Current Regulatory Requirements for Conducting Clinical Trials in India

Dr. Dhananjay K. Sable
Department of Biotechnology, Ministry of Science and Technology
Department of Higher Education, Ministry of Human Resource Development, Government of India

Lecture – L6
Drug Development Process – Overview

Hello friends, welcome back to the course Current Regulatory Requirement for Conducting Clinical Trials in India. Lecture 6; Drug Development Process Overview. So, this is one of the important lecture we are going to see.

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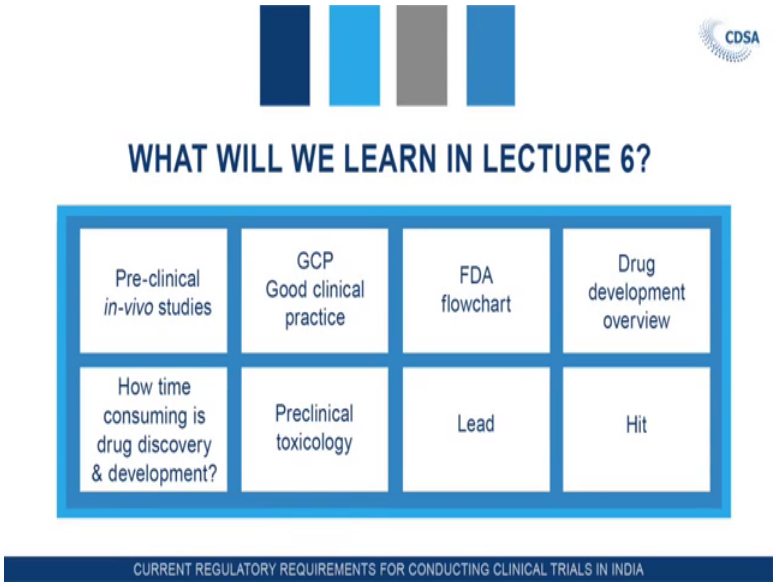

What we will we learn here, drug development overview, then drug discovery and developmental stages, how costly it is to develop a new drug, then why this much time is require for developing new drug? Then pathways involved, then what are the preclinical testings require, then what are the clinical testing requires that is phase I, 2 and 3 then what is heat, what is lead? All this things we are going to see.

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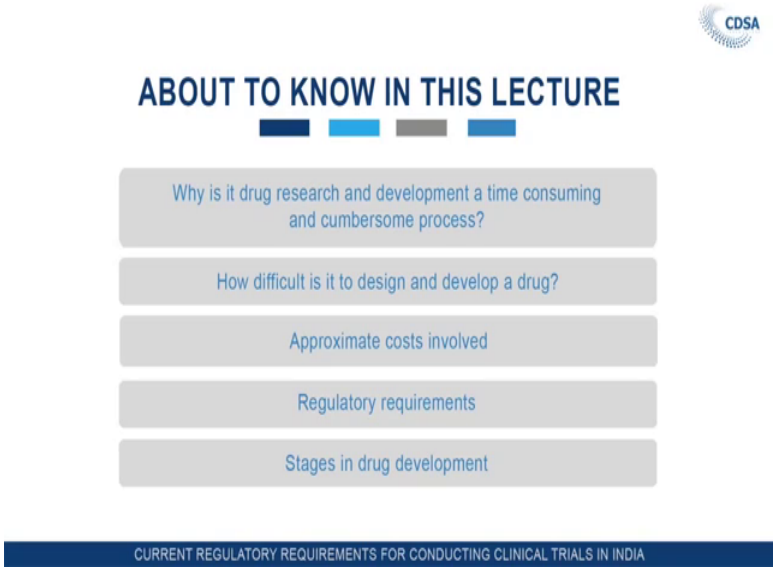

About to know in this lecture as I have mention, why it is time consuming, why it is combustion, then how difficult it is to have the new drug in the market then approximately costs involved then regulatory requirement, what are the forms, what is the fees and the stages in drug development. So, let us start with the introduction.

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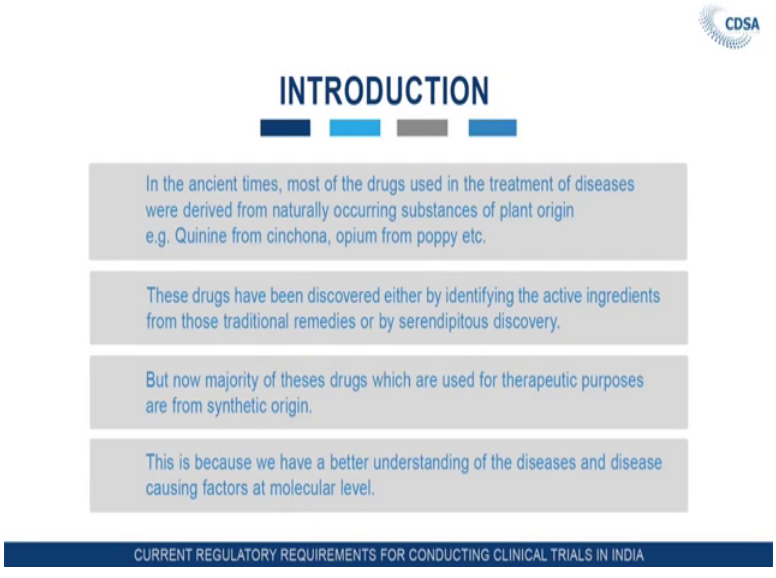

Friends as you know in the ancient times most of the drugs used for the treatment of any disease or disorder, where derived from naturally occurring substances of plant origin that we call some ayurvedic drugs or herbal drugs. For example, quinine derived from a

cinchona plant then opium from the poppy plant and the other drugs that we are derived from the plant extracts.

These drugs have been discovered either by identifying the active ingredient from those traditional remedies or by serendipitous discovery. Serendipitous discovery is also called as a happy observation or accidental observation or accidental discovery. But today majority of these drugs which are used for therapeutic purpose are from synthetic origin. If you see the most of the drugs they are from the chemical and synthetic origin because of having the faster action and some of the other advantages. This is because also the well understanding of the diseases and disease causing factors at molecular level and at atomic level also.

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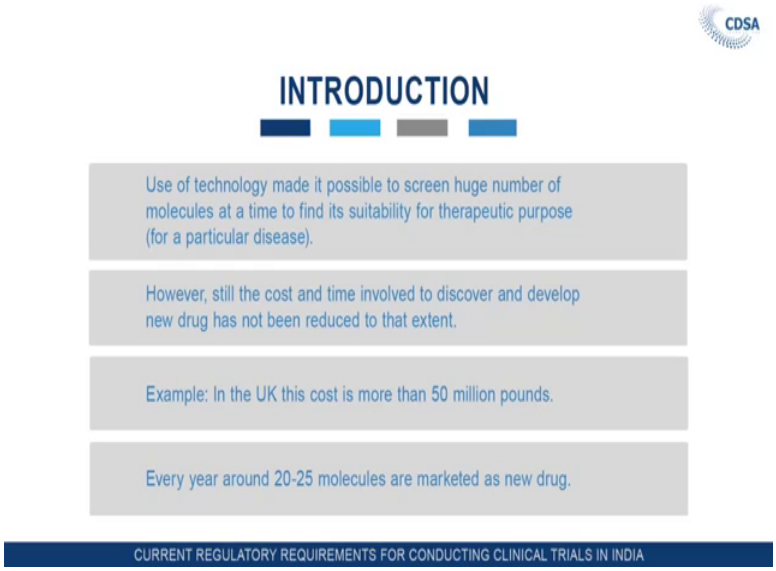

Use of technology made it possible to screen huge number of molecule at a time, to find its suitability, for therapeutic purposes, for particular diseases. Even we can screen more than 1 million of the molecule at a time see whether it is particularly feet into the target or the protein receptor or not. So, this the technology has made it possible. Though the technology has developed too much, the cost and time involved to discover and develop a new drug has not been reduced to that much significant level or do that expectation.

For example if we see in UK it is more than 50 million pounds require to discover and develop a new drug. If we see every year 20 to 25 molecules only are coming into the market. Why this number is very less? Let us see, why and how where this much cost

and this much time is requiring for this we require to see the drug discovery and development procedure.

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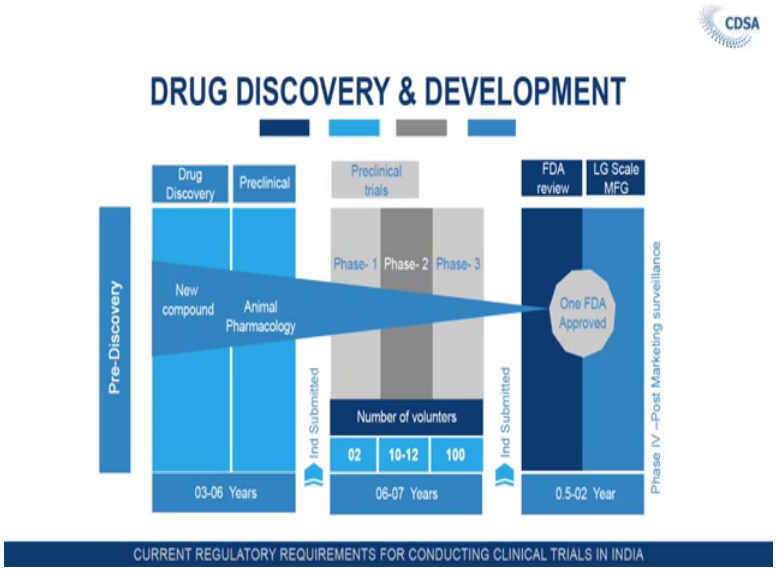

So, this is the flowchart how the drug is from then its a laboratory stage that is a discovery stage and how it is reaching to the patient, what are the different phases it is crossing thrown. Here it is mentioned drug discovery. Pre discovery then drug discovery then after drug discovery it is a preclinical. So, the drug discovery has been made through nowadays it is a most of the time it is based on the computational and that is a STS or CADD that is Computer Aided Drug Design these softwares are also used for the drug discovery. Once it is found that there is a some promising molecules, we call it as a lead or hits then after its a characterization and after finding its suitability, it enters into the preclinical study.

In the pre clinical study, we can see the animal pharmacology and animal toxicology can be ascertain and after the successful result of this preclinical study, then one has to apply for the phase I clinical trial that is a new drug or IND application to the CDSCO. Phase I generally at least two subject should be there, this is as per our all CDSCO guidelines; however, it is not mentioning schedule Y.

In schedule Y it is mentioned that the subject and sites that are mainly depend upon the type of drug for the study and the objective of the study, it is same for the phase 2 and phase 3 also. After completion of the phase 2 and 3, the CDSCO review the results and

after having some assurance that drug is safe and effective then it can be marketed into the market for the patients. These may be some of the time with the phase for study condition or without phase for study conditions.

Let us see how much time is required. So, for this drug discovery and preclinical stage, it takes around up to a 6 years to reach these the two stages, it takes around 1 to 3 to 6 years. In the clinical trial stage it takes around 6 to 7 years and for the review it takes around 0.5 to 2 years. This may vary from the different sources little bit there maybe variation.

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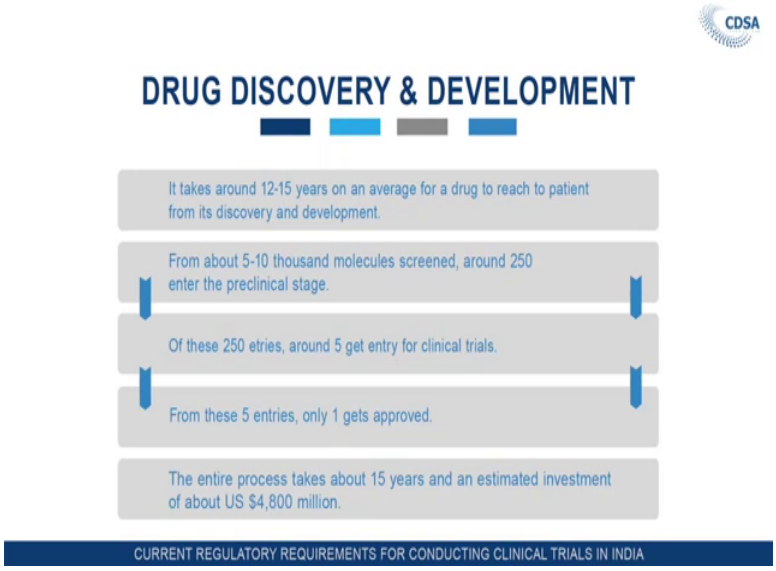

So, in average we can say it takes around 12 to 15 years for a drug to reach to a patient from its a discovery and development stage. From about 5 to 10 thousand molecules screened in drug discovery, around 250 molecules enter into the preclinical study. And from these preclinical studies that is from 250 5 molecules great entry into the clinical trails and after having the clinical trial with these 5 molecules only 1 molecule get approved. So, this is the whole process time require and cost involves. The whole process it takes investment about US dollar 4800 million over a period of 15 years this may vary again from the country to country.

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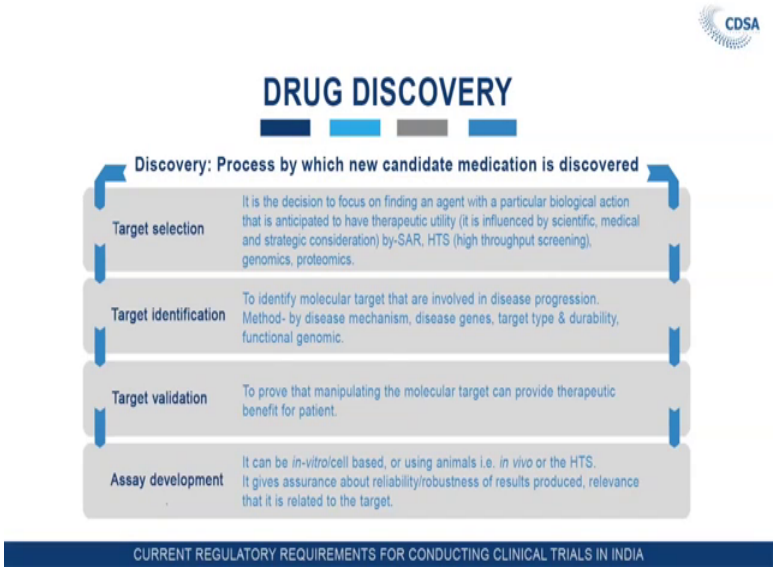

Let us see the various stages involve in the drug discovery that is discovery and design. Discovery is a process by which new candidate medications are discovered. So, the first procedure while discovering the new drug that is a target selection. Target selection is the decision to focus on finding and agent with a particular biological action that is anticipated to have therapeutic utility. This decision is influenced by the many of the factors and have to be balanced; this is influenced by scientific, medical and strategic consideration.

This target selection can be done by the various computational methods and other methods; like, a SAR that is Structure Activity Relationship, then HTS High Throughput Screening, genomics, proteomics then chemical synthesis in vitro study sometime it can be selected through the mode of action of the diseases. Then after the target selection the process is target identification. Target identification is to identify molecular target. Molecular target that are involved in disease progression means the factor which is responsible for the disease that factor have to be identify.

The first target has been selected, then the second the target identification that is a factor responsible for the disease has to be identified. These are may be the proteins or receptors all this. This can be done by disease mechanism if we know the disease mechanism, then target can be identify or this is genes then target time durability

functional genomics all these methods are applied for the target identification. Then after target selection, target identification it is a time to have the validation of this target.

Validation of the target it means to prove that manipulation of this molecular target can provide therapeutic benefit for the patient. So, this is a target validation. After the target validation the method that is assay development. Assay development is the key factor it can be in vitro or cell based or using animal that is that maybe in vivo or through the HTS that is High Throughput Screening.

So, this is to give the assurance about the reliability, robustness of the result produced to find out the relevance whether that is related to the target or not.

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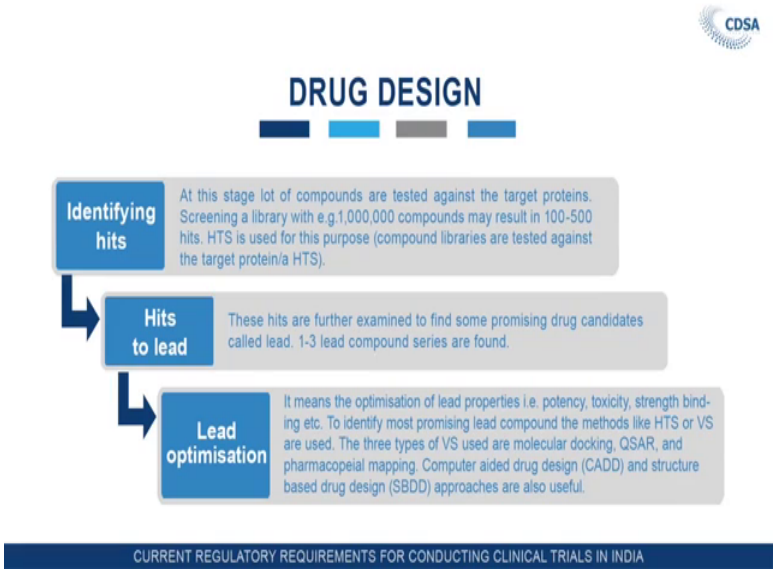

Now, let us see the design how to identify this target and its identifying the hits. At this stage lot of compound are tested again the target proteins. Screening library of lot of number of molecules that is more than 1 million also have to cross checked for the identifying the hits.

And from these around 1 million compounds only 100 to 500 hits are observe, hits are the most promising compounds. So, for this method as I have said HTS that is high throughput screening use compound libraries the HTS is the compound libraries are tested again the target proteins, then it is called the high throughput screening. Then once these hits are obtained then there is a hits to lead identification. It means these hits are

further examined or modified to find some promising drug candidate, that is we called as a lead means after finding out the hits, again the modification to ascertain again the most promising lead compound.

From this hits 1, 2, 3 lead compounds here is are obtained and once this leads are obtained, then optimization of these leads is require. Optimization of the lead property that is with respect to its a potency, toxicity, then strength binding all these parameters have to be optimized. To identify most promising lead compound, the method like HTS or VS are used. VS is the Virtual Screening method this can also be used actually there are three types of virtual screening methods that is molecular docking, then QSAR and pharmacopeial mapping.

In the drug design process the other methods like as CADD that is Computer Aided Drug Design then SBDD that is Structure Based Drug Design these methods are also useful.

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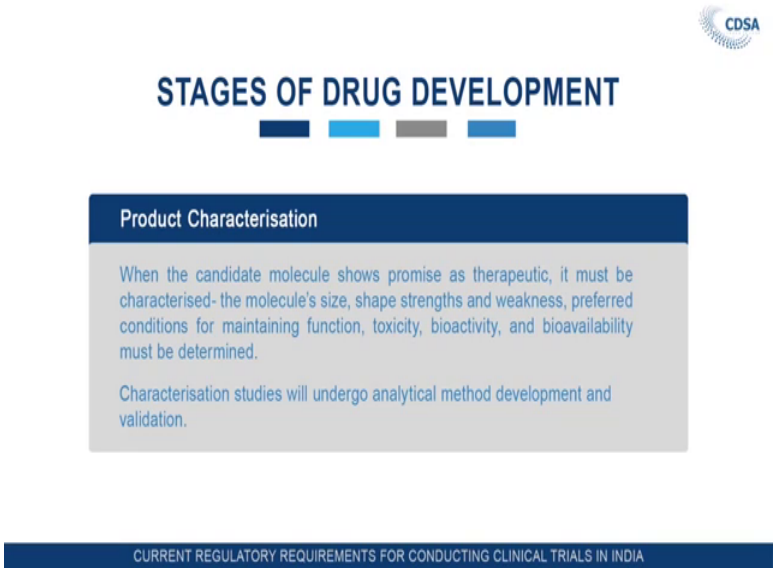

So, after finding out these and optimization of the lead there is a product characterization. When the candidate molecule shows promise as a therapeutic, it must characterize for its a other characteristic that is molecule size, then shape, strength and weakness preferred condition for maintaining functional toxicity bioactive and bioavailability it must be determined.

Characterization studies we will undergo analytical method development and analytical validation. So, after the characterization it is a time to have the formulation.

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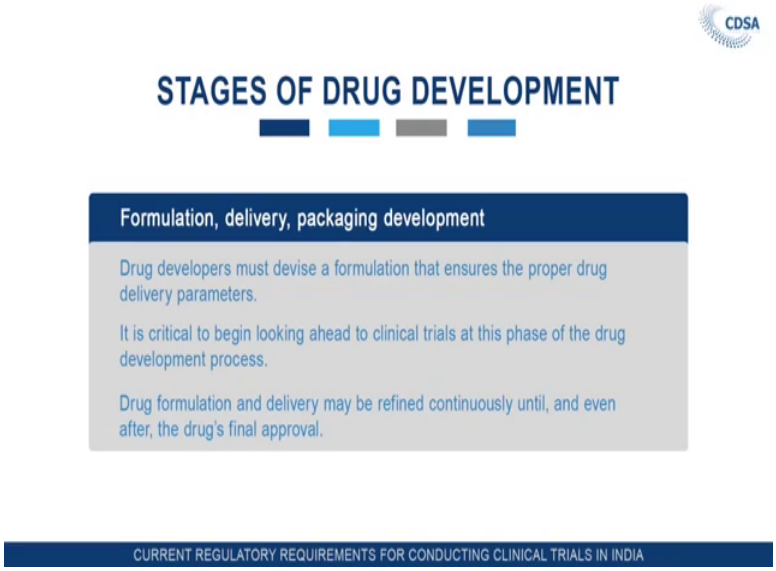

So, before going any animal studies the drug has to be formulated. Drug developers must device a formulation that ensure the proper drug delivery parameters, the drug should be properly deliver. It is critical to begin looking ahead to clinical trial at this phase of the drug development process. Drug formulation and delivery may be refined con continuously until and even after the drugs final approval. So, this is a continuous procedure until its get the final approval it has to refine continuously.

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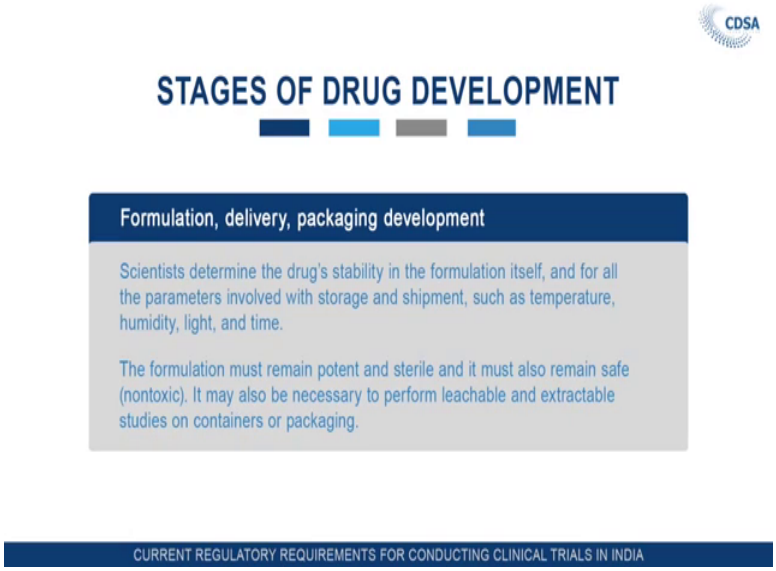

Scientist determine the drug stability. The stability is also most important whether the drug sustain the relative humidity temperature in that formulation that has to be ascertain and for all the parameter involved with the storage and shipment, in the transportation whether that drug we will retain its a potency and stability and that has to be ascertain. The formulation must remain potent and sterile.

So, during transportation and other conditions; it must also remain safe that is it should not; it should not lose its a potency and safety also. It may also be necessary to perform leachable and extractable studies on containers or packing. The drug in which it is packed that packing material has also to be tested. If it is a solution or syrup or any other liquid preparation and if the bottles are used whether that bottles are leaching the material into the content, which may make it more harmful or which may cause its loose the potency of the drug. So, for that the packaging material studies also require.

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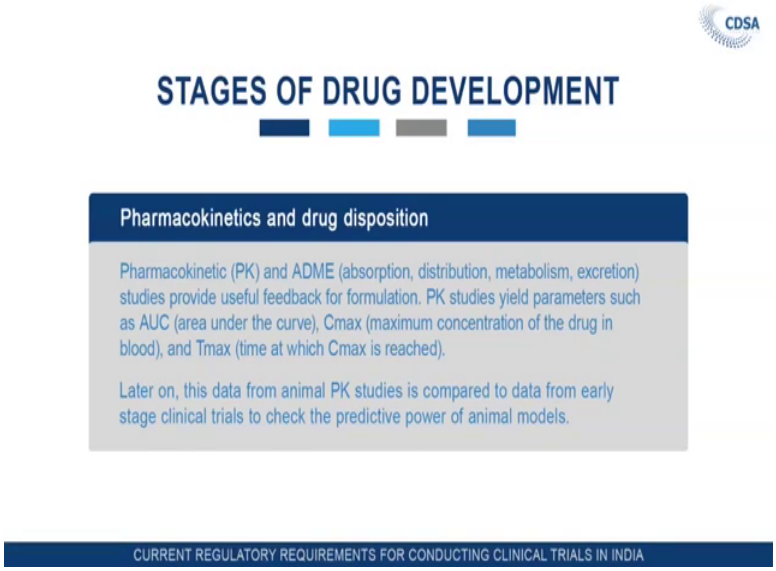

After having this formulation, the pharmacokinetic and drug disposition study. The studies are primarily in animal models. Pharmacokinetic that is a PK and ADME that is Absorption Distribution Metabolism Excretion these studies provide the useful feedback for formulation. These studies are have these studies have to be conducted while making the formulation and it will help in the making the formulation; if we know how it is a distributed, how it is going to excrete then that will help in the formulation.

This PK study yield parameters such as AUC that is Area Under Curve then Cmax maximum concentration at which the drug is in blood Tmax and the other parameters. Later on this data from animal PK studies is compared to data from early stage clinical trial to check the predictive power of animal model. The predictive power of animal model has to be check you know in the clinical trial phase.

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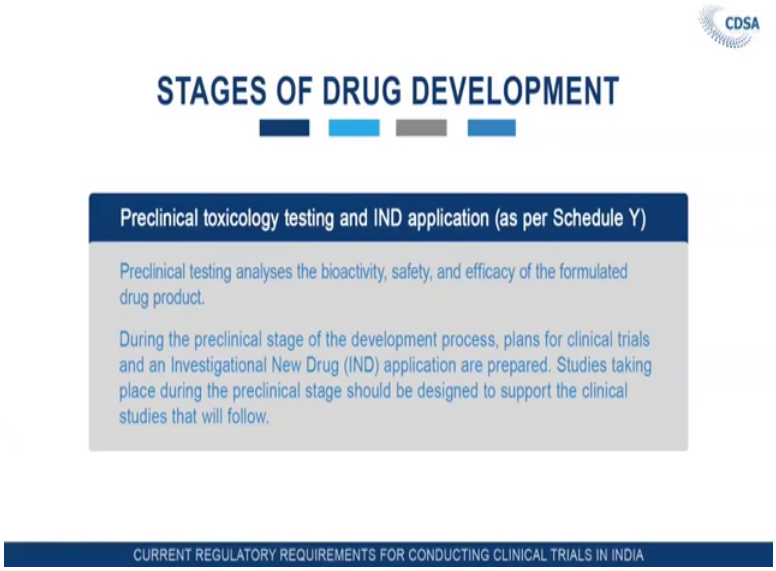

Preclinical toxicity testing and IND application. After having this data with the applicants then preclinical toxicity study has to be conducted to this preclinical toxicity study after this preclinical stock this toxicity study, application can be made for the phase I as I have mentioned. So, during the preclinical stage of the development process, plan for clinical trial and investigational new drug application are prepared. Studies taking place during the preclinical stage should be designed to support the clinical study that will follow.

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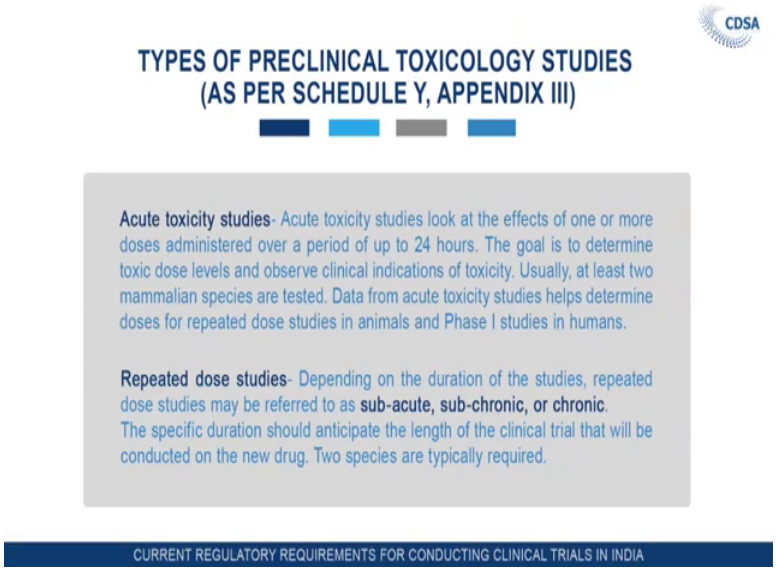

So, there are types of studies which is mention in the schedule Y appendix 3 we have seen in our previous lecture all this appendixes. So, what are these studies? Acute toxicity studying. Acute toxicity study is to look at the effect of one or more dose administer over a period of up to 24 hours. The goal is to determine toxic dose level and observe clinical indication of toxicity. Usually at least two mammalian species are tested here and data from this acute toxicity studies help to determine the doses for repeated dose, in animal and in also in human clinical trial that is a phase I studies.

The next is for the repeated dose toxicity studies. Depending on the duration of the studies, repeated dose studies may be referred to as sub acute or sub chronic studies sometime it is also referred as a chronic studies. The specific duration should anticipate the length of the clinical trial, that will be conducted on the new drug again here two species are typically required.

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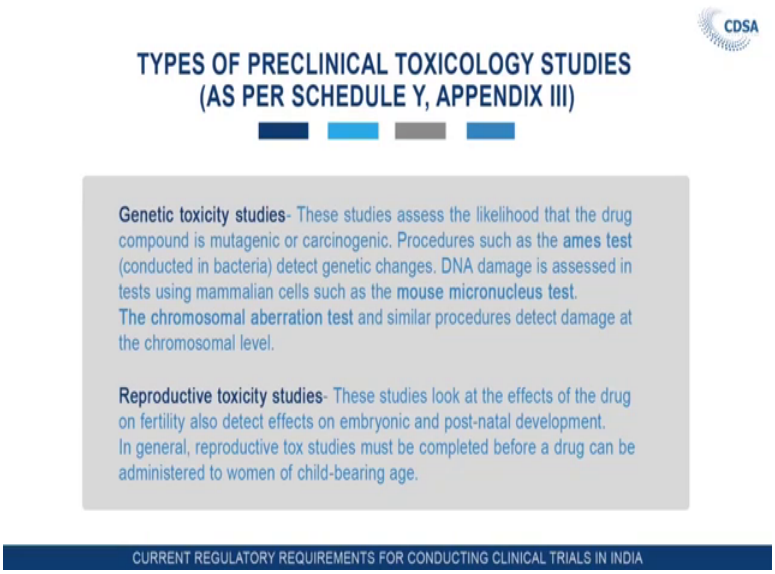

Then genetic toxicity studies. This studies assess the likelihood that the drug compound is whether it is mutagenic or carcinogenic that has to ascertain in these studies. For this type of studies procedure such as Ames test that is conducted in a bacteria to detect genetic changes are used; DNA damage is assessed in some other test the test is called as a mouse micronucleus test.

The chromosomal aberration test and similar procedure to detect damage at the chromosomal level, then further the reproductive toxicity test. Look at the effect of the

drug on fertility also detect effect to embryonic and postnatal development. In general reproductive toxicity studies must be completed before a drug can be administrator to women of childbearing age if the drug is of particular nature then this studies is required.

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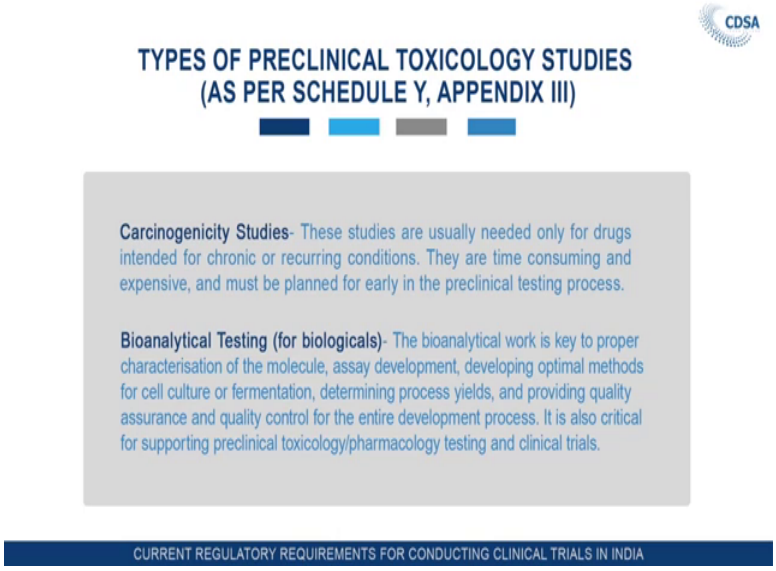

Carcinogenicity said studies these are usually needed only for drugs intended for chronic or recurring conditions. They are time consuming and expensive and must be planned for early in the preclinical testing. Then bio analytical testing. The bio analytical testing work is a key to proper characterization of the molecule as a development developing optimal method for cell culture of fermentation determining process yield and providing quality assurance and quality control for the entire development process. It is also critical for supporting preclinical toxicology, pharmacology testing and clinical trial.

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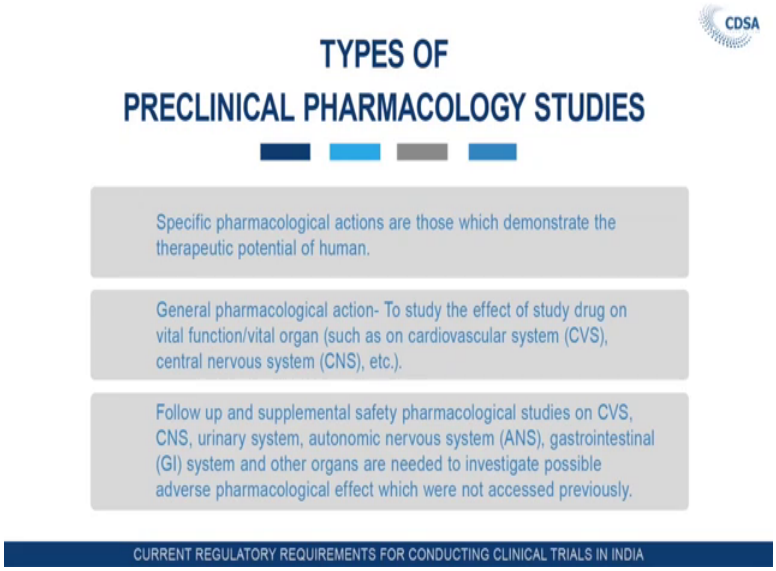

So, these where the toxicities testings now let us see the type of preclinical pharmacological testing. After having the toxicity testing pharmacological that is safety study also has to be ascertain in the animals. Specific pharmacological actions were given in the schedule Y and this specific pharmacological actions are those which demonstrate the therapeutic potential of human. Then some general pharmacological actions these are also mentioned, these are to study the effect of study drug on vital functions and the vital organs such as the effect of the dragon cardiovascular system on central nervous system, all this has to be demonstrated.

After completion of this pharmacological general actions, then follow up and supplemental studies are also require. The follow up and supplemental safety pharmacology study on CVS and CNS as we have seen in previous. Here this study can also be conducted on urinary system ANS GI and other organs to investigate the possible adverse pharmacological effect, which are not assessed in previous that is in general pharmacological actions. So, other system that is GI and these are also have to be tried here and demonstrated.

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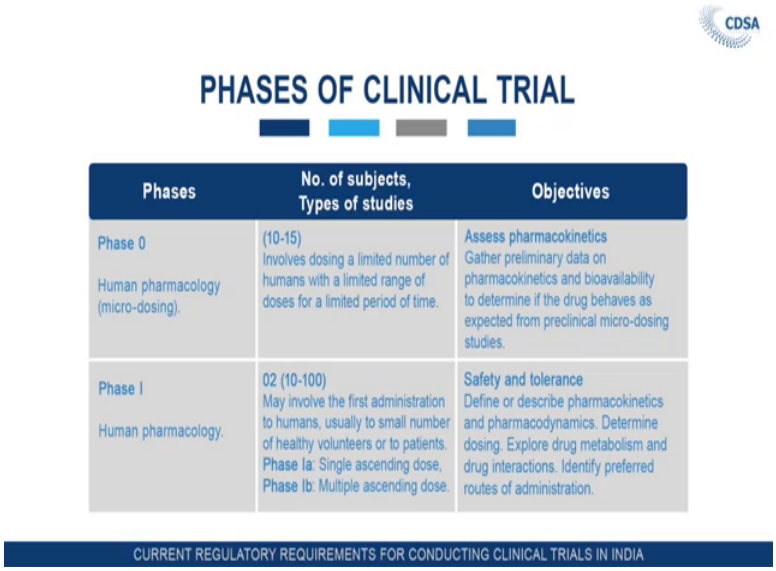

After a successful completion of this preclinical stage that is study in animal. Once it is demonstrated that the drug is safe in the animals and there is no toxicity then it enter into the clinical trial phase, then one has to apply to the central drugs standard control organization that is a CLA of India Central Licensing Authority for a phase I. Here it is given the phase 0 also this is human pharmacology and micro dosing.

So, this phase 0 this is not in India. So, it is a out of the India around 10 to 15 subjects are taken in this study and it involves a dosing a limited number of humans with a limited range of doses for a limited period of time. So, before phase I in other countries they do the phase 0 study also.

The objective of this study is to assess pharmacokinetics, then gather preliminary data on pharmacokinetics that is PK and bioavailability to determine if the drug behave as expected from preclinical studies the study is also called as the micro dosing studies. So, whether the drug is behaving as expected from the preclinical, this micro studies has been done.

Then phase I study that is a human pharmacology again. So, in our guideline that is a Indian guideline at least two subjects are required and in other countries the number of subject mention are 10 to 100 it varies from country to country. So, this may involve the first administration to humans usually to small number of healthy volunteers. So, in these study small number of healthy volunteers are used sometime if the drug is of that nation,

then patients also use single ascending dose and multiple ascending dose has been studies phase I a phase I b.

So, in India it is only phase I we consider. The objective of these study is safety and tolerance. Define or describe pharmacokinetics and pharmacodynamics determine the dosing, explore drug metabolism and drug interaction to identify preferred route of administration. So, these are the objective of phase I studies.

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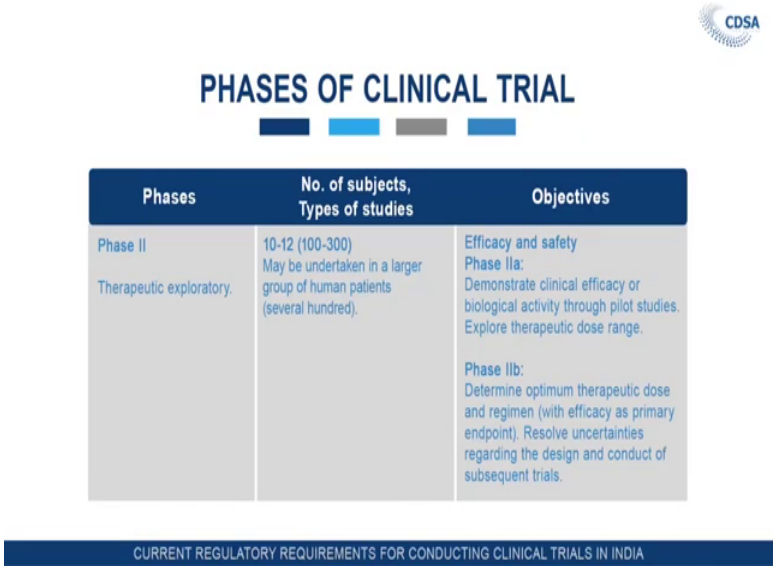

Now, after getting the successful result of the phase I studies, then it has to enter into the phase II studying. The applicant has to submit the phase I data to the regulatory authority and after review of the phase I data the licensing authority may grant permission for the phase II study.

The phase II study is also called as a therapeutic exploratory study. The number of subject involve at least 10 to 12 in other countries it is 100 to 300 may be undertaken in a larger group of human patient. So, here more than the what we have seen in phase I studies, there are the small population here the population size has to little bit increase with the confidence of the drug and the safety. So, the objective of this phase II studies efficacy and safety here also it is given phase II a and phase II b. So, in India it is only phase II we consider. So, phase II a demonstrate clinical efficacy or biological activity through pilot studies.

Explore the therapeutic dose range and phase II to determine optimum therapeutic dose and regiment. So, here we determine the therapeutic dose and also resolve uncertainties regarding the design and conduct of subsequent trials; after the completion of these phase then it is a time for the phase III study.

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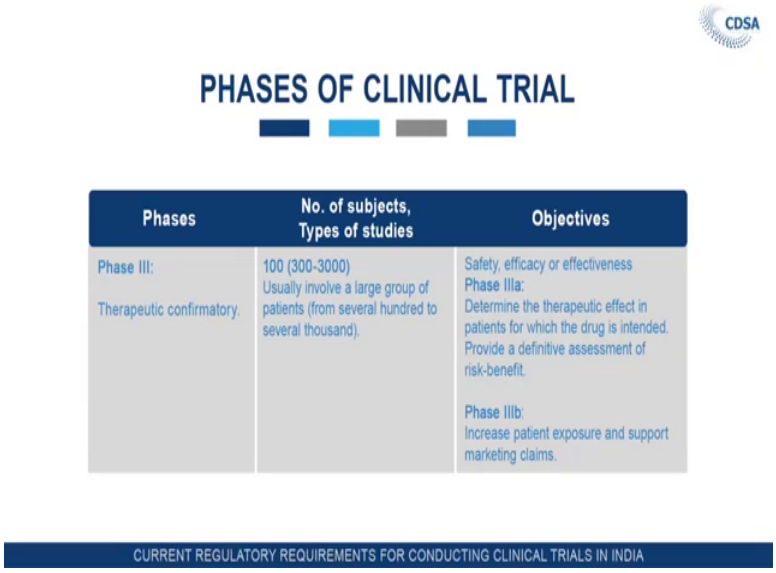

Phase III study these are the therapeutic confirmatory studies means here the therapeutic indication has to be confirm in this studies. So, at least 100 subject as I have mentioned it is in our Indian guidelines and in other countries it may vary from 300 to 3000.

This study usually involve a large group of patient. So, the number of patients and number of the subjects we have seen from phase I to phase III it is continuously increasing as we know the drug safety. The objective of these study it is clear from the its a name of the phase that is therapeutic confirmatory. So, to determine the therapeutic effect in patient for which the drug is intended. If any particular indication is mentioned or propose, then here that has to be confirm it provide definitive assessment of risk benefit. So, in this stage we can ascertain whether the drug is having more benefit than there is risk or not.

Then increase patient exposure and support marketing claim. So, after this after this phase one can apply for the marketing permission. Once it has been completed successfully and the result are there with the positive indication, once it is conform that

the drug can be used in the propose indication, then the licensing authority may grant approval with or without condition of the phase IV.

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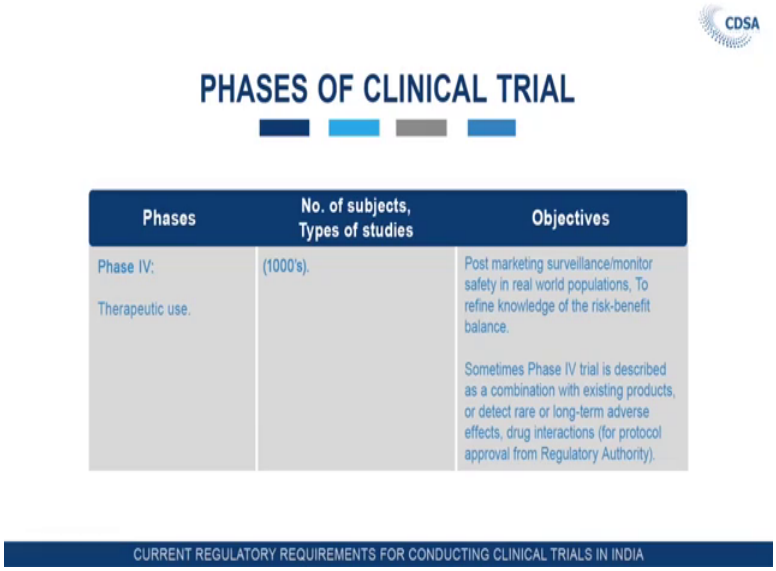

Let us see what is the phase IV study. Phase IV these are mark after the drug has been marketed. So, this also called as a post marketing study. The number of patient is a not mentioned in our guideline because it is a wide range study and the many thousands of the subject patients are involved in this studies

So, as I have mentioned it is a post marketing surveillance study. So, the objective to monitor safety in real world. So, till now we have seen all in the limited population now it is in the real world. To refine knowledge of the risk benefit balance. So, we have taken the limited subjects in the phase I II and III subject now it is in a wider range. Sometime describe phase IV trial as combinations with existing product or to detect rare or long term adverse effect. We have seen that phase III phase II phase I these are for the limited time of duration within that period the sponsor or the CRO the monitor the patients to see its a adverse effect.

Now, the phase IV in which the longer duration is taken. So, this is about the all phases involve in the clinical trials and drug discovery development.

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Let us see what is the future direction? So, the future direction involve the current approach in drug development is a focused on targeting specific signaling pathways. Then despite the new target such as receptor proteins, then receptor like tyrosine kinases tumour necrosis factor even though all this targets have been identify, still these are not that much effective and the in effective therapies with the serious side effects are available.

100s of gene could be disrupted in different cancer and in other diseases. Then multiple molecular players and signalings networking diseases that is also probabilities and. So, it need better understanding of again the drug target and long term safety outcomes.

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The target for drug development and the challenges are the un met unmet medical needs. In the country and all over again there is a unmet need for the lot of drug for the diseases like oncology angiogenesis cell signaling receptor and molecules in tumor growth.

Then cardiovascular and metabolic diseases type two diabetes, obesity, atherosclerosis thrombosis, then central nervous system related some diseases like Alzheimer's disease Parkinson's disease HIV aids and the genuine problem. Novel target in viral life cycle is required. Then some infectious diseases like a hepatitis B and hepatitis C influenza asthma, COPD.

Then some array diseases and autoimmune and inflammatory diseases like arthritis psoriasis inflammatory bowel disease; these are the target for a drug development and these are the unmet medical need. So, this is all about the drug discovery the phases involved and the challenges ahead. So, let us see the questions that is to test your knowledge.

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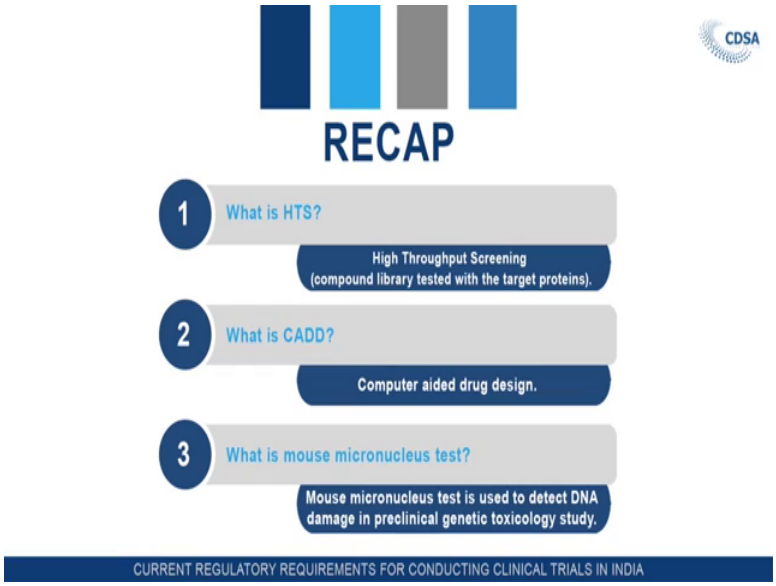

The first question is what is HTS it is mention in one of the slide? So, HTS is a High Though put Screening. We have seen it is a compound library to a tested with the target protein through high through put screen what is a CADD? CADD is a Computer Aided Drug Design. So, this is a computational. The next question is mouse micronucleus test used to detect you have to tell what for this test is use in preclinical. So, this test is to assist DNA damage in preclinical genetic toxicity study.

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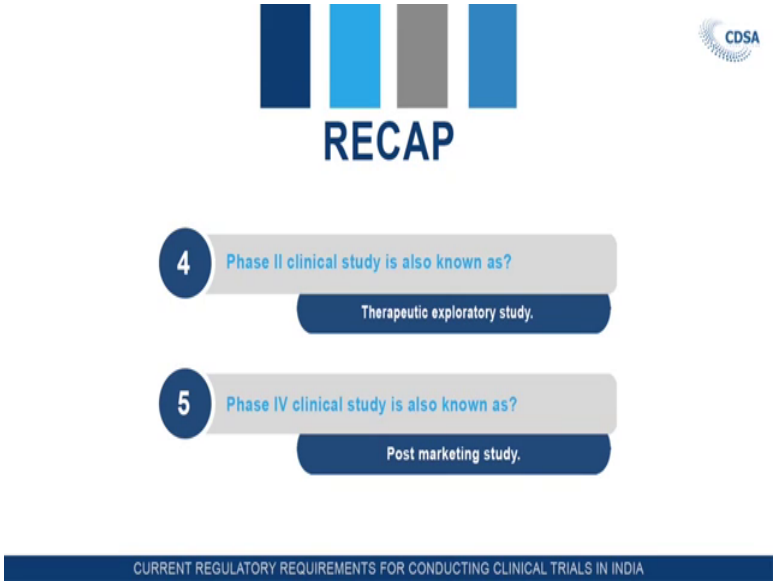

The next question that is question 4; phase II clinical trial study is also known as what is the phase II clinical trial study is also called as? So, this is also called as therapeutic exploratory studying. The similar question that is a question 5 what is phase IV clinical study is also known as? So, it is a post marketing study that has after marketing the product in the market. So, let us summarize what we have learn in the lecture 6 that is a drug discovery and its a over view.

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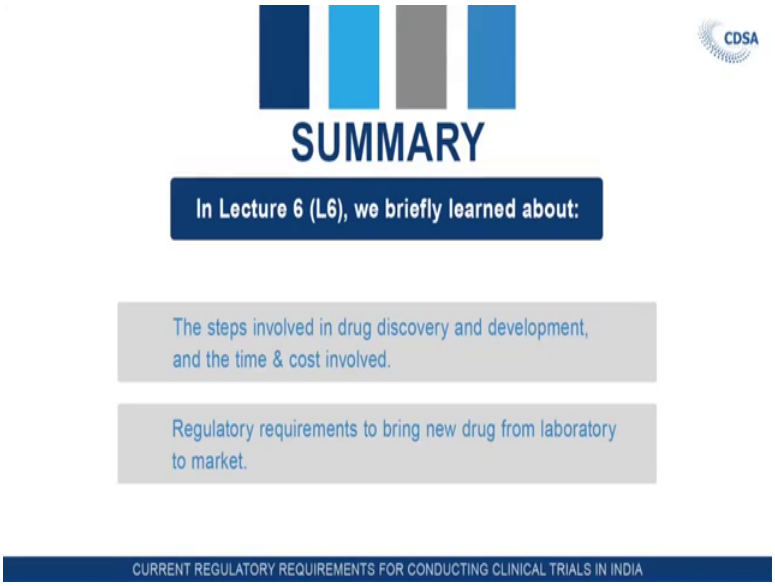

So, we briefly learn about the stages involved in drug discovery and development. We came to know the time required it is around 12 to 15 years it takes and the cost involved that is around 4800 million. We also learn about the regulatory pathways then requirement to bring new drug from lab to the market. We also learn about what is heat what is lead what is the optimization of the lead compounds, what are the pre clinical stages, what are the clinical stages the number of subjects require. So, this all we have seen in these lecture. So, let us wait for the next lecture, we will see in the next lecture till then bye bye.

Thank you and all the best.