REGULATORY INTERVENTIONS OF NEW DRUG APPROVAL
AND CONDUCT OF CLINICAL TRIALS IN INDIA

Introduction: India is expected to be major pharmaceutical hub by the year 2020. The total production was estimated to be around Rs. 50,000 crores during 2005-06 and total export was around Rs. 18,000. The Indian pharmaceutical industry is ranked 4th in terms of volume and 13th in terms of value in the world. We are having the highest number of FDA approved manufacturing units outside the USA and second highest number of abbreviated new drug approval (ANDA) filed. There were 441 new drugs approved during 1988 – 20002. The pharmaceutical industry had performed better even during the time of recession across the globe.

The central drugs standard control organization (CDSCO) is having control over the research and manufacturing of drugs and pharmaceuticals in India. The Government of India set up department of pharmaceuticals under the ministry of chemicals and fertilizers during the year 2004 to promote research and development in pharmaceutical field. The industries are promoted to invest in research and as a result Indian pharmaceutical industries have grown with good research aptitude. The council of scientific and industrial research (CSIR) have also started drug research program and created platform for interaction with the scientists involved in the pharmaceutical research. With all the directed effort taken jointly through industry and government agencies like CSIR, DST, DBT, ICMR, DRDO etc. many of the new drugs are coming up, several are in the pipeline to be marketed. All these new drugs have to go for the New Drug Approval (NDA) which is a bounding legislative framework for a drug to get permission for marketing.

What is new drug? In generally speaking any biologically active molecule which is safe, efficacious and approved by the concerned authority as a drug- can be treated as a drug. The new drug can be a new molecule with biological activity and low toxicity level, i.e. a new molecule which is safe and efficacious can be treated as new drug. But the schedule Y of Drugs and Cosmetics act (D&C act) is having different definition of new drug that will be discussed later.

Statutory requirement for NDA: “Compliance with schedule Y”: A new drug substance which has shown sufficient therapeutic activity will go for clinical trials, phase I to IV depending on the success of the molecule, and these clinical trials are governed by the schedule Y of D&C act. The data obtained from the study (clinical trials) has to be submitted through proper channel in specified application format to the drug control authority for getting new drug approval.

Clinical research in India: The clinical research market was about $30-35 million during 2002 that is projected to grow to about $250-300 (Centre watch). India has emerged as major clinical research platform in the world through its large population and racial diversity. Here we have about 700 – 1000 investigators working presently and

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around 100 clinical trials have been conducted in India. Most of the major pharmaceutical companies have established their clinical research unit. But still there are certain problems and peculiarities in India associated with clinical trials, like (1) patients/subjects are not aware of their rights (2) patients are having full faith on doctors and equate them to god while the doctors/scientists not be aware of obligations (3) Status of Institutional Ethics Committee (4) Monitoring Mechanism (5) Diversity of Population (6) Poor Awareness – transfer of Biological material, data transfer, intellectual Property Rights, Social and political sensitivities in collaborative research (7) Practice of different systems of medicines. There are several example of unethical clinical trials conducted (Table 1):

<table>
<thead>
<tr>
<th>Unethical clinical trials in India</th>
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<tr>
<td>Norplant Contraceptive</td>
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<tr>
<td>Quinacrine Anti malarial as contraceptive</td>
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<tr>
<td>Citalopram anti psychotic</td>
</tr>
<tr>
<td>Letrozole Anticancer used as fertility enhancer</td>
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<td>Clinical trial of anti-fertility vaccine</td>
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Role of Legislation:
- To decide what is mandatory and what is recommendatory.
- To create a fear on those who take liberties with others rights.
- To provide easy access to justice by compensatory relief.
- To upgrade norms of ethical research.
- To create public interest to monitor, review and advice policy development.
- To honor human rights obligations and rule of Law.
- Justice ultimately is the function of law and not ethics of mortality alone
- All ethical guidelines cannot be legislated, ethics will still be relevant.

Important Legislations:
- Ethical Guidelines for Biomedical Research on Human subjects, Indian Council of Medical Research, New Delhi 2000.
- Schedule-Y, Requirements and Guidelines for permission to import and/ or Manufacture of new drugs for sale or to undertake clinical trials, Drugs & Cosmetics Rules 2005.

Schedule – Y: The schedule Y prescribing the “Requirements and guidelines for permission to import and / or manufacture of new drugs for sale or to undertake clinical trial” was introduced in Drugs Act in the year of 1998. This initiative encouraged the industry to conduct Phase III trials for registering new drugs for marketing in the Indian market. It also provides requirement for registering new molecules as drugs. However it was not considered comprehensive enough in comparison to the standards set by other countries/ organizations. However as a result of this initiative, 441 new drugs were approved for marketing in India during 1988-2002.

New drugs as per schedule Y: The new drugs are defined under section 122-E of schedule Y as: 122-E(a): A drug, as defined in the Act including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized as effective and safe by the licensing authority under rule 21 for the purpose
claims; provided that the limited use, if any, has been with the permission of the licensing authority. **122-E(b):** A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration. **122-E(c):** A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz., indications, dosage, dosage form (including sustained release dosage form) and route of administration. All vaccines shall be new drugs unless certified otherwise by the Licensing Authority under Rule 21. A new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia whichever is earlier.

**Application for permission to import or manufacture new drugs for sale or to undertake clinical trials:** For getting such permission the form 44 accompanied with following data has to be submitted with requisite fee to the drug control authority:

**Chemical and pharmaceutical information like:**

- Information on active ingredients Drug information (Generic Name, Chemical Name or Investigational new name “INN”).
- Physicochemical data: Chemical Name and structure, Empirical Formula, Molecular Weight.
- Physical Properties: Description, Solubility, Rotation, Partition Coefficient, Dissociation constant.
- Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification.
- Complete monograph specification including Identification, quantification of impurities, Enantiomeric purity, Assay.
- Validations, Assay method, Impurity estimation method.
- Residual solvent / other volatile impurities (OVI) estimation method.
- Data on Formulation Dosage form Composition, Master manufacturing formula, Details of the formulation, In process quality control check, Finished product specification, Excipient compatibility study, Validation of the analytical method, Comparative evaluation with international brand(s) or approved Indian brand if available, Pack presentation, Dissolution Assay Impurities, Content uniformity, pH, Force degradation study, Stability evaluation in market intended pack at proposed storage condition, Packaging specifications, Process validation.

**(ii)Animal pharmacology data:**

- Summary.
- Specific pharmacological actions as prescribed in item 3.2 of Appendix I and demonstrating therapeutic potential for humans shall be described according to the animal models and species. Wherever possible, dose-response relationships and ED 50 shall be submitted. Special studies conducted to elucidate mode of action shall be described(Appendix-IV).
– General pharmacological actions as prescribed in item 3.3 of Appendix I and item 1.2 of Appendix IV.
– Pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance as prescribed in item 3.5 of Appendix I.
– Wherever possible, the drug effects shall be correlated to the plasma drug conc.

(iii) Animal toxicology data: (as prescribed in item 4 of Appendix I and Appendix III)

(iv) Human Clinical Pharmacology data: (as prescribed in items 5,6 and 7 of Appendix I and as stated below):
– For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as required under items 1, 2, 3, 4, 5 (data, if any, from other countries), and 9 of Appendix I
– For new drug substances discovered in countries other than India, Phase I data as required under items 1,2,3,4,5(data from other countries) and 9 of Appendix I should be submitted with the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted.
– The data required will depend upon the purpose of the new drug application. The number of study subjects and sites to be involved in the conduct of clinical trials depends upon the nature and objective of the study. Permission to carry out the trials shall generally be given in stages, considering the data emerging from earlier Phase(s).
– Application for permission to initiate specific phase of clinical trial should also accompany Investigator’s brochure, proposed protocol (Appendix X), case record form, study subject’s informed consent document (s) (Appendix V), investigator’s undertaking (Appendix VII) and ethics committee clearance, if available (Appendix VIII).
– Reports of clinical studies submitted under items 5-8 of Appendix I should be in consonance with the format prescribed in Appendix II of this Schedule. The study report shall be certified by the Principal Investigator or, if no Principal Investigator is designated, then by each of the Investigators participating in the study. The certification should acknowledge the contents of the report, the accurate presentation of the study as undertaken and express agreement with the conclusions. Each page should be numbered.

(v) Regulatory status in other countries.

(vi) Full prescribing information should be submitted as part of the new drug application for marketing.

(vii) Complete testing protocol/s for quality control testing together with a complete impurity profile and release specifications for the product.

REvised Schedule Y: This schedule was revised in January 2005 to remove its limitations and to encourage clinical trials, protecting the rights of the trial subjects. The
scope and definition of clinical trials are more clear and pragmatic in the amended version. Rights of the human subjects are also protected by stipulations like adhering to GCP, formation of ethics committee, prescribing formats for documents like, informed consent, report, EC approval reporting, ADR reporting, undertaking by the investigator etc. The earlier restriction on the no. of subjects and no. of sites has been omitted allowing flexibility to the investigator in this regards and has encouraged researchers. The new amendment allows concurrent phase II, III & IV trials also encourage clinical trial in India.

**Trial on FDCs- Group I:** The first group of FDC includes those in which one or more of the active ingredients, is a new drug. Such FDC are treated in the same way as any other new drug, both the clinical trials and for marketing.

**Trial on FDCs- Group II:** The second group of FDC includes those in which active ingredients already approved / marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. For permission to carry out clinical trials with such FDC, a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as there combination in the proposed ratio. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory trials should be stated. For marketing permission, the reports of clinical trials carried out with the FDC in India should be submitted. The nature of trials depending on the claims to be made and the data already available.

**Trial on FDCs- Group III:** The third group of FDC includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDC, the therapeutic rationale should be submitted to obtain permission for clinical trials and the reports of trials should be submitted to obtain a marketing permission. The nature of trials will depend on the claims to be made and the data already available.

**Trial on FDCs- Group IV:** The fourth group of FDC includes those whose individual active ingredients have been widely used in particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No animal or human data are generally required for those FDC, and marketing permission may be granted if the FDC has an acceptable rationale.

India filled maximum ANDA next to USA it proves the potential of India in the field of generics. Generics in the field of HIV/AIDS improved the reputation of India. A few transnational from our country making good business.