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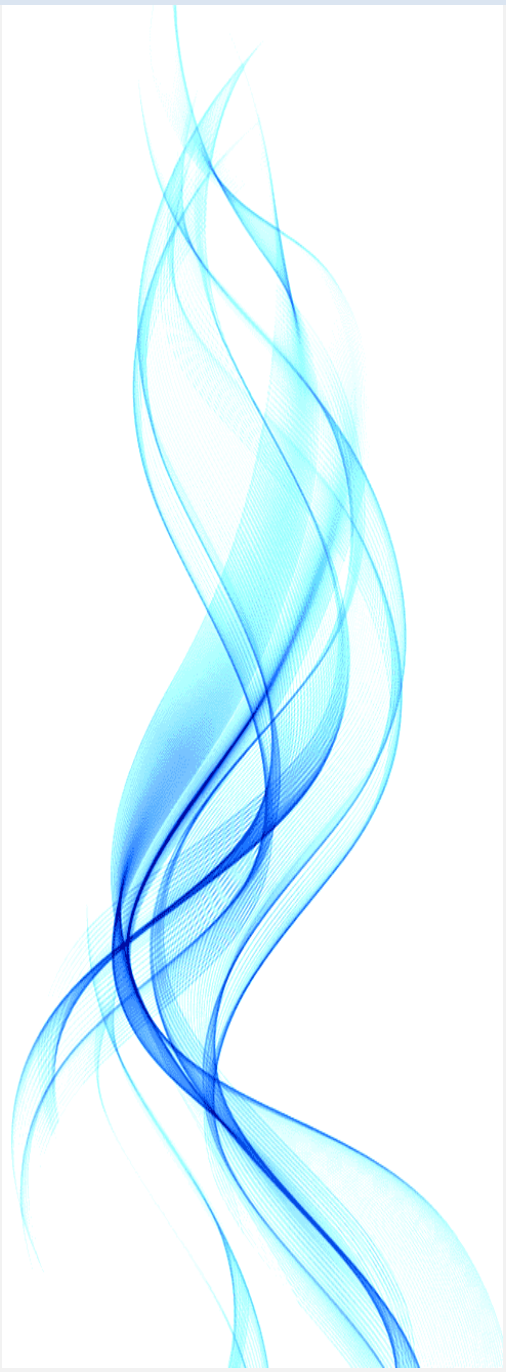

Legal framework and Requirements to Conduct Non-Clinical & Clinical Trial And Bioavailability & Bioequivalence Study of a New Drug before its commercial production.

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The novel corona virus has caused an unprecedented grim situation for the humanity across the globe. It has caused stirring effects to human minds. Both Hopelessness and helplessness are looming large. Despite being in the age of science and technology and, despite the virus is wreaking havoc in our socio-economic lives, we are unable to find any authentic remedy against the virus. In the age of information-technology and social-media, the population, left oblivious of the general panic is very low, therefore Anxiety is as widespread as the virus itself. Discussions as well as rumours and humours related to Corona virus and situations caused by its spread are the biggest talk at social media platforms in the year 2020. The situation has so adversely affected the humanity that everybody's fervent desire is to hear declaration of an authentic cure for Corona. Therefore, all associated with Research and Development in the field of medicine, science and conventional treatment of diseases avidly desires to blitz the gloom by such declaration. Even quacks are not lagging in their efforts to claim their share of credit of ameliorating humanity off its plight. In such a situation, there grows a general curiosity to know as to why there should be a clinical trial and why it is taking so long in coming with and an effective cure for corona.

Though the people are struggling against the virus with their own self immunity, ray of hope is still from the R&D in medical science. But despite a cure being found it, it cannot be allowed for treatment of patient unless it is approved for its safety and efficacy. This writing is an effort to explain the legal framework and process of approval necessary for manufacturing an 'Investigational New Drugs', testing its safety and therapeutic effects, grant of permission to manufacture for sales and distribution as a 'New Drug' and licensing before its availability in the market.

LICENSING REQUIREMENT FOR MANUFACTURE FOR SALE AND DISTRIBUTION, SALE ETC OF DRUG:

Clause (c) of Section 18 of the Drugs and Cosmetics Act, 1940 prohibits manufacturing for sale or for distribution, or sale, or stocking or exhibition or offering for sale, or distribution of any drug or cosmetic except under and in accordance with condition of licence issued by the Licensing Authority. Contravention of provisions of section 18 clause (c) of the Act is a punishable offence under section 27(b)(ii) of the Act with imprisonment for a term of not less than 3 years which may extent to 5 years and fine of not less than one Lac rupees or three times of value of the drugs confiscated, whichever is more. On commission of subsequent offence the terms of imprisonment is minimum imprisonment for 7 years and up to 10 years and minimum fine of Rupees two Lacs.

This said provisions make it clear that manufacturing for sale or for distribution, or sale, or stocking, exhibition or offering for sale, or distribution of any drug or cosmetic, without licence or in violation of conditions of licence is a crime punishable with Imprisonment and fine. In terms of provision of Part II of the First Schedule of the Code of Criminal Procedure 1973, the offence punishable under the provisions of 27(b)(ii) of Drugs and Cosmetics Act is non-bailable. Therefore licence is mandatory legal requirement for manufacturing a drug and commercial dealing with the same. Here I have tried to explain the processes and prerequisites, in law, for commercialization of a new drug. Because of nature of the subject use of some technical terms of medical science could not be avoided. Such terms may not be explained with precision and standard of medical science but the purpose here is to provide idea about legal framework and legal requirements of commercial production of a new drug.

NEW RULE REGIME

Before March, 2019, Clinical Trial and manufacturing and commercialization of a New Drug used to be governed by the provisions of under Part XA and Schedule -Y the Drugs and Cosmetic Rules, 1945. However, some writ petitions were filed before the Supreme Court raising concern over dealing with the human subjects of clinical trial and compensation in case of injury and death of the trial subjects and the supreme court sought responses from the Central and State governments on the issue. However, during pendency of the writ Petition the Central Government framed new rules dealing with the aspects ranging from permission to manufacture Investigational New Drug for clinical and investigational purpose to permission to manufacture a New Drug for sales and distribution. The said rules are known as the New Drugs and Clinical Trials Rules, 2019, which came in force on its publication in official Gazette on 19th March, 2019 as G.S.R.227(E) except part IV which also came into force after 100 days thereafter. Permission to manufacture an Investigational New Drug[1], Clinical Trial and Permission to manufacture a New Drug for sale are governed by the New Drugs and Clinical Trials Rules, 2019 (hereinafter referred to as New Rules). Only on permission to manufacture a New Drug for sale being granted by the Central Licensing Authority, the process of licensing of manufacture a New Drug for sale and distribution can be undertaken under the Drugs and Cosmetic Rules, 1945, without which manufacturing and sales of any drug is punishable offence.

[1] Clause 2 (r) of the New Drugs and Clinical Trials Rules, 2019 defines "investigational new drug" means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country;

In terms of Clause 3 of the New Rules, the Drug Controller, India appointed by the Central Government in Ministry of Health and Family Welfare is the Central Licensing Authority (CLA). Provision contained in Part-A Chapter V of the New Rules deals with permission and process etc of Clinical Trial and Part- B of the same deals with Bioavailability and Bioequivalence study. Both Clinical Trial and Bioavailability and Bioequivalence study[2] are necessary to understand and assess the toxicity, safety and efficacy of a New Drug. Neither a Clinical Trial and nor a Bioavailability and Bioequivalence study can be initiated or conducted without prior permission of Central Licensing Authority (CLA) and without Protocol being approved by the Ethics committee. Clause 21 of the New Rules makes it mandatory to seek permission of CLA to conduct Clinical Trial. Similarly Clause 33 makes it mandatory to seek permission of CLA to conduct Bioavailability and Bioequivalence Study on human subjects. The application seeking permission to manufacture new drug under clause 80 of New Rules must be made with information about the components of drug, data gathered in non-clinical study including data on animal toxicology and with data pertaining to safety and efficacy of drug on human subjects in clinical trial. No drug[3] can be manufactured for sale, distribution etc. except under licence and in accordance with the conditions of licence granted by CLA. For commercial production of a New Drug there are additional requirement of seeking permission of the CLA to manufacture a new drug for sale and distribution. Only after permission for manufacture and sales under New Rules are granted, licence for manufacture and distribution of a Drug including a new Drug is granted under the provisions of the Drugs and Cosmetic Rules, 1945.

Manufacture and marketing of New Drug in form of Active Pharmaceutical Ingredient or Pharmaceutical Formulations:

Clause 2 (w) of the New Drugs and Clinical Trials Rules, 2019 defines a "**New Drug**" means:

i. a drug, including active pharmaceutical ingredient (API) or phytopharmaceutical drug, which has not been used in the country to

[2] **Bioavailability and Bioequivalence Study** the concepts process etc are dealt in details after clinical trial.

[3] Section 3(b) of the Drugs and Cosmetics Act, 1940 defines drugs. Drugs in terms of the Act not only includes all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes but also includes such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of vermin or insects which cause disease in human beings or animals and also all substances intended for use as components of a drug including empty gelatin capsules; and such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals.

any significant extent and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or

ii. a drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

iii. a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

iv. a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

v. a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

An application for manufacture of a New Drug in from of Active Pharmaceutical Ingredient[4] or Pharmaceutical Formulations[5] can be made to the CLA under clause 80 of the New Rules and permission to manufacture is granted by the CLA under Clause 81 of the New Rules. Clause 83 of the New Rules provides that only after permission to manufacture a New Drug has be granted by the CLA a person, intending to manufacture for sale and distribution any new drug, can apply for licence to manufacture the new drugs for sales and distributions etc under the Drugs and Cosmetics Rules, 1945. A person seeking pre-licence permission to manufacture a New Drugs in from of Active Pharmaceutical Ingredient or Pharmaceutical Formulations having unapproved new molecule is required to make application to the CLA seeking permission to manufacture a New Drug with requisite data as per table 1 of Second Schedule of the New Rules along with result of Local Clinical Trial

[4] Clause 2 (a) of the New Drugs and Clinical Trials Rules, 2019 defines **Active Pharmaceutical Ingredient (API)** is a substance which can be used in a pharmaceutical formulation with the intention to provide pharmacological activity; or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease; or to have direct effect in restoring, correcting or modifying physiological functions in human beings or animals. API can be said to be raw materials.

[5] Clause 2 (y) of the New Drugs and Clinical Trials Rules, 2019 defines **Pharmaceutical Formulation**" means any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives, that is formulated to produce a specific physical form, such as, tablet, capsule or solution, suitable for administration to human or animals.

(LCT). Requisite data[6] for permission to manufacture New Drug contains information pertaining to active ingredients of the drug, chemical name and structure, physical property, analytical data, complete monograph specification, validation, assay method, stability study data formulation of the new drug. The applicant must furnish information pertaining to Animal pharmacology[7] including on specific and general pharmacological actions, Pharmacokinetics[8], Animal toxicology including Systemic[9] toxicity studies in respect of Male fertility, Female reproduction, Local toxicity, Allergenicity or Hypersensitivity, Genotoxicity, Carcinogenicity and information on Human or Clinical pharmacology data on Specific and general Pharmacological effects, Pharmacokinetics and Pharmacodynamics (Clinical Trial phase I); data of Therapeutic exploratory trials (Clinical Trial Phase-II) and data of Therapeutic confirmatory trials (Phase III) and data of Special studies on Bio-availability or Bio-equivalence and study data on geriatrics, paediatrics, pregnant or lactating women in respect of the new drug etc..

From the above it is apparent that for seeking permission of CLA to manufacture a New Drug for sales and distribution information on following broadly determined aspects have to be provided along with the application:

i. Pharmaceutical Information of the New Drug
ii. Animal pharmacology data,
iii. Animal toxicology data,
iv. Human clinical pharmacology data,
v. Therapeutic Value (exploratory and confirmatory data),
vi. Bioavailability and bioequivalence,
vii. Regulatory status in other countries,
viii. Prescription,
ix. Sample and testing,
x. New chemical entity

Information on aspect (i) is basically physical, compositional and analytical information about the New Drug. Information on aspect (ii) & (iii) pertains to non

[6] For complete details of information to be furnished with application seeking permission to manufacture new drug for sale and distribution see Second Schedule of the New Drugs and Clinical Trials Rules, 2019 and table-1 thereof.

[7] **Pharmacology** is study of the interactions that occur between a living organism and chemicals that affect normal or abnormal biochemical function.

[8] **Pharmacokinetics (PK)** is characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion. It attempts to analyze chemical metabolism and to discover the fate of a chemical from the moment that it is administered up to the point at which it is completely eliminated from the body. Pharmacokinetics is the study of how an organism affects a drug,

[9] **Systemic Circulation** carries oxygenated blood from the left ventricle, through the arteries, to the capillaries in the tissues of the body. [From the tissue capillaries, the deoxygenated blood returns through a system of veins to the right atrium of the heart.]

clinical study[10] which includes in-vivo[11] and in-vitro[12] study of the new drug or its components on rodent and non rodent animal subjects. Information on aspects (iv) and (v) pertains to physiological study on human subjects which is in three phases on clinical trial. Information on aspect (vi) is special study of absorption etc. of components of drug and their availability in systemic circulation. Aspect (vii) pertains to status of the said drug in other countries, aspect (viii) pertain to sample and dose and Aspect (ix) to assessment of risk versus benefit, innovation vis-a-vis existing therapeutic option and unmet medical needs.

SPECIAL SITUATIONS:

Item 2 of Third Schedule provides for special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered. The said provision provides that depending on categories and nature of new drugs to be imported or manufactured for sale or clinical trial to be undertaken, requirements of chemical and pharmaceutical information, animal pharmacology and toxicology data, clinical data may differ. The requirements may also differ depending on the specific phase of clinical trial proposed to be conducted as well as clinical parameters related to the specific study drug. Besides, accelerated approval process and quick and expeditious process of for review of new dug is provided for drugs intended to be used in life threatening or serious disease conditions or rare diseases and for drugs intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defence use e.g. haemostatic and quick wound healing, enhancing oxygen carrying capacity, radiation safety, drugs for combating chemical, nuclear, biological infliction etc., following mechanism may be followed to expedite the development of new drug and approval process.

CLINICAL TRIAL & BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

Since Clinical Trial & Bioavailability and Bioequivalence Study are conducted on human subjects with a new Active Pharmaceutical Ingredient or a new pharmaceutical formulation or new molecule, selected human volunteers are exposed to high risk of adverse effects of untested pharmaceutical components which may result to serious injuries and sometimes even death of the concerned persons. Therefore Clinical Trial & Bioavailability and Bioequivalence Study need to be conducted under strict regulatory environment and observation. Accordingly prior

[10] For detail see clause 2 of Second Schedule of the New Drugs and Clinical Trials Rules, 2019
[11] **In vivo** refers to in living body of a plant or animal.
[12] In Vitro literally means in glass and broadly refers to something done outside the living body and in an artificial environment,

permission of the Central Licensing Authority under Ministry of Health and family Welfare of Central Government and prior approval of 'trail & study protocol' must be approved by the Ethics Committee. Even Manufacturing of the new drug or investigational new drug to be used in trial and study are subject to prior permission of the CLA.

CLINICAL TRIAL

Rule 2 (j) of the New Drugs and Clinical Trials Rules, 2019 defines "clinical trial" in relation to a new drug or investigational new drug to mean any systematic study of such new drug or 'Investigational New Drug' in human subjects to generate data for discovering or verifying its,-

(i) clinical or;
(ii) pharmacological including pharmacodynamics, pharmacokinetics or;
(iii) adverse effects,

with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;

The definition of clinical trial as per rules indicated that its purpose is to conduct systematic study of a 'New Drug' or an 'Investigational New Drug' in trial subjects with intention to generate data to discover and verify clinical, pharmacological including pharmacodynamics, pharmacokinetics and adverse effects of the 'New Drug' or the 'Investigational New Drug', the object of the clinical trial is to assess safety efficacy and tolerance of the New Drug. Clause 52 of the New Rules prohibits manufacturing of a 'New Drug' or an 'Investigational New Drug' even for Clinical Trial or for Bioavailability and Bioequivalence Study or for test or analysis without permission of the CLA. For making such application, the applicant needs to make application along with such information as is required for conducting bioavailability and bioequivalence study as mentioned in the Forth Schedule of the New Rules. Permission granted under clause 53 of the Rule for manufacturing of a 'New Drug' or an 'Investigational New Drug' for Clinical Trial or for Bioavailability and Bioequivalence Study or for test or analysis used to be valid for 3 years and is extended for further period of one year for reason to be recorded. Clause 19 of the New Rules prohibits any clinical trial of New Drug or Investigational New drug without permission granted by CLA and without protocol of clinical being approved by the Ethics Committee[13]. First Schedule of the New Rules contains general principles for clinical trial which provides general principle, approach in design and

[13] The provision of the New Drugs and Clinical Trials Rules, 2019 provides for Ethics Committee and its registration and to perform function under Clause 11 of the New Rules.

analysis, development methodology, phases in clinical trial, studies in special population i.e. geriatrics, pediatrics and pregnant and nursing women and conduct analysis and reporting.

The general principle of clinical trial indicates that there should already be study of the 'New Drug' or 'Investigational New Drug' and the results of 'Non-Clinical Studies' or 'Previous Clinical Trials' sufficient to ensure that the 'New Drug' or 'Investigational New Drug' is safe for the proposed 'Clinical Trial'. Throughout the clinical trial and drug development process, animal toxicological data and clinical data generated should be evaluated to ensure their impact for safety of the trial subjects. Non clinical study should be to determine the characteristics of the new drug or investigational new drug; disease of conditions for which the New Drug or Investigational New Drug is intended to be indicated; duration and exposure in clinical trial subjects and route of administration. A clinical trial generally consists of four phases mentioned in First Schedule, which are as under:

Phase I.

The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic[14] drugs are usually studied in patients. Phase I trial should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the subjects.

Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives: -

(a) **Maximum tolerated dose**: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) **Pharmacokinetics, i.e., characterisation of a drug's absorption, distribution, metabolism and excretion**: Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) **Pharmacodynamics**: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic or pharmacodynamic studies) may be conducted in healthy volunteer subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

[14]Cytotoxic refers to a substance or process which results in cell damage or cell death

(d) **Early measurement of drug activity**: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

Phase II.

(i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

Phase III.

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drugs.

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies may need to be carried out if scientifically and ethically justified, primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Central Licencing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

In case of an application of a new drug already approved and marketed in other country, where local clinical trial in India is waived off or not found scientifically justified for its approval for manufacturing first time in the country, the bioequivalence studies of such drug, as appropriate, is required to be carried out and the test batches manufactured for the purpose shall be inspected before its approval.

Phase IV

Phase IV or post marketing trial of new drugs are performed after the approval of the drug and related to the approved indication. Such trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Such trial might not have been considered essential at the time of new drug approval due to various reasons such as limitation in terms of patient exposure, duration of treatment during clinical development of the drug, need for early introduction of the new drug in the interest of patients etc. Phase IV trials include additional drug-drug interaction, dose response or safety studies and trials design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies, etc.

The data pertaining to Phase-I, II and III of the clinical Trial of are required to be furnished along with the application seeking permission to manufacture new drug for sale and distribution. The Phase-IV clinical trial data is for post marketing assessment of the drug from safety, efficacy and tolerance point of view.

BIOAVAILABILITY & BIOEQUIVALENCE STUDY

Clause 2 (e) of the New Drugs and Clinical Trials Rules, 2019 defines **Bioavailability Study** means a study to assess the rate and extent to which the drug is absorbed from a pharmaceutical formulation and becomes available in the systemic circulation or availability of the drug at the site of action.

Clause 2 (f) of the New Drugs and Clinical Trials Rules, 2019 defines **Bioequivalence Study** means a study to establish the absence of a statistically significant difference in the rate and extent of absorption of an active ingredient from a pharmaceutical formulation in comparison to the reference formulation having the same active ingredient when administered in the same molar dose under similar conditions;

Bioavailability or Bioequivalence Study focus on the release of an active drug from its dosage form and subsequent absorption into the systemic circulation. Bioavailability or Bioequivalence study is done to ensure efficacy and safety of pharmaceutical product. Bioavailability study measures the drug or its metabolite concentration in the systemic circulation overtime. Bioequivalence study is conducted to ensure therapeutic equivalence between two pharmaceutically equivalent products i.e. a test product and a reference product. Bioavailability or Bioequivalence study is also conducted to ensure therapeutic equivalence at any phase of clinical trial of a new chemical entity for establishing bioequivalence between two products of the chemical entity, which is important for certain pharmaceutical formulation or manufacturing changes occurring during the drug development stages. Bioavailability including dissolution study is intended to provide information that assures bioequivalence or establishes bioavailability and dosage

correlations between the formulations sought to be marketed and those used for clinical trials during clinical development of the product.

In terms of sub-clause 2 of clause 31 of the New Rule Bioavailability or Bioequivalence study on human subjects cannot be conducted without prior permission of the CLA and without approvals of protocol by the Ethics Committee. The permission granted for Bioavailability or Bioequivalence study on human subjects shall remain valid for a period of one year. However, this validity period can be extended for a further period of one year for reason to be recorded in writing. Item 10 of clause 1 of the Fourth Schedule of the New Drug provides that Bioavailability or Bioequivalence study can be conducted only at Bioavailability or Bioequivalence Study Centre registered under the New Rules. Besides, the Bioavailability or Bioequivalence Study should be conducted in compliance of general principle and practice of clinical trial as specified in the First Schedule of the New Rules.

Marketing of a Phytopharmaceutical Drug:

Phytopharmaceutical Drug is a kind of herbal medicine and is a separate class of drug. This is why clause 80 of the New Drugs and Clinical Trials Rules, 2019, the applicable provision in regard of application for permission for manufacture new drug for sales, deals Phytopharmaceutical Drug differently from New Drug of Active Pharmaceutical Ingredients and Pharmaceutics Formulations. The provision does not mention for manufacture of Phytopharmaceutical Drug rather use word marketing of Phytopharmaceutical Drug. This indicates that Phytopharmaceutical Drug is a different class for being in form of plant fractions which are already assessed for at least four bioactive or phytochemical compounds and which are not to be administered through parental route i.e. intravenous, intraosseous infusion, subcutaneous or intramuscular. The New Rules defines phytopharmaceutical drug as under:

> Clause 2 (aa) of the New Drugs and Clinical Trials Rules, 2019 defines "phytopharmaceutical drug" means a drug of purified and standardised fraction, assessed qualitatively and quantitatively with defined minimum four bio- active or phytochemical compounds of an extract of a medicinal plant or its part, for internal or external use on human beings or animals, for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include drug administered through parenteral route.

Sub-clause 6 of clause 80 of the New Drugs and Clinical Trials Rules, 2019 provide for completely different format for making application for marketing

phytopharmaceutical drug which may not require human clinical trial. The data required with the application is in terms of table 4 of the Second Schedule. Item 2 of the said table requires rather published scientific report in respect of pharmacological human study or clinical study and requires pharmacodynamic information if it is so available. Therefore unlike the cases of new drug API or Pharmaceutical formulations, in case of marketing of phytopharmaceutical drug clinical trial and bioavailability study is not mandatory.

SUMMARY

- An 'Investigation New Drug' or 'New Drug' cannot be manufactured even for Clinical Trial and Bioavailability or Bioequivalence Study without permission of the CLA.

- Before a New Drug is marketed there is licensing requirement for its manufacture for sale and distribution in terms of the Drugs and Cosmetics Rules, 1945. But no application for licence of manufacturing a new drug for sale and distribution can be made unless there is permission of the CLA for manufacturing the same. Licensing manufacturing of a drug for marketing purpose is governed by the Drugs and Cosmetics Rules, 1945, whereas permission to manufacture for sale and distribution, which is requirement prior to licensing, is governed by the New Drugs and Clinical Trials Rules, 2019.

- Permission to manufacture a new drug for sale and distribution cannot be granted unless the CLA is satisfied about safety, efficacy and tolerance of the new drug. Therefore application seeking permission to manufacture a new drug for sale and distribution has to be filed along with information about Pharmaceutical components of the new drug, data on Animal pharmacology and toxicology, Human clinical pharmacology data, therapeutic value (exploratory and confirmatory) data and Bioavailability and bioequivalence Study.

- Non clinical trial is conducted in-vivo on rodent and mammal animal subjects. Data is also generated through in vitro experiments. Clinical trial on human subjects is conducted to generate human pharmacology data. Bioavailability Study is conducted to understand absorption of the drug component into the systemic circulation. Bioequivalence Study is conducted to understand dosage correlations between the formulations sought to be marketed and those used for clinical trials during clinical development of the product. These studies and trials are to ensure safety and efficacy of the drug for human. There is provision for acceleration of the process in emergency and unmet situations, but in any case safety and efficacy parameters cannot be avoided.

- Neither Clinical Trial not Bioavailability & Bioequivalence Study can be initiated or undertaken without prior permission of CLA and without approval of Protocol by Ethics Committee.

- Clinical trials are conducted in four phases, of which first to third phase trials are conducted prior to permission for manufacturing for marketing a new drug and fourth phase trial is conducted post marketing.

- Phytopharmaceutical Drugs are a different class and clinical trial etc. may not be required before its marketing. However, only those medicines come under its definition which are already assessed qualitatively and quantitatively with defined minimum four bioactive or phytochemical compounds and which are administrated through non-parental routes only.

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