Issues of clinical trials in india by vallinadh karamcheti

Abstract: Clinical trials are conducted to ensure the safety and efficacy of the drug. They are conducted on the human subjects. Hence the clinical trials are liable to many legal aspects. Clinical trials are conducted in four phases. (Phase I, Phase II, Phase III, & Phase IV). All the phases of the clinical trials should comply with several legal aspects, as life of a person may be at risk if anything goes wrong with the clinical trials. They should comply with the Schedule Y of Drugs and Cosmetics Act, 1940, Drugs and Cosmetics (II Amendment Rules) Rules 2005, Good Clinical Practices guidelines, 2001 etc. What are clinical trials?

Clinical trials are the tests conducted on human subjects to test the safety, efficacy, tolerability, and phamaco-kinetic properties of the drug. Why and how are they conducted? Clinical trials are conducted in four phases

• Phase I trials are performed on a small group (normally 20-80) of normal healthy volunteers, and their aim is to check for safety (does the drug produce any potentially dangerous effects, for example on cardiovascular, respiratory, hepatic or renal function?), tolerability (does the drug produce any unpleasant symptoms, for example headache, nausea, drowsiness?) and pharmacokinetic properties (is the drug well absorbed? What is the time course of the plasma concentration? Is there evidence of cumulation or non-linear kinetics?). Phase I studies may also test for pharmacodynamic effects in volunteers (e. g. does a novel analgesic compound block experimentally induced pain in humans? How does the effect vary with dose?).

• Phase II studies are performed on groups of patients (normally 100-300) and are designed to test for efficacy in the clinical situation, and if this is confirmed, to establish the dose to be used in the definitive phase III study.

Often, such studies will cover several distinct clinical disorders (e. g. depression, anxiety states and phobias) to identify the possible therapeutic indications for the new compound and the dose required. When new drug targets are being studied, it is not until these phase II trials are completed that the team finds out whether or not its initial hypothesis was correct, and lack of the expected efficacy is a common reason for failure.

• Phase III studies are the definitive double-blind randomised trials, commonly performed as multicentre trials on 1000-3000 patients, aimed at comparing the new drug with commonly used alternatives. These are extremely costly, difficult to organise, and often take years to complete, particularly if the treatment is designed to retard the progression of a chronic disease. It is not uncommon for a drug that seemed highly effective in the limited patient groups tested in phase II to look much less impressive under the more rigorous conditions of phase III trial Increasingly, phase III trials are being required to include a pharmacoeconomic analysis, such that not only clinical but also economic benefits of the new treatment are assessed. The whole process has to comply with an elaborate code known as Good Clinical Practice, covering every detail of the patient group, data collection methods, recording of information, statistical analysis and documentation.

At the end of phase III, the drug will be submitted to the relevant regulatory authority for licensing. The dossier required for this is a massive and detailed compilation of preclinical and clinical data. Evaluation by the regulatory authority normally takes a year or more and further delays often arise when

aspects of the submission have to be clarified or more data are required. Eventually, about two-thirds of submissions gain marketing approval

•Phase IV studies comprise the obligatory post marketing surveillance designed to detect any rare or long-term adverse effects resulting from the use of the drug in a clinical setting in many thousands of patients. Such events may necessitate limiting the use of the drug to particular patient groups, or even withdrawal of the drug

Preclinical trials: Before conducting clinical trials every new drug should undergo pre-clinical trials to check whether it is safe to conduct clinical trials in human subjects or not. Pre-clinical trials includes •Pharmacological testing to check that the drug do not produce any hazardous effects such as cardiac arrest, cardiac dysrhythmias, acute bronchoconstriction etc.

•Preliminary toxicological testing to eliminate genotoxicity and to determine the maximum non-toxic dose of the drug. As well as being checked regularly for weight loss and other gross changes, the animals so treated are at the end of the experiment to look for histological and biochemical evidence of tissue damage. •Pharmacokinetic testing, including studies on the absorption, metabolism, distribution and elimination (ADME studies) in laboratory animals. •Chemical and pharmaceutical development to assess the feasibility of large-scale synthesis and purification, to assess the stability of the compound under various conditions, and to develop a formulation suitable for clinical studies.

Much of the work of preclinical development, especially that relating to safety issues, is done under a formal operating code, known as Good

Laboratory Practice (GLP). The aim of GLP is to eliminate human error as far as possible, and to ensure the reliability of the data submitted to the regulatory authority, and laboratories are regularly monitored for compliance to GLP standards.

Roughly half the compounds identified as drug candidates fail during the preclinical development phase; for the rest, a detailed dossier is prepared for submission to the regulatory authority, whose permission is required to proceed with studies in humans.

Issues of conducting clinical trials in India: Clinical trials are required to be carried out in India before a new drug is approved for marketing Phase of clinical trials to be carried out depends on the status of the drug in other countries. If the drug is already approved/marketed, Phase III trials usually are required 1. If the drug is not approved/marketed, trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.

For new drug substances discovered in other countries phase I trials are not usually allowed to be initiated in India unless Phase I data2 from other countries are available. However, such trials may be permitted even in the absence of Phase I data from other countries if the drug is of special relevance to the health problem of India. .

For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I2 though Phase III3 permission to carry out these trials is generally given in stages, considering the data emerging from earlier phase Geriatrics can be included only in Phase III and in Phase II

trials at sponsor’s option only if Disease intended to be treated is a disease related to ageing Population intended to be treated include substantial number of geriatrics There is reason to expect that common conditions in elderly age are to be encountered When a new drug is likely to alter geriatric patient’s response than non-geriatric patients Otherwise generally geriatrics cannot be included in clinical trials. Pediatrics:

Pediatrics can be included in clinical trials only if: •The new drug is intended to treat serious or life-threatening diseases, occurring in both adults and pediatric patients, for which there are currently no or limited therapeutic options, pediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. •The new drug has a potential for use in pediatric patients - pediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited pediatric data at the time of submission of application - more data in pediatric patients would be expected after marketing authorization for use in children is granted

1. Under Item 7 of Appendix 1of schedule Y of Drugs and Cosmetics Act 2. Under Item 5 of the Appendix 1 of schedule Y of Drugs and Cosmetics Act 3. Under Item 7 of the Appendix 1 of schedule Y of Drugs and Cosmetics Act

Issues related to Sponsor/Investigator:

Sponsors are required to submit to the licensing authority4 an annual status report on each clinical trial, namely, ongoing, completed, or terminated. In

case a trial is terminated, reason for this should be stated. Any unusual, unexpected or serious adverse drug reaction (ADR) 4 / serious adverse events (SAE)4 detected during a trial should be promptly communicated by the sponsor to the licensing authority5 within 14 calendar days and to the other investigators. In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months to licensing authority. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions6 if any, and the reason for discontinuation of the study or non-pursuit of the new drug application