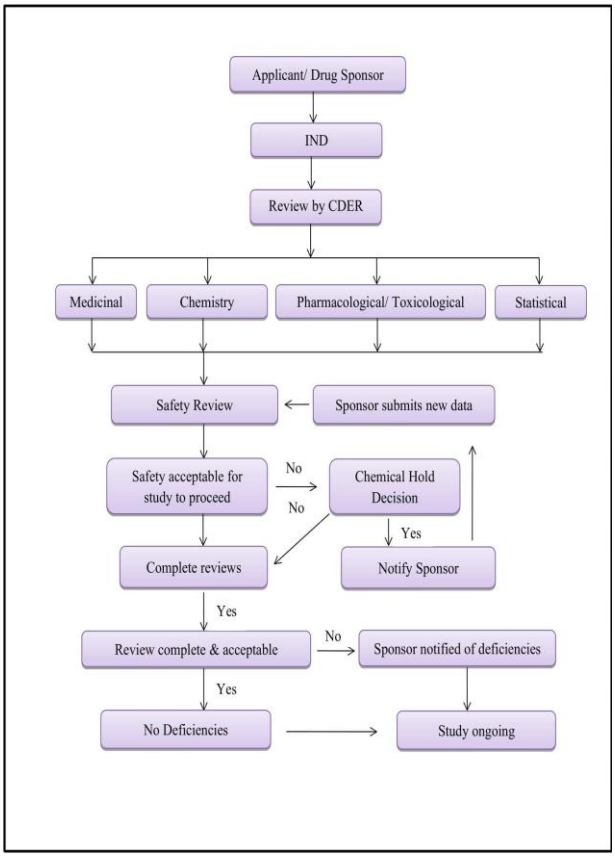

Figure 2: Investigational New Drug Application (IND)

This type of meeting's should helpful for the person to organize the animal research and gathering the data. These meetings will helpful in designing the clinical protocol based on the suggestions given by FDA.[iii] Figure 2 illustrates the IND procedure.

b) New Drug application (NDA)

The studies should confirms that the new drug product should be comparatively safe and do not cause any problems to the patients. Then the person should file an application for (NDA).It is an actual request given by the manufacturer to manufacture the drug and sell the drug in US. The NDA may only be filed after the completion of three levels of clinical trials. It includes the data regarding the animal studies and human studies, analysis, Pharmacokinetic studies of the drug. It also includes the manufacturing and anticipated labelling. The reports regarding the Preclinical studies, clinical studies and the risk benefit analysis can be studied at the centre for drug evaluation.

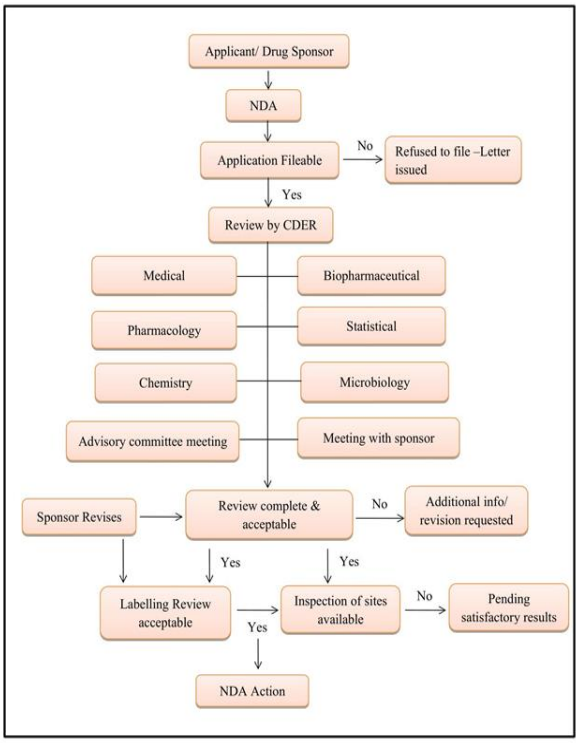

Figure 3: New Drug Application (NDA)

In general, an NDA application should be approved within 2 years. Then the further process should be completed within 2 months (or) it takes time for several years. Then the company should get permission for marketing the drug, only after the approval of a new drug application and it is considered as phase IV trials.

2. Drug approval process in Europe: -Same as the United States specifications, there are 2 regulatory steps should be taken before the drug is permitted for sale in the EU. The two regulatory steps such as clinical trial application and the MAA. Clinical trial application should be submitted to state's component regulatory authority for conducting the clinical trials in European Union. The member state's competent authority shall reviews the request. Only after the approval the clinical trials are conducted. The marketing authorization application (MAA) is filed after the completion of all three phases of clinical trials. The European Union has 28 member states (as per July 2013). The applications regarding the clinical trials were accepted at member state level, however the applications for marketing authorizations were permitted both at member state level and centralized level.[iv]

a) Centralized procedure

It is the one that allows the applicants to get an authorization ship for marketing the drug that is only valid within the European Union. The committee should check out the applications which are acquired by EMEA. In the view of preference of an applicant, the CHMP agreements carry out the assigned task in any one of the membered states. Upon completion of the assigned work, then the authority should submit its opinion regarding the assessment to the EU commission within 210 days. Then the European Union Commission shall make an appeal to other member states; regarding the clear judgement is come from the board for the Human Medicinal Products is acknowledged. Then the other member states may answer within 28 days. An assessment report should be

given by the European commission, and the authorization is also issued for marketing the drug. This license is indorsed throughout the EU and it is valid for 5 years, if any extension is required then the application should be applied for an extension to the European medicines evaluation agency.[v,vi] Figure 4 should illustrate about the detailed centralized procedure. The Centralized process should be necessary for

- Medications obtained from genetic engineering.
- Medications used to treat Cancer, diabetes, HIV/AIDS, autoimmune diseases (or) neurodegenerative disorders.
- Those medications which are called as 'Orphan medicines' (the medications which are used for the rare disorders).

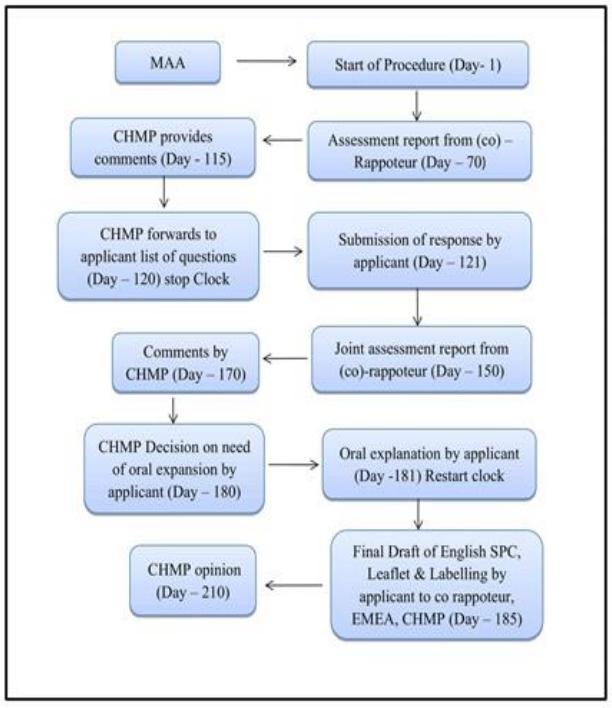

Figure 4: Centralized Procedure

b) Decentralized Procedure: - Only the Centralized method is not mandatory in order to receive the authorisations for marketing the drug product in several membered states, in that type of extents the "Decentralized procedure" is used. By using this method companies that simultaneously applied for an authorisation ship in European Union country for the drug products until they are not approved in any one of the European Union and effectively do not fall under the list of essential drugs of the centralized procedure. The applicant should apply an application to the each member state authority. The reports regarding the quality and safety, effectiveness should be given to the authority. 1 member state should be considered as the Reference member state (RMS) shall be submitted. A draft report should be prepared on the medicinal products and the CMS and RMS shall validate the report within '14 days' time period. The Reference membered state should make a report, which includes the characteristic features of the product, labelling details and the details regarding the package leaflet, should be prepared within the time period of 120 days.

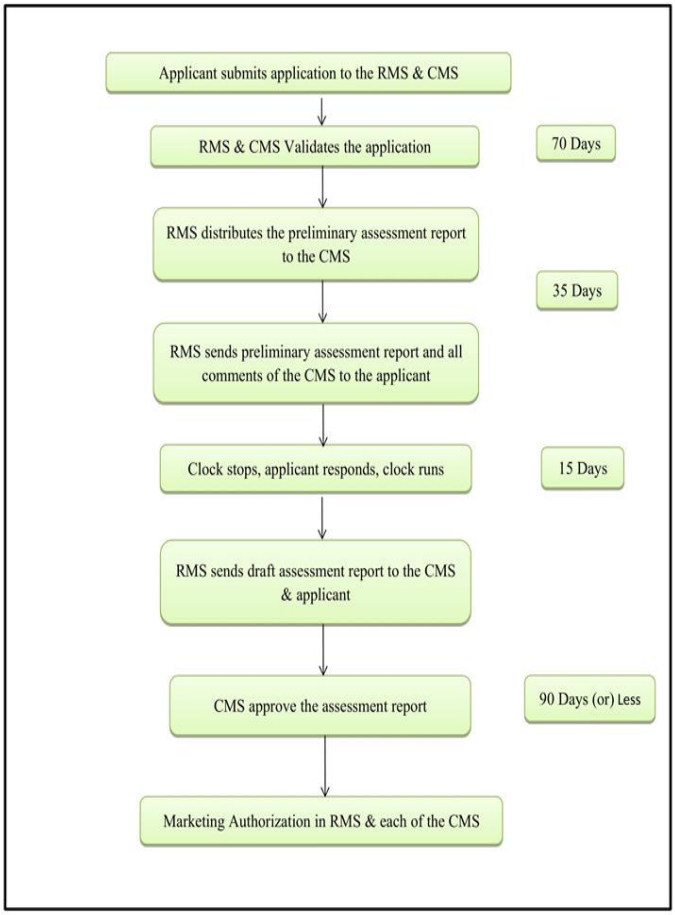

Figure 5: Decentralized Procedure

Then this report should be approved within the time period of 90 days. Then if any one of the drug products were expected to cause any serious risk to the health of the public, then the CMS's must notify to other CMS, RMS and applicants then the further decision will be made within 30 days in this regard. Within the time period of 60 days the dispute points being conveyed, all the member states should take an action regarding the dispute and what was the action to be taken must reaches an agreement. Thereafter the member states reach an agreement, the Reference member state should records an agreement then the information should be given to applicant. However, despite the applicant's written or oral representations, if the member states could not reach an agreement, committee for the Human Medicinal Products (CHMP) intervenes and takes a final decision.[vii]

c) Mutual Recognition Procedure: This process should permit's the aspirants to acquire an authorisation for marketing the drug in CMS other than the RMS where ever the drug product has been approved before. Figure 6 should illustrate about the mutual recognition procedure.

- The applicant should submit the identical dossier to all the European Union membered states where they wish to obtain an authorisation for marketing the drug product.
- The Reference member state should give a report by taking the own decision's.
- These type of approvals should be given to Generic industry
- This type of process should take's390 days.[viii]

d) Nationalized Procedure

This procedure permits the applicants to receive a marketing authorisation only in one member state.

- An application must be submitted to the competent authority of the member state for obtaining a national marketing authorisation.
- The active substances which are new and they are not mandatory in the centralized procedure should get an authorisation for marketing in this procedure.
- The whole process should take a time period 210 days.

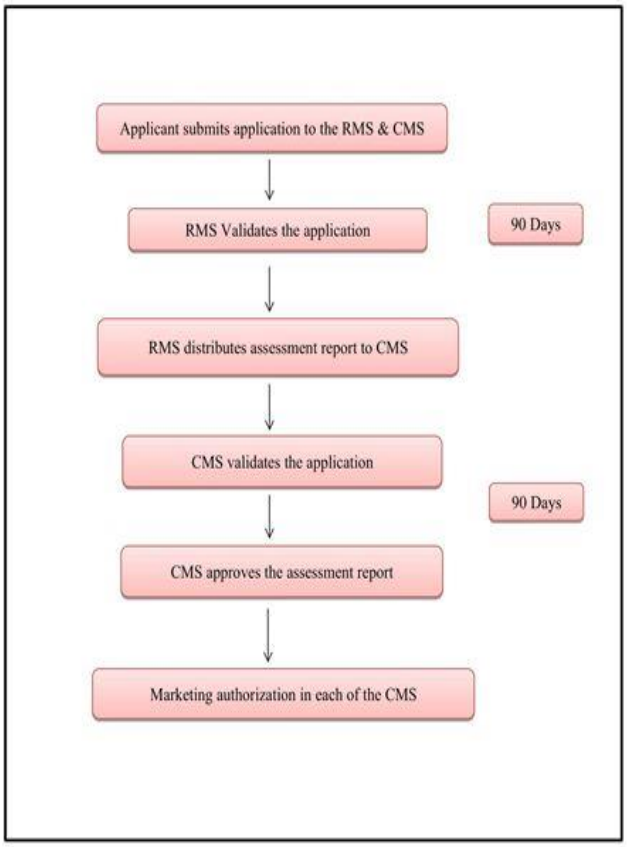

Figure 6: Mutual Recognition Procedure

3. The approval process of drug in India:-

The Indian legislative body should proclaimed the Drugs and cosmetic Act 1940 and Rules 1945 to govern the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs standard control organization (CDSCO) and the Drug Controller General (DCGI) have been established. In the year 1988 the Indian Government should added Schedule - Y to the Drugs and cosmetic rules 1945. Schedule -Y should provide the guidelines and the requirements that are necessary to conduct clinical trials. Then they were further revised in the year 2005 to suit the globally recognized Protocol. Demonstration of the drug product's safety and efficacy for use in humans is necessary before the CDSCO can authorize the drug product for import or manufacture of the new drug product by the aspirant. There are some modifications that are made in D and C act which comprises the definitions for the clinical trials Phases i.e., I-IV and it also includes the responsibilities for the researchers and sponsors**.** In India an application regarding the conduction of clinical trials should be submitted to the Drugs Controller General of India (DCGI) along with the details of animal studies, chemistry data, manufacturing data etc. The date for the trial procedure, brochures for the investigator and what are all the documents required should also be submitted. A copy of the application should be send to the ethical committee and there after the clinical trials will be performed only after the approval is given by the ethical committee and the Drug controller general of India (DCGI). "Phase-1"clinical trials were performed to monitor the optimal tolerated dosage in patients and also monitor the adverse drug reactions on the healthy human beings. In "phase-2"clinical trials the therapeutic uses of the drug and the effective dose ranges were determined by taking 10-12 persons at each dosage level. Then the Confirmatory studies "Phase-3" clinical trials were performed to produce data on the drug's efficacy and safety in approximately 100 persons (in 3-4 centres) to validate claims for the efficacy and safety. When a company can sell and market the product after the NDA approval, it is considered to be in Phase IV clinical trials. In this trials the new Communities (or) new users, long term effects were explored. In India any one of the company needs to import/manufacturing a new drug it must apply to obtain the licensing authority then the company should take permission from the Drug Controller General of India (DCGI). Then the data to be filed and submitted in Form 44 according to the Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. The drug safety and efficacy should be proved in the Indian residents, Clinical trials shall be conducted according to the guidelines set out in Schedule Y and such clinical trials reports shall be submitted in a specified manner. However, the rule 122A should specifies that the authority should perform certain trials if it is considered in the interest of health of the public, then the licensing authority could grant authorisation for the import of new drugs on the basis of evidence should be taken from the trials that are performed in other nations. The Section 2.4(a) should Specifies that to conduct clinical trials of all phases which is required for those drugs which are discovered in India. The Section 2.4(b) should specifies that those drugs which were discovered in other nations except India, in such type of instances the applicant must submit the data regarding the drug which is obtained from other countries then the regulatory authorities should repeat all the studies. The Division 2.8 should specifies that the authorising authority should conduct bioequivalence studies (Pharmacokinetic studies)to check the data that was then it is compulsory generated in the Indian Publics is the same as the data generated in other countries and then it is compulsory that the licensing authority should carry out phase III trials. At the end of the summary, it should specify that the exact necessities for conducting the clinical trials can be different from country to country and it should depend upon how satisfied the authority about its safety and efficacy. The process of approval for new drugs in India is very difficult procedure; the new drugs

should meet the essential requirements along with the new drug application to the Food and Drug Administration.[ix,x,xi]

New drug application: The application that was submitted to Food and Drug Administration for requesting an authorisation to market a new drug. A sponsor should submit the preclinical test data to FDA for reviewing of drug product data, explanation of manufacturing processes, to receive this authorization. After securing NDA from the agency, then it is undergoing a review. Then this assessment should confirm that the adequate data and what was the information required have been provided in all category to support the "filing" of a formal review requested by the FDA. At the end of the FDA review, the following are the 3 types of actions that can be sends to the applicant.

(a) Not approved – which includes the list of deficiencies and their reasons.

(b) Approved– The drug may be permitted but there are some deficiencies that should be corrected.

(c) Approval- states that the drug is approved.

If it is given as either approved or not approved, then Food and Drug Administration will give one chance to the applicant to consult with the agency and should discuss about the deficits. Figure 7 should illustrates about the detailed drug approval process in India

Stages of drug approval

- ❖ Submit the clinical trial application to evaluate safety and effectiveness.
- ❖ Requirements for the approval of new drugs.
- ❖ Changes in the post – approval of biological products: Quality, safety and efficacy documents.
- ❖ Preparing the quality information for drug submission for the approval of new drug.[xii]

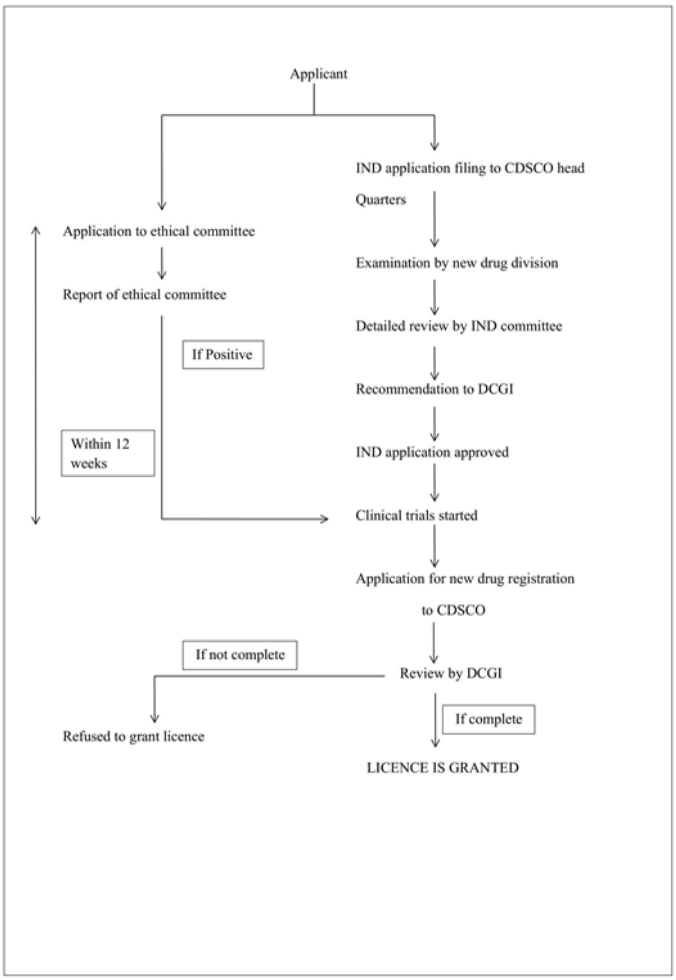

Figure 7: The approval process of drug in India

CONCLUSION

The process for the approval of new drugs should differ from one nation to another nation. In some of the countries, only one regulatory organisation should organize all regulatory activities such as approving new drug and issuing license. For example in US the FDA should perform all the activities. But in several countries all functions were not carried out by a single regulatory organisation. For example, in India the activities are split between the central authorities and the state authorities. The new drug approval process in United States, Europe and India are the most challenging in the World. The primary purpose of US, European and Indian regulations governing pharmaceutical products is to safeguard public health. It is the responsibility of the regulatory bodies to ensure that the

pharmaceutical companies should comply with the regulations. There are some legislation that requires the development, testing, tracing and manufacture of drugs in accordance with the guidelines to ensure that they are safe and well-protected for the patients.

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