Current Regulatory Requirements for Conducting Clinical Trials in India for IND/New Drug Version 2.0

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Lecture - 21
Drug development process: Overview

Hello friends, welcome back to the course Current Regulatory Requirement for Conducting Clinical Trial in India. This is our Lecture 21 and it is related to the Drug discovery and Development and Overview.

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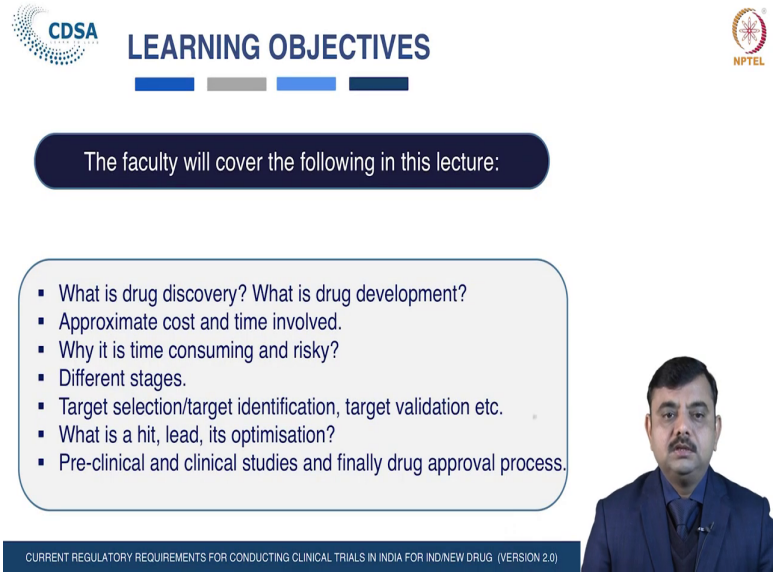

So, the learning objective upon completion of the session you will learn about what is mean by drug, what is mean by drug discovery, drug development. The approximate cost and time involved and as we know why it is time consuming and risky pathway. You will come to know

the different stages involved in drug discovery and drug development like; target selection, target identification, target validation and other things.

Also you will come to know what is means by hit, what is mean by lead and what is it is optimization. Then pre-clinical and clinical studies and finally, how the drug get approval from the licensing authority.

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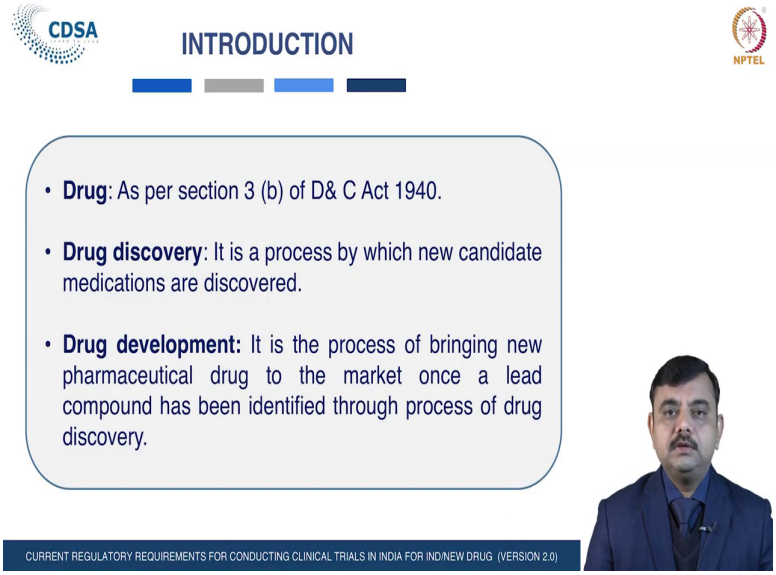

So, let us begin with the introduction to drug discovery and development. Dear friends we know what is means by drugs. So, drug has been defined in the drug and cosmetic act in the secs section 3 b. As per this definition we know, all the substances and all the medicines which are used for diagnosis treatment, mitigation prevention of the disease and disorder in animals and in human being for internal or external purpose for the disease and disorder that that is called as the drug. We have seen this is in a our previous lectures.

Let us see what is means by drug discovery? Drug discovery is the process by which new candidate medications are discovered and the drug development it is the process of bringing new pharmaceutical drug to the market once lead compound has been identified through process of drug discovery.

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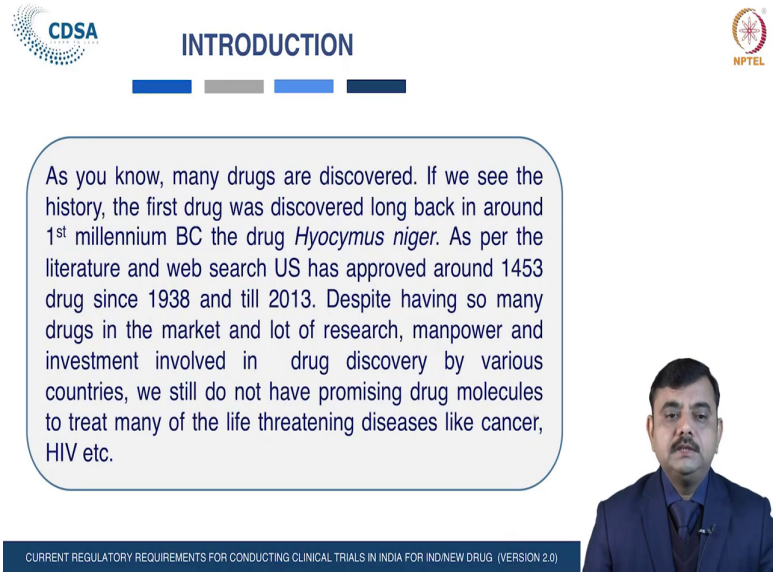

Dear friends, as you know we have discovered lot of drugs. If we see the history, the first drug was discovered long back in around 1st millennium BC and that drug was Hyocymus niger. Then in 600 BC we have discovered glycerol and then in 3,000 BC Morphine that is well known to all. If we see the literature and web search we will come to know that US has approved around 1400 and 53 drug since it is inception as a food and drug administration in 1938 and till 2013.

Despite having so many drugs in the market and lot of research manpower and investment involved in the drug discovery by various developing countries still we do not have promising drug molecule to treat many of the life threatening diseases like cancer, HIV and other drugs other diseases.

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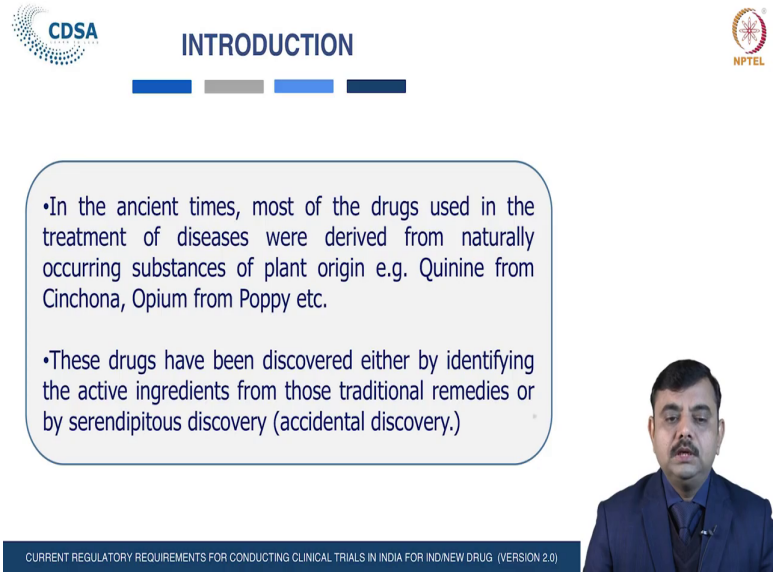

In the ancient time, most of the drugs used in the treatment of diseases were derived from naturally occurring sources like plant, animals and the other sources. We know that Quinine from Cinchona has been discovered, then Opium from Poppy has been discovered. These drugs have been discovered either by identifying the active ingredient from those traditional remedies or by the serendipitous discovery we know that; serendipitous discovery it is a discovery by chance like a penicillin drug it is a serendipitous discovery or we can call it as an accidental discovery also.

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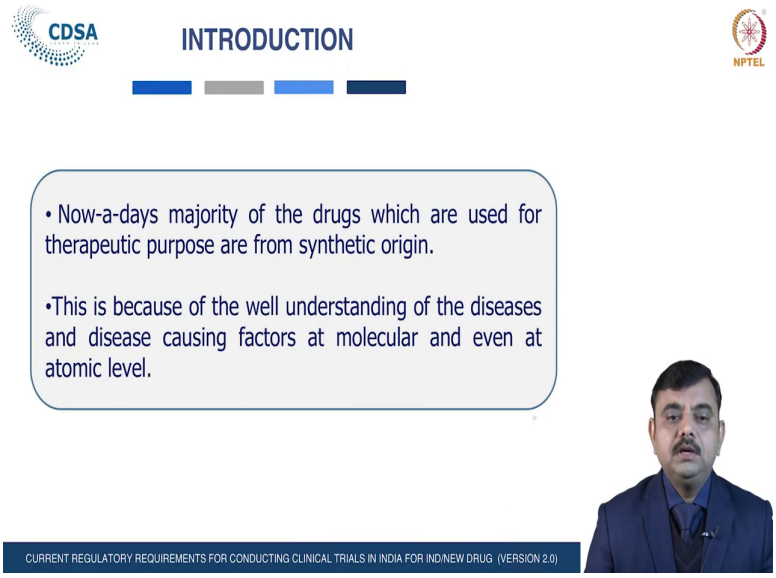

But now, majority of these drugs which are used for therapeutic purpose are from a synthetic origin and this is because of the well understanding of the disease, disease mechanism and disease causing factor at molecular and even at atomic level.

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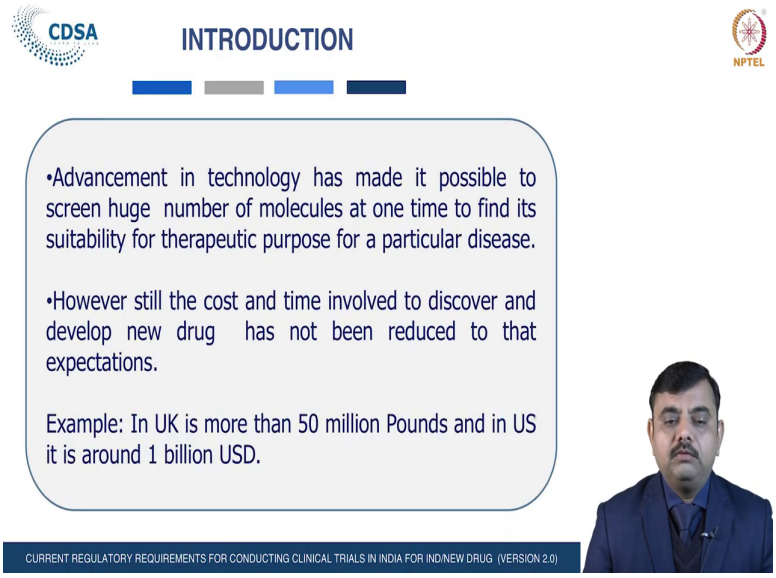

Advancement in technology made it possible to screen huge number of molecule thousand and million of the molecule to screen at a time to find it is suitability for therapeutic purpose for particular diseases.

However, if we see still the cost and the time involved to discover and develop a new drug or IND has not been reduced to that expectation. For example, if we see in UK it is more than 50 million pounds to discover a new drug and that is also not certain whether it would be effective or not. If we take a example of US it is around 1 billion US dollar that is why the drug discovery is very risky pathway.

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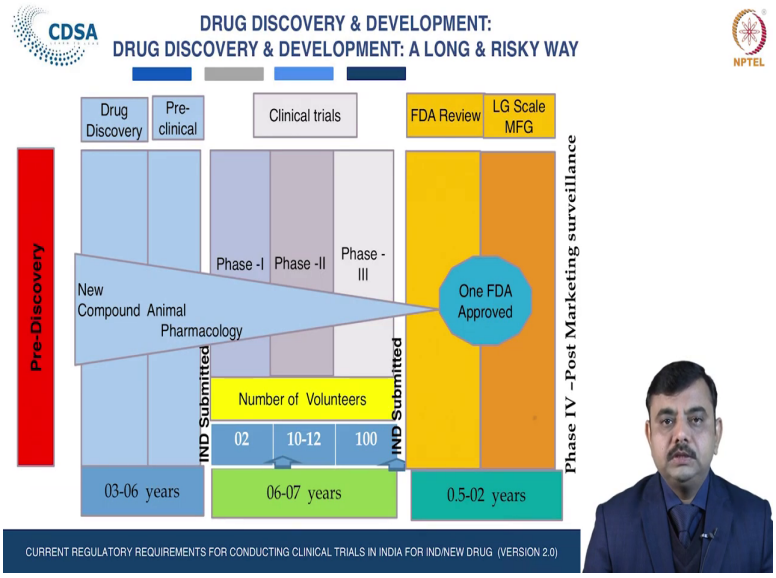

Let us have a look at this floor diagram whereby you will come to know, why it is a long pathway and why it is a risky way. So, the first stage for the drug discovery it is start from the pre-discovery. So, it the pre-discovery it is a understanding of the disease then identification of the target then it is validation that is a pre discovery. Once the target has been identified then the work for the discovery of the drug started.

So, the drug discovery it comes the identification of hit, identification of leads and lead optimization it comes into that phase that the drug discovery. Once the lead optimization has been over and one of the promising molecule has been found, then it enters into the preclinical that is; to identify the toxicity and the pharmacology of that drug into the animal model.

Once it has satisfactorily completed the animal study then it enter into the clinical trial and here the regulatory works actually starts. No doubt the pre-clinical and the animal studies also

require a permission for using the animals, but that is from the different authority that is a CPSCA board, animal ethics committee that that you require the permission.

Once you have completed and generated the data of the pre-clinical study then you require to apply for the phase-1 clinical with the CDSCO here the regulators work start. Then you need to enter into the phase-I and after completion of phase-1 then subsequently phase-II and phase-III once the result has been found satisfactory for phase-1 phase-II and phase-III.

See here below, you can see the time required has been given. So, the drug discovery and pre-clinical it takes around 3 to 6 year in different countries it varies and for the clinical trial it takes around 6 to 7 years. Here it is mentioned the number of volunteers also that is; number of subject participant for the phase-I phase-II and phase-II.

For phase-I it is approximately 2, then for phase-II it is 10 to 12 and for phase-3 it is a 100 though it has not been given in our Indian context, because it varies from the case-to-case and depending upon the nature and complexity of the drug the sample size is decided after the detailed deliberation and discussion about the drug.

Once this phase-3 has been completed then here the manufacturer or importer or we can say the applicant they can apply to manufacture or the import the drug. So, phase-3 is mandatory to come the drug into the market. That phase-III after the phase-III the marketing permission or importing permission can be associated with the condition of the phase-IV trial. So, after the drug approval for the marketing and for the import into the country the condition may be imposed to conduct a phase-IV trial and these review and phase-IV it takes around 0.5 to 2 years.

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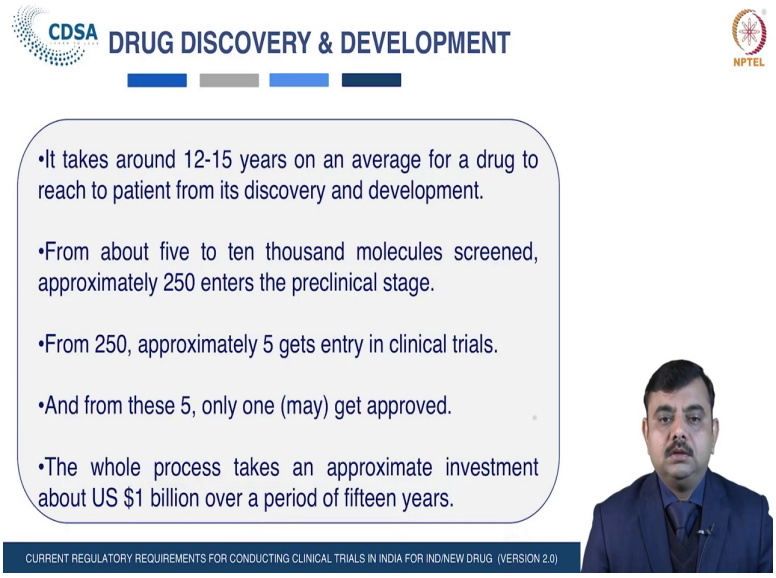

So, as we have seen it takes around 12 to 15 years on an average for a drug to reach to patient from it is a discovery and it is a development. And we have seen it is a first it is a identification of hits, identification of leads, so around 5 to 10,000 molecules screen and from these 5 to 10,000 molecules only 250 molecules enters into the pre-clinical stage. And from this 250 only around 5 gets entry into the clinical trial.

And from these 5 molecules, only one get a chance to be approved. The whole process takes investment as I have mentioned about US dollar 1 billion and the time required is around 15 years. That is why this process is process and this pathway is risky, time consuming and it require a lot of investment.

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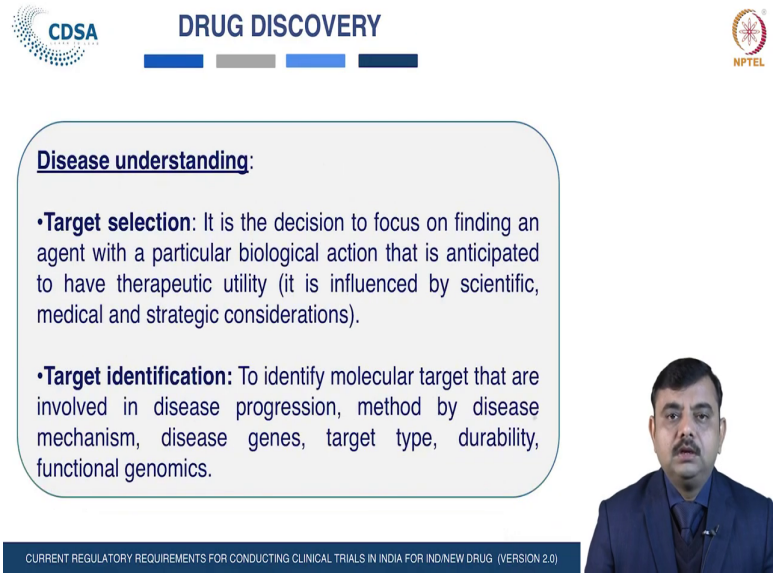

Let us begin with the what are the stages involved in the pre-discovery, discovery and development. So, the very first stage in the drug discovery we can say this is a pre-discovery also the disease understanding. The what type of disease for which the manufacturer would like to have the new drug or the IND. The mechanism of the disease the bio-chemical, pathological and physiological process of the disease must be understood.

Then the target selection; target selection it is the decision to focus on finding an agent with a particular biological action that is; anticipated to have therapeutic utility. And this decision is always influenced by scientific medical and strategic consideration also.

Then the target identification; the target identification to identify the molecular target that are involved in disease progression most of the time it is a protein or receptor. Method by disease

mechanism or it can be a disease gene, we will see it later on what is target and what it is a probability.

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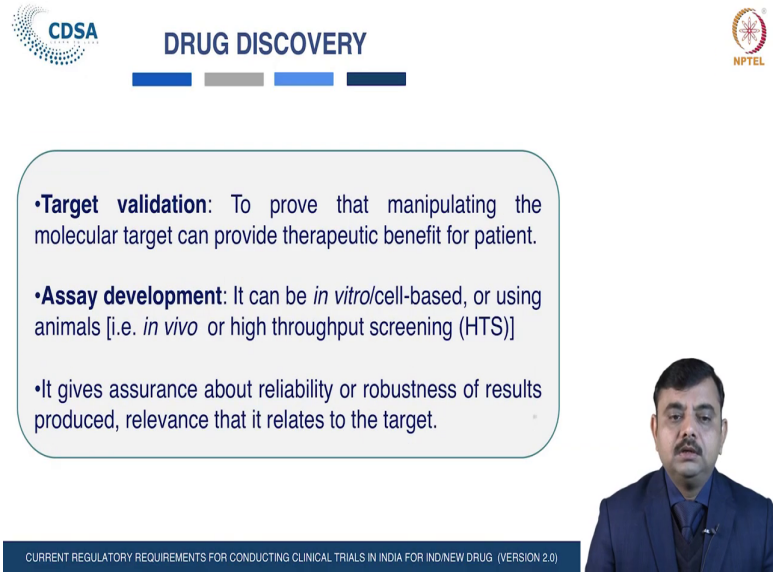

Then once it has been identified there is a target validation to prove that manipulating the molecular target which have been identified and provide therapeutic benefit to patient.

After target validation, then it is a assay development, it can be in vitro cell based, or using animal, that is; in vivo or through the HTS. This gives assurance about the reliability robustness of result produced and relevance that related to the target.

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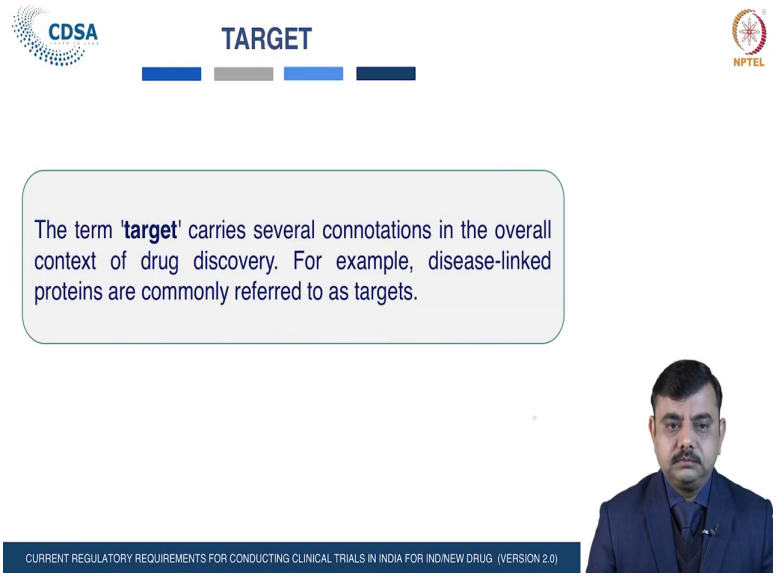

As I have mentioned the term target carries several connotations in the overall context of drug discovery. For example, disease-linked proteins are commonly referred to as a target.

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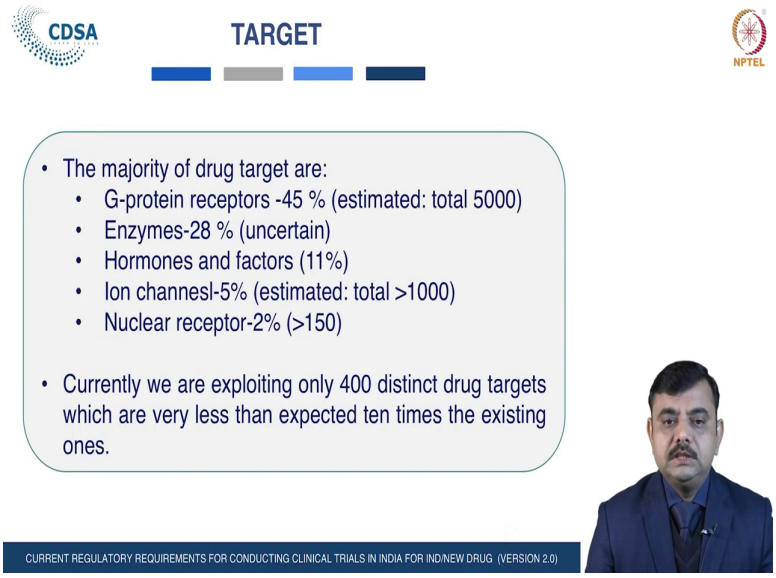

These are the majority of drug target and the uses of that has been given into the percentage. So, the G-protein receptor the 45 percent, enzymes 28 percent, then the hormones factors that is 11 percent, ion channels 5 percent and nuclear receptor 2 percent these are the probability of the target which are used for the drug discovery. If we see currently, we are exploiting only 400 distinct drug target which is very less than the expected 10 times the existing one.

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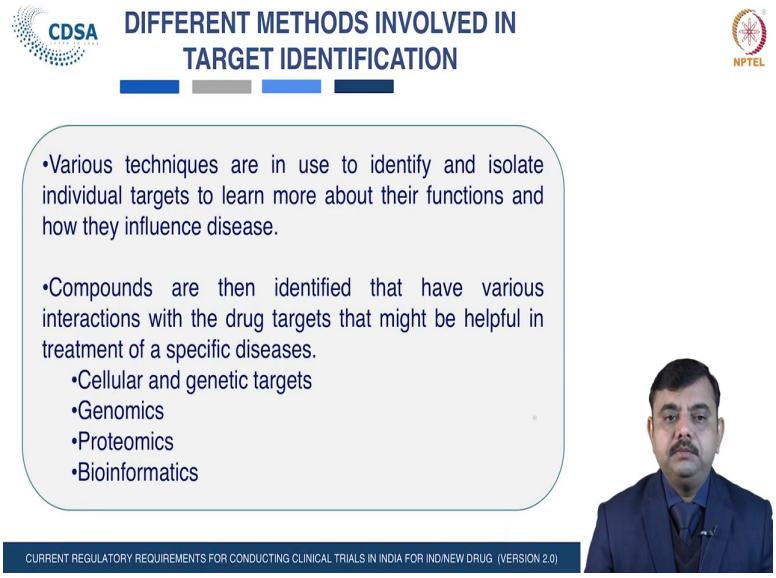

There are many methods for the target identification various techniques are in use to identify and isolate individual target to learn about their functions and how they influence the diseases. Compounds then identified that have various interaction with the drug target that might be helpful in treatment of specified diseases. So, these are the methods like cellular and genetic target, then genomics, proteomics and the bioinformatics which is well known to all of us.

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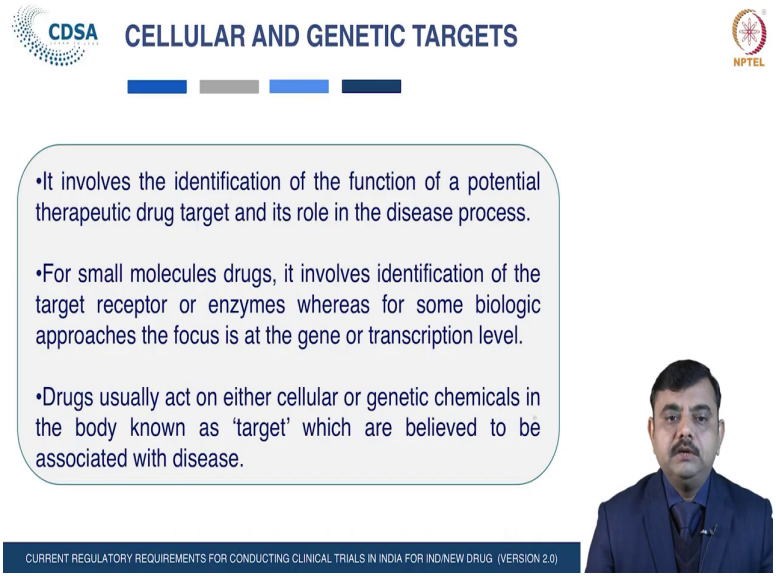

Let us see in brief what is this cellular and genetic target method. It involves the identification of the function of a potential therapeutic drug target and it is role in the disease process. For small molecules drug, it involves identification of the target receptor or enzymes whereas, for some biological approaches the focus is at the gene or transcription level. Drugs usually act on either cellular or genetic chemicals in the body known as the target which are believed to be associated with the diseases.

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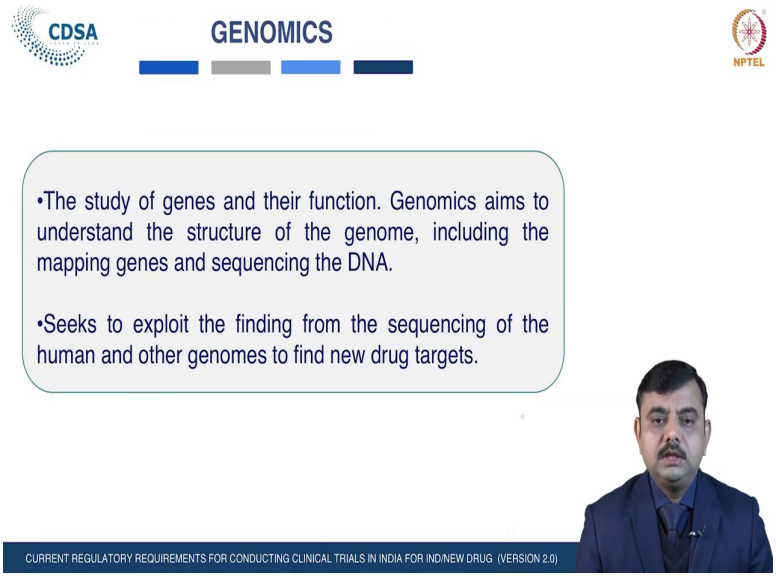

The study of gene and their function. Let us see now, what is genomics this is also one of the method to identify. The study of gene and their functions. Genomics aims to understand the structure of the genome, including the mapping gene as sequencing the DNA. It seeks to exploit the finding from the sequencing of the human and other genomes to find a new drug target.

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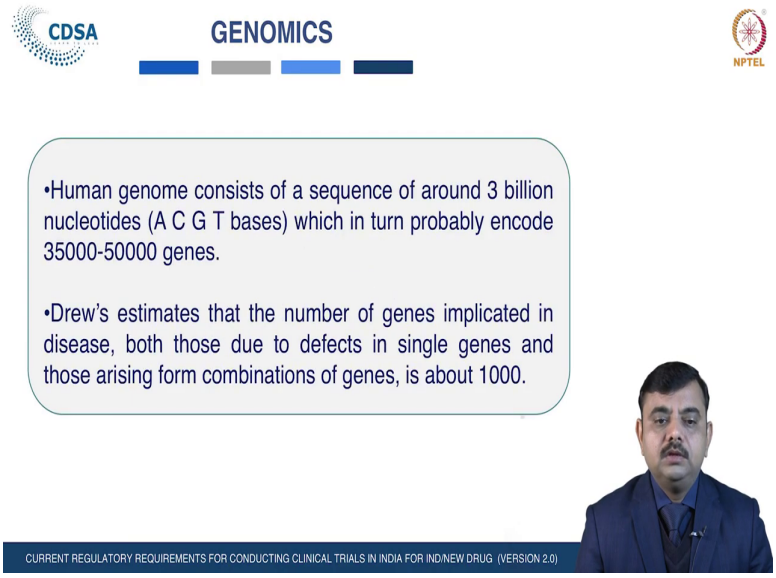

Human genome as we know consist of sequence of around 3 billion nucleotides that A C G we know that, adenine guanine on all these which in turn probably encodes 35000 to 50,0000 genes.

Drew's estimate that the number of genes implicated in disease, both those due to defect in single gene and those arising from combination of gene, is about 1,000.

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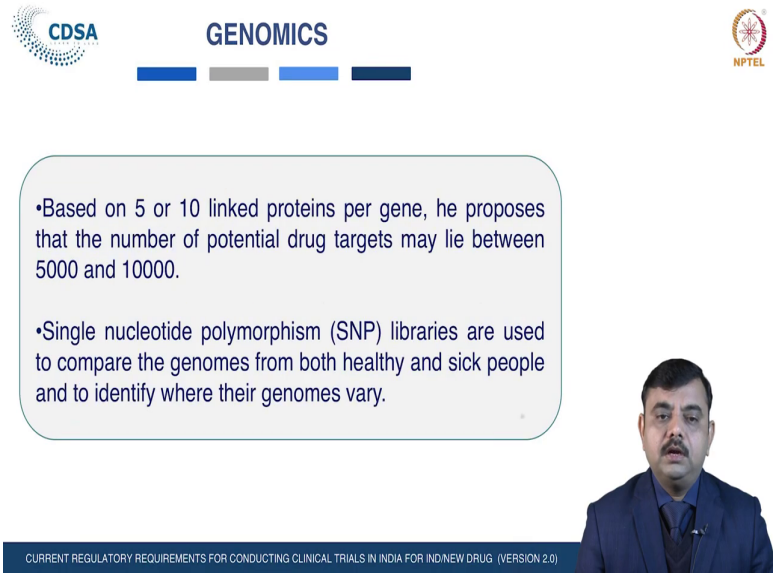

And based on 5 or 10 linked protein per gene. He also proposes that the number of potential drug target may lie between 5,000 and 10,000. Single Nucleotide Polymorphism that is SNP libraries are used to compare the genomes from both healthy and sick people to identify where their genomes are varying.

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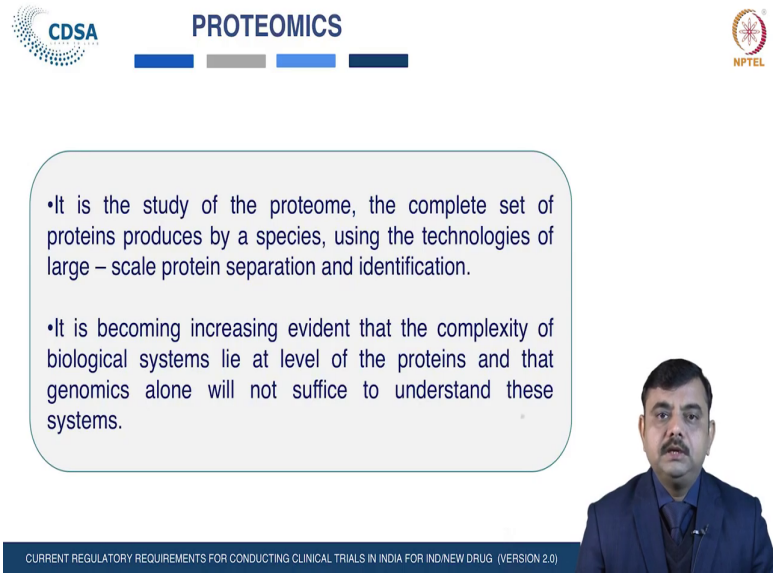

The other method that is; the proteomes, it is the study of the proteome, the complete set of a protein produces by a species, using the technologies of large-scale protein separation and identification.

It is becoming now a day's increasing evident that the complexity of biological system lie at level of the proteins and that genomics alone will not suffice to understand these systems.

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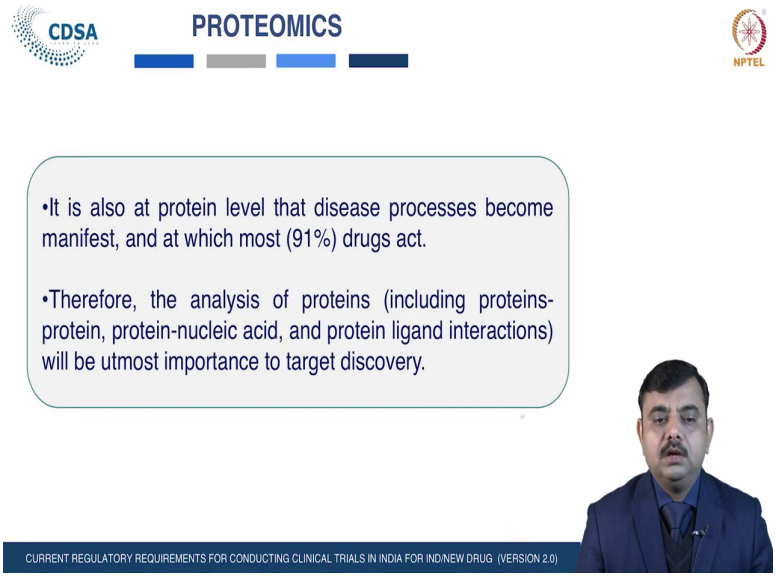

It is also at protein level that diseases processes become manifest this disease processes become manifest, and at which most drugs act. Therefore, the analysis of proteins including protein-protein, protein nucleic acid and protein ligand interaction will be at most importance to drug discovery.

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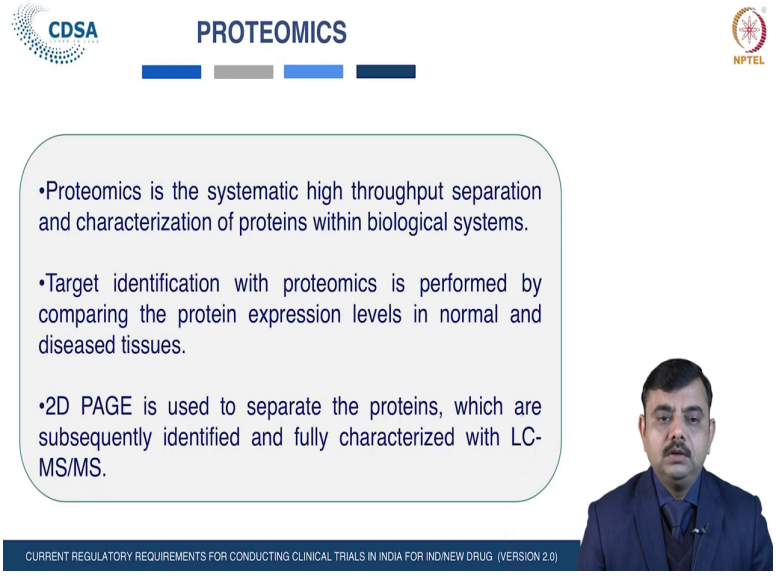

Proteomics is the systematic high throughput separation and characterization of proteins within biological systems. Target identification with proteomics is performed by comparing the protein expression level in normal and diseased tissues. 2D page is used to separate the proteins which are subsequently identified and fully then characterized with LC-M S and MS.

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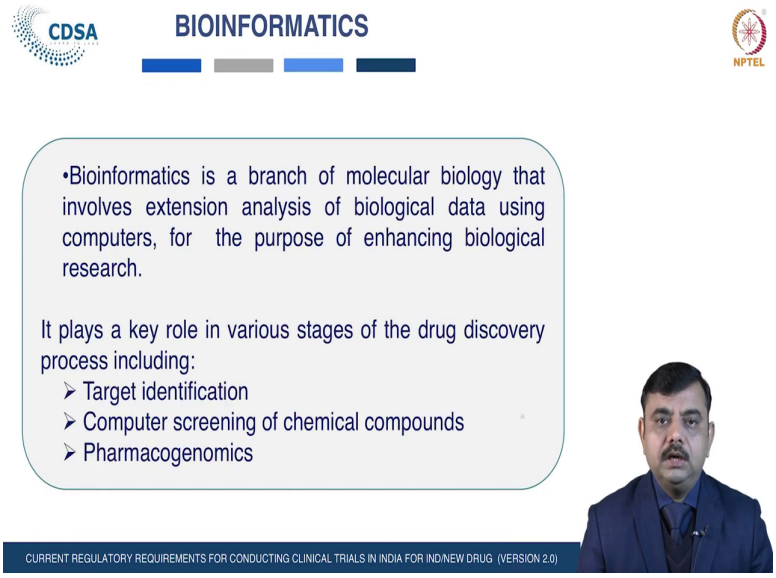

The another method is bioinformatics as we know it is a branch of molecular biology that involves extension analysis of biological data using computer, for the purpose of enhancing biological research. It plays a key role in various stages of the drug discovery like a; target identification, computer screening of chemical compound or the pharmacogenomics.

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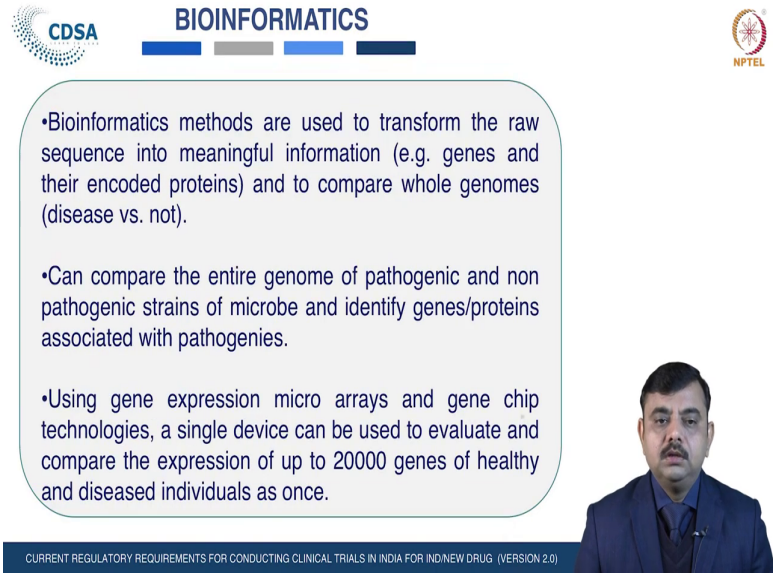

This is the methods used to transform the raw sequence into a meaningful information. For example, genes and their encoded proteins and also to compare whole genome that is disease versus not in the disease. It can compare the entire genome of pathogenic and non pathogenic strains of microbe and identify genes protein associated with this phatogenism

Using gene expression micro arrays and gene chip technologies, a single device can be used to evaluate and compare the expression of up to 20,000 genes of healthy and diseased individual as once.

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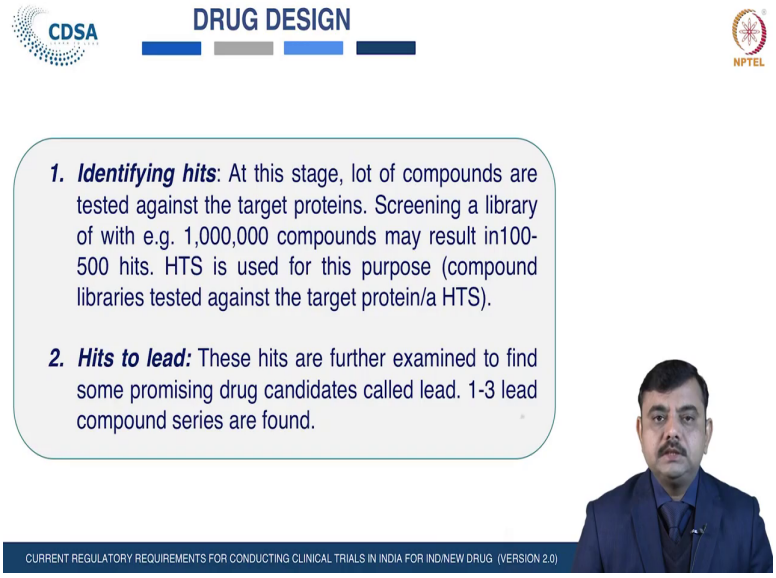

Now, let us see the drug designs as I have mentioned in the introduction slide; the first stage is uh, identifying the hits. At this stage a lot of compound are tested against the target proteins by screening a library of with for example, having 1 lakh or more than that compounds even million of compound, may result this may result in 100 to 500 hits. This used for this HTS that is a; High Throughput Screening used for this purpose this is the compound libraries HTS is the compound libraries tested against the target proteins.

Then once this 100 to 500 hits are identified, then there is a process for the hits to lead these hits are further examined to find some promising drug candidate and that drug candidate is called as a lead candidate. From this 100 to 500, 1 to 3 lead compound series can be found.

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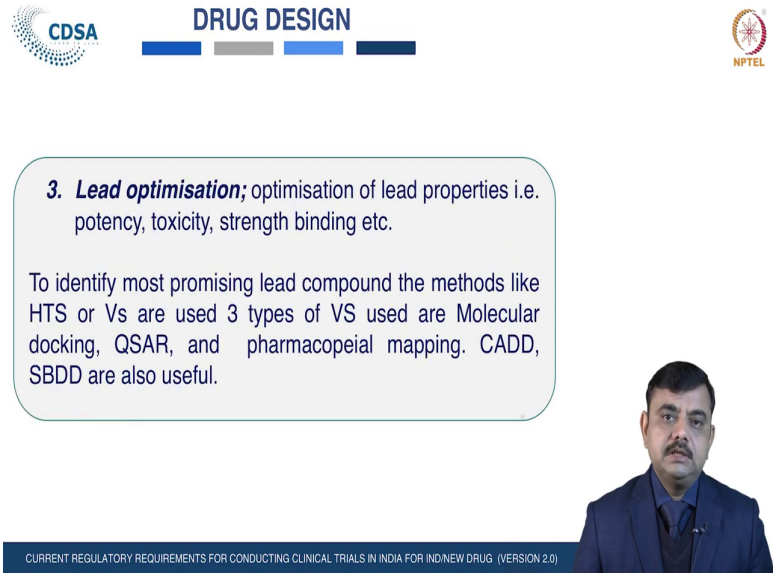

Once this lead compound has been found, then it is a optimization it is not always that the lead compound is having all the properties with respect to safety and efficacy that is; why the lead optimization is required. The optimization of lead properties that is with respect to the it is potency, toxicity, strength binding and other properties

To identify this most promising lead compound the methods like HTS or virtual screening are used, 3 types of virtual screening used are molecular, docking then QSAR that is; Qualitative Structure Activity Relationship and pharmacopeial mapping. Other methods like CADD as we know that computer aided drug design a structure based drug design that are also useful.

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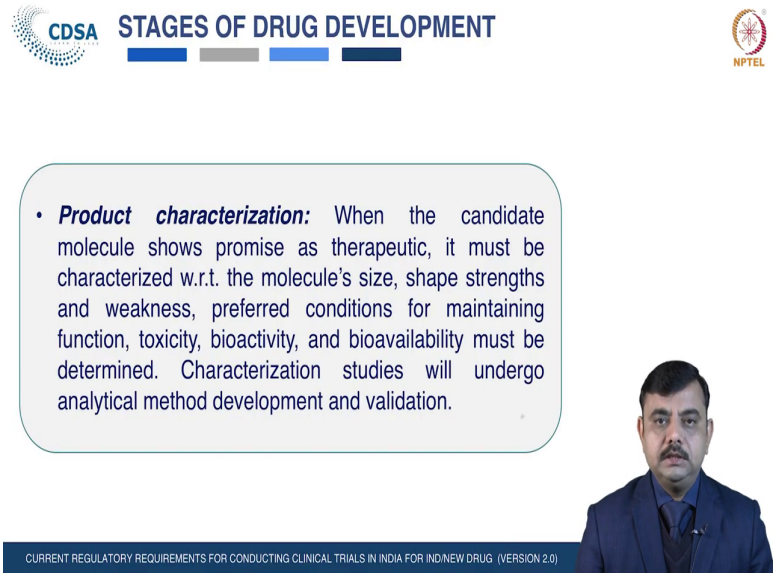

Once these has been identified then it is a product characterization when the candidate molecule shows promise as a therapeutic, it must be characterized with respect to the molecule size, then shapes, strength and weakness preferred conditions for maintaining it is function, toxicity, bioactivity and it is a bioavailability must be determined. Characterization studies will undergo analytical method development and method validation.

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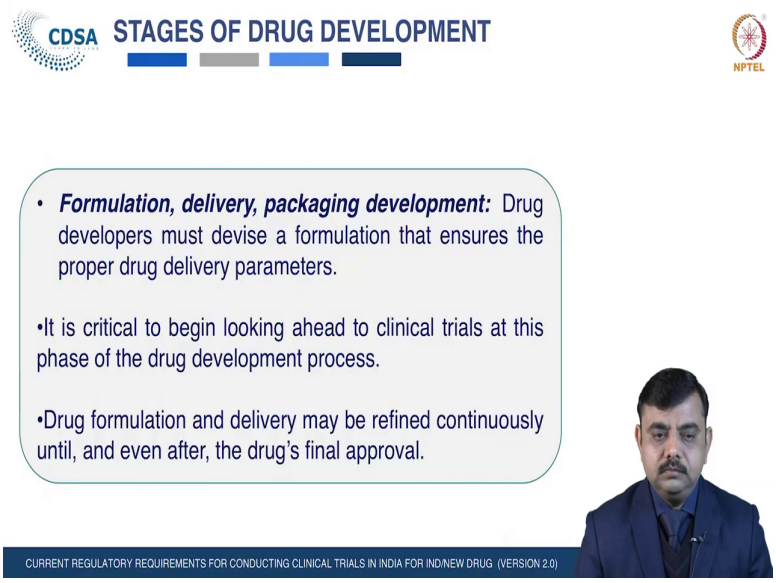

Then it comes to the formulation, delivery and packing development. Drug developers must devise a formulation which will ensure the proper drug delivery parameters. It is critical to begin looking ahead to a clinical trial at this phase of the drug development process. Drug formulation and delivery maybe refined continuously until, and even after, the drugs final approval.

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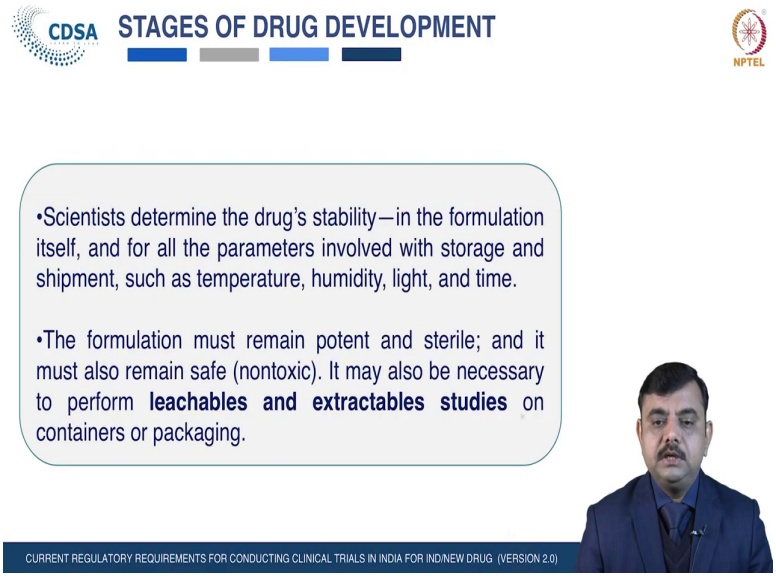

Scientists determine the drug stability-in the formulation itself, and for all the parameters involved with a storage and shipment, such as temperature, humidity, light and time. The formulation must remain potent and sterile in case, of the parental and sterile product and it must also remain safe that is why it should not be a not toxic.

It may also be necessary to perform leachable and extractable studies on containers or packing this is also necessary to maintain the safety of that drug or otherwise if the for example, from plastic container there is a leachability then that may render the product harmful.

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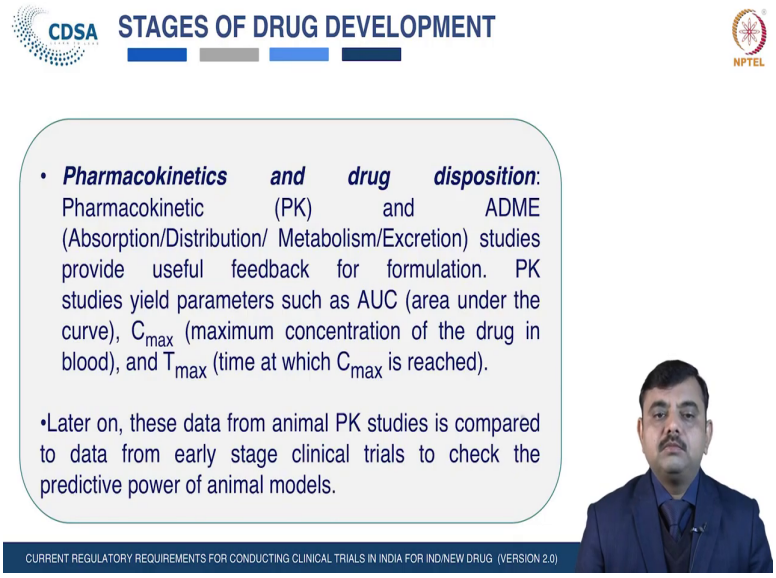

Then it comes to the pharmacokinetic and drug disposition, PK and PD we know that pharmacokinetic like absorption, distribution, metabolism and excretion. These studies provide useful feedback for the formulation. PK studies yield parameter such as AUC and C max and T max. Later on, these data from animal PK study is compared to data from earlier stage clinical trial to check the predictive power of animal model.

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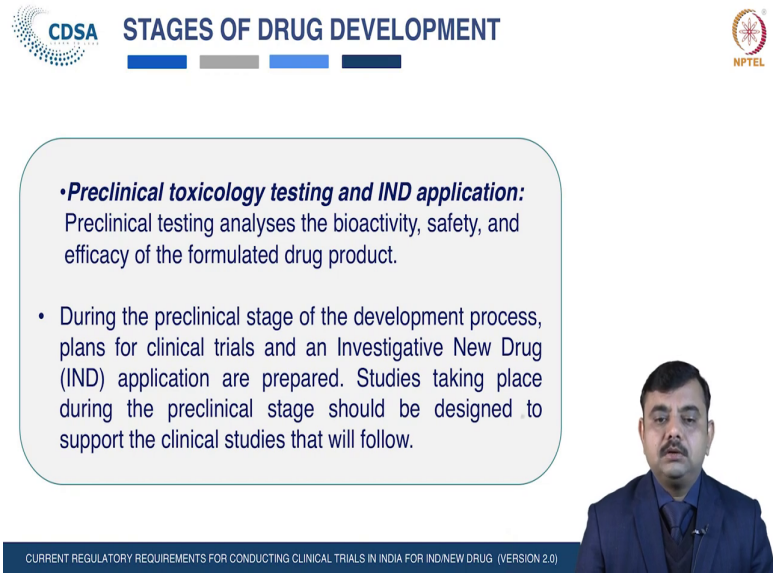

Then it comes to the pre-clinical toxicology testing and the IND application; pre-clinical testing analyzes the bioactive, safety and efficacy of the formulated drug product. During the pre-clinical stage of the development process plans for clinical trial and investigational new drug application are prepared. Studies taking place during the preclinical stage should be designed to support the clinical studies that will follow.

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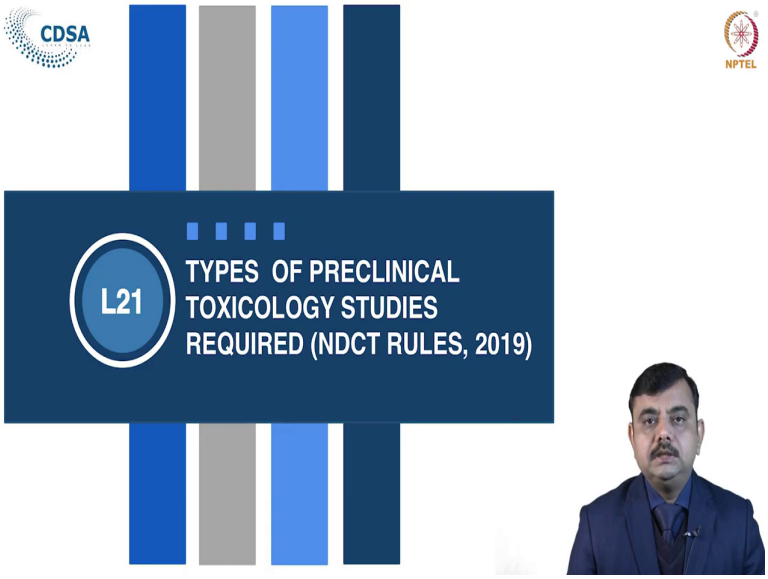

Actually, these preclinical study they are they can be divided into the pre-clinical toxicological study and the pharmacological study and these studies are required as per the new drug new NDCT rule 2019.

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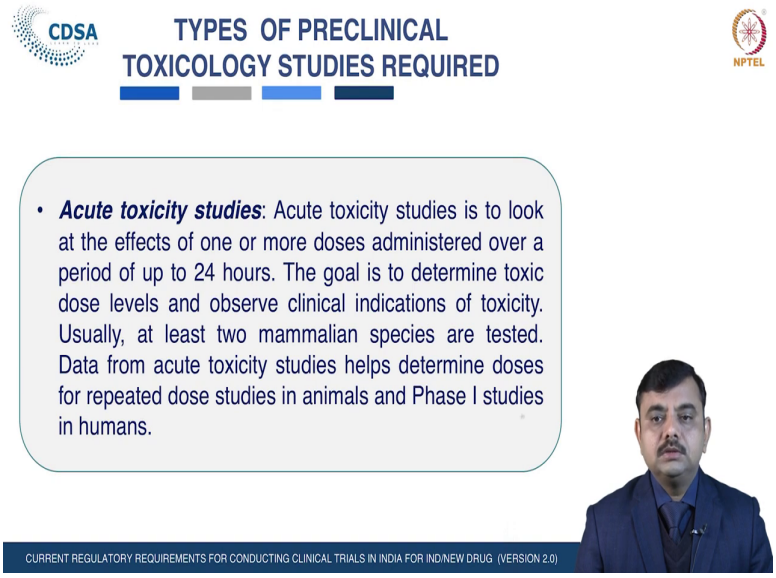

The studies like acute toxicity studies, these acute tox study is to look at the effect of one or more doses administered over a period of up to 24 hours. The goal is to determine toxic dose level and observe clinical indication of toxicity. Usually, at least two mammalian species are tested and the data from acute toxicity studies help to determine doses for repeated dose studies in animal and phase-1 studies in human.

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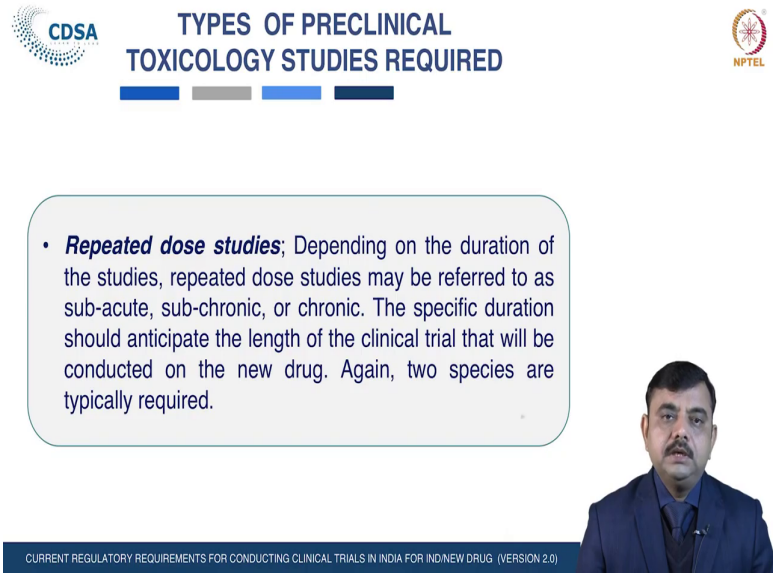

Repeated dose studies, it is depend upon the duration of the studies, repeated dose studies maybe referred to as sub-acute, sub-chronic or the chronic studies. The specific duration should anticipate the length of the clinical trial that will be conducted on the new drug. Again here two species are typically required.

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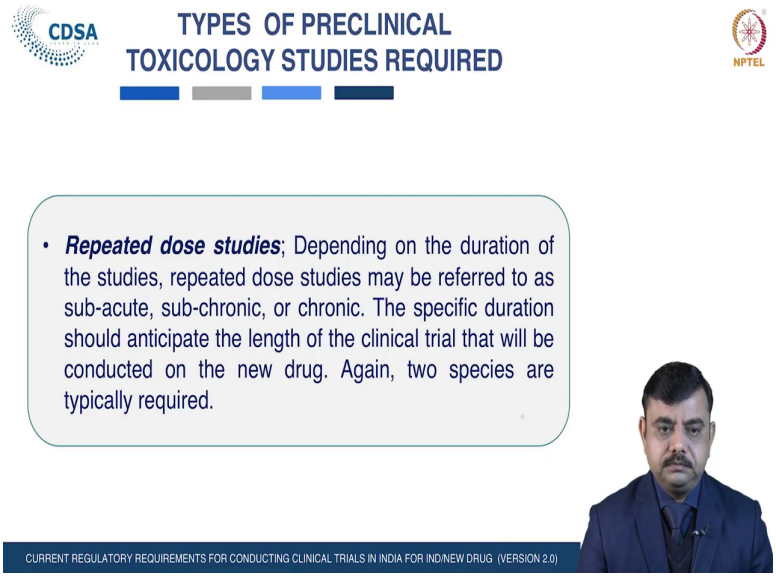

Genetic toxicity studies; these are very important studies and these studies assess the likelihood that the drug compound is whether mutagenic or carcinogenic. Procedure such as; Ames test which is conducted in bacteria to detect the genetic damage and the other test to detect the DNA damage which is assessed in the test using mammalian cell such as the Mouse Micronucleus Test. The Chromosomal Aberration Test and similar procedure to detect the damage at the chromosomal level this test has also been used.

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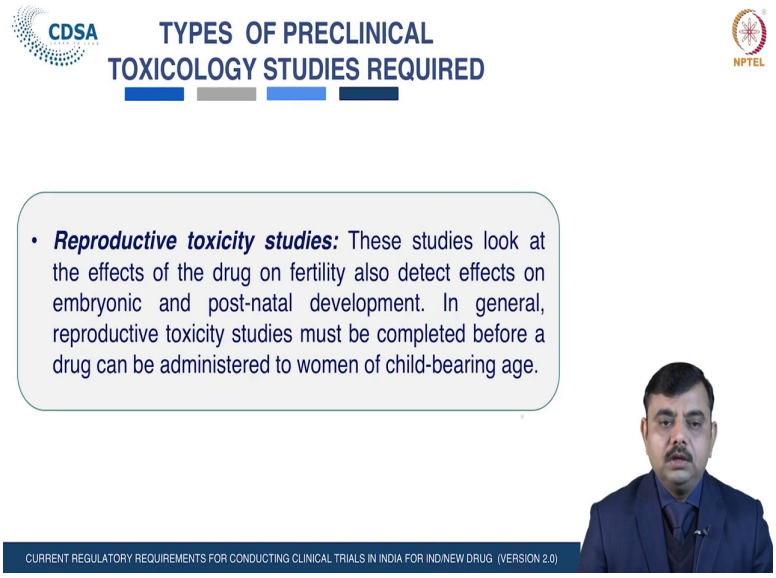

In the reproductive toxicity studies; these studies look at the effect of the drug on fertility and also detect effect on embryonic and post-natal development. In general, reproductive toxicity studies must be completed before a drug can be administered to woman of child-bearing age.

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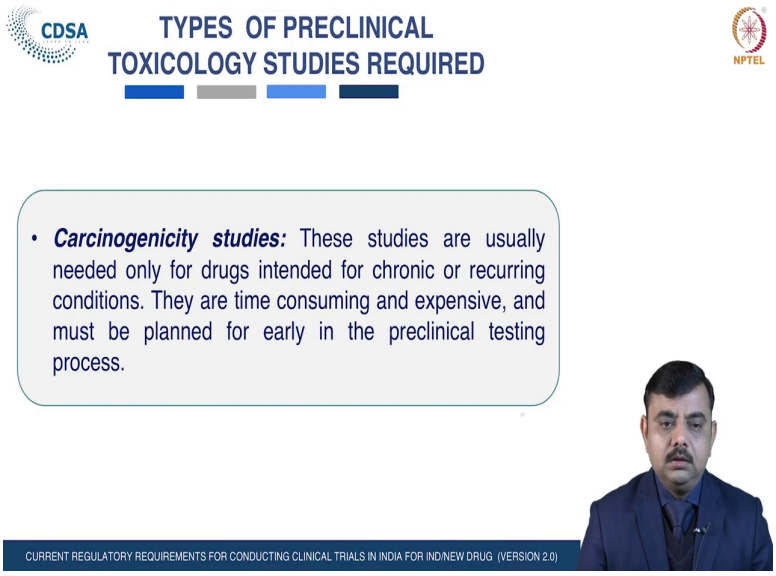

Carcinogenicity studies; these are usually needed only for drugs intended for chronic or recurring conditions. They are time consuming and extensive and must be planned for early in the preclinical testing processes.

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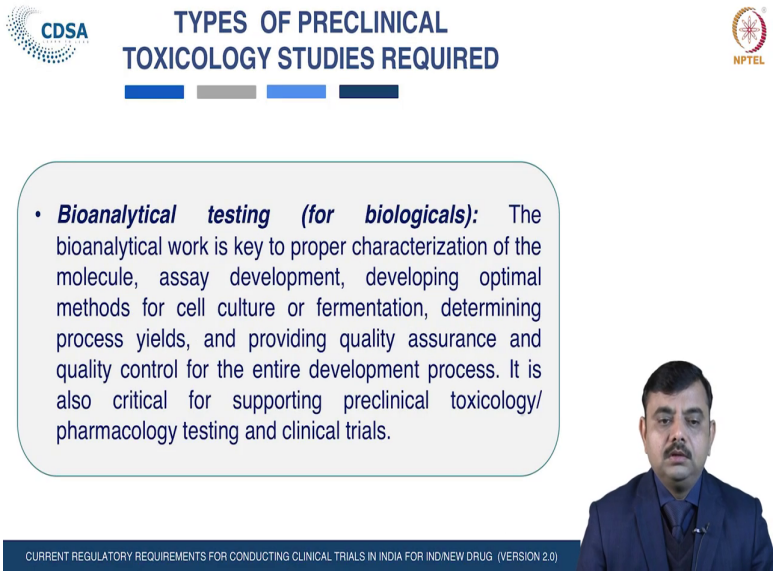

Then bioanalytical testing, the bioanalytical work is key to proper characterization of the molecule, assay development, developing optimal method for cell culture or fermentation, determining process yield, and providing quality assurance and quality control for the entire development process. It is also critical for supporting pre-clinical toxicology pharmacology testing and clinical trials. So, these are the animal toxicological test let us see the type of pre-clinical that is animal pharmacological studies.

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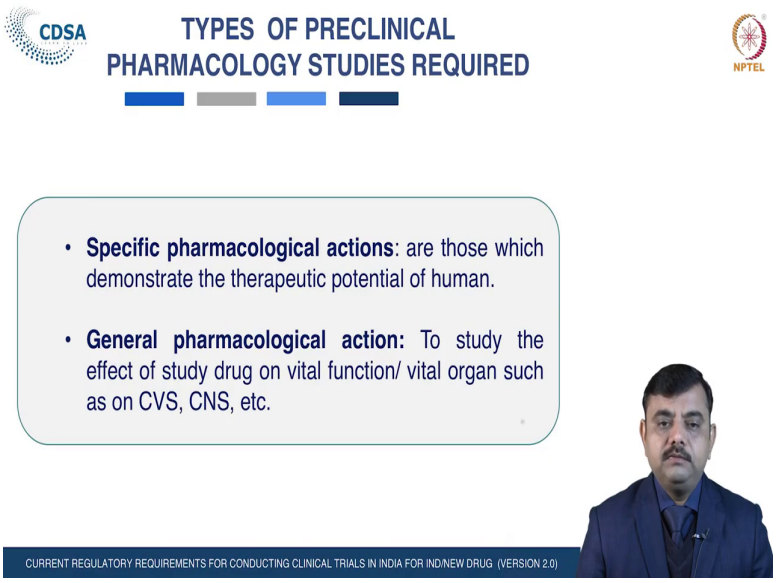

In the new drug and clinical trial rule the these studies they have been given and these are the specific pharmacological actions these are those which demonstrate the therapeutic potential of human. Then the general pharmacological actions to study the effect of study drug on vital functions, vital organ such as CVS or CNS and other.

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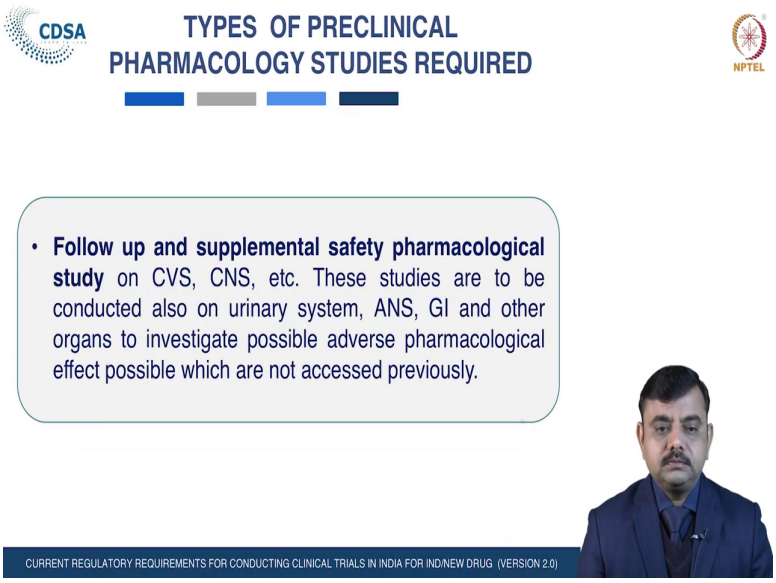

Follow up and supplemental safety pharmacological study; on C V S and C N S and also on urinary system, ANS, GI and other organs to investigate the possible adverse pharmacological effect possible which are not assessed previously. So, once we get the satisfactory pre-clinical studies then there would be a application for the clinical trial it start with the phase-I in India, if it is a IND drug.

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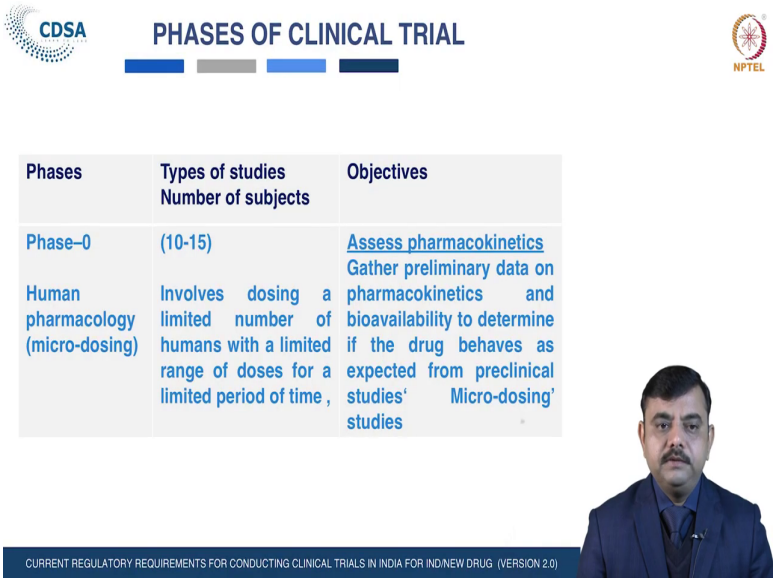

Let us see the different stages of the clinical trial. So, the phase-0, this phase-0 actually it is not in our country, but in some countries, they are applying for the phase-0 this is a this is called a micro dosing phase or human pharmacology. It involves around 10 to 15 subject and it involves dosing a limited number of human with a limited range of dosage for a limited period of time.

And the objective of this micro dosing is to assess pharmacokinetics to gather preliminary data on pharmacokinetics and bioavailability to determine if the drug behave as expected from pre-clinical studies that is micro dosing studies.

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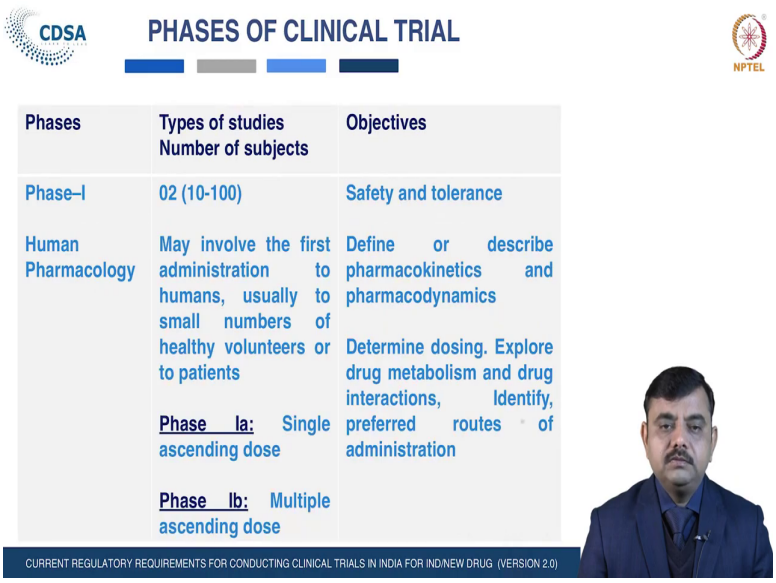

Phase-I is a human pharmacological study, it is approximately in 10 to 100 subjects. It may involve the first administration to humans usually to small number of healthy volunteers or to patient depending upon the drug. It can also be divided into the phase-Ia and phase-Ib. Phase-Ia, is single ascending dose, phase-Ib is a multiple ascending dose. And the objective of the study is safety and tolerance it would define or describe the pharmacokinetics and the pharmacodynamics to determine the dosing to explore the drug metabolism and the drug interaction to identify the preferred route of administration these studies required to be conducted.

Phase-II study that is the therapeutic exploratory, the number of subjects involved maybe 10 to 12 or a 100 to 13 in the different countries the different sample size has been mentioned.

This may be undertaken in a larger group of human patient than of phase-1 and the objective of this phase-II study is efficacy and safety.

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Phase-IIa to demonstrate clinical efficacy or biological activity through pilot studies, to explore therapeutic dose range. And phase-IIb to determine optimum therapeutic dose and regimen, to resolve uncertainties regarding the design and conduct of subsequent trials.

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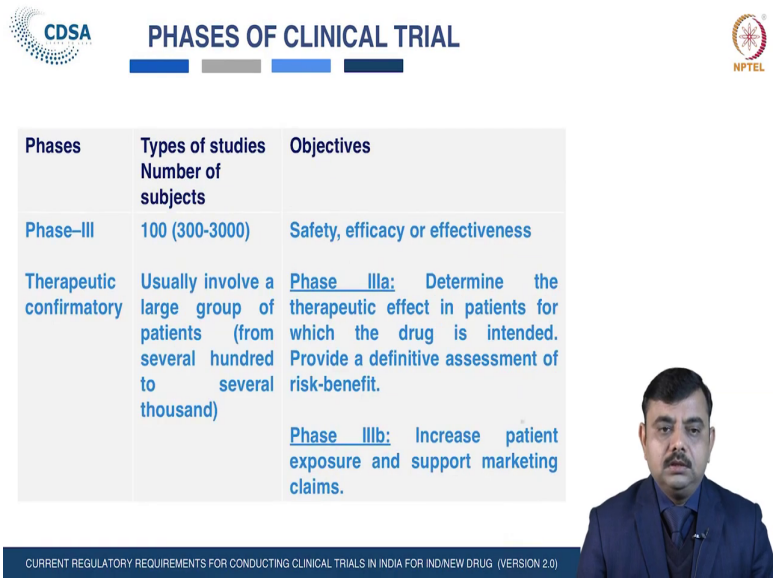

Then it is phase-III we call it as a therapeutic confirmatory phase and further the number of subject is increased here. It is around 300 to 3,000 and certainly the number of subjects are more than from the phase-II usually, it involve a large group of patient from several 100 to several 1,000. And the objective of this phase-II safety efficacy or we can call effectiveness to determine the therapeutic effect in patient for which the drug is intended and to provide a definitive assessment of benefit to increase the patient exposure and support marketing claim. So, this is the confirmatory therapeutic phase.

Then it comes to a phase-IV. So, before phase-IV the permission can be granted to conduct to manufacture the drug and to make it available in the market depending upon the results obtained.

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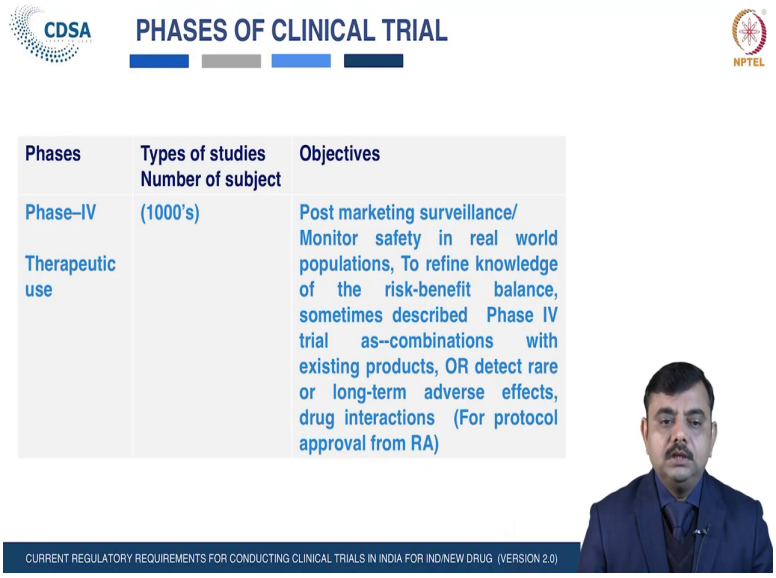

Then phase-IV as I have mentioned this phase-IV may be associated with the conditional approval or it can be exempted. So, this is again in the larger population say for example, thousands or more than that and again it is depend upon the nature of the drug and complexities involved. The objective of this phase-IV is it is a post marketing surveillance to monitor safety in a real world to refine knowledge of the risk benefit balance. Sometimes described phase-IV trial as combination with existing product or detect rare or long-term adverse effect or the drug interaction.

So, this is up to the phase-IV clinical trial and once this phase-III and phase-IV clinical trial are completed as I have mentioned the drug can be marketed by taking the manufacturing permission in India, it is from the state licensing authority. And if it is import then the applicant

has to apply for the import of this a drugs and after having the import license and the registration then again that has to be enter into the market.

So, this is all about the new drug discovery development and the regulatory process, the regulatory pathway to be followed we have already covered in our previous lectures. So, you can refer that for it is better understanding.

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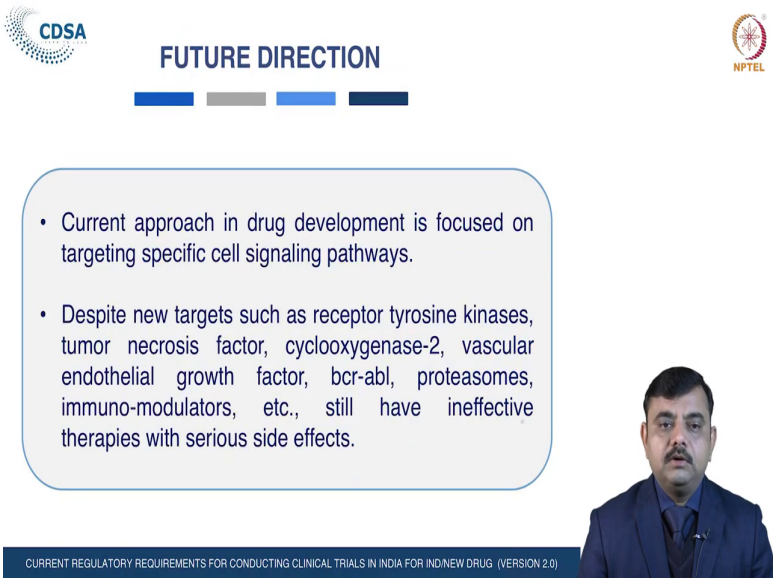

Let us see what is the future direction. So, the current approach in drug development is focused on targeting specific cell signaling pathways. Despite having new targets such as receptor tyrosine kinases, tumor necrosis factors.

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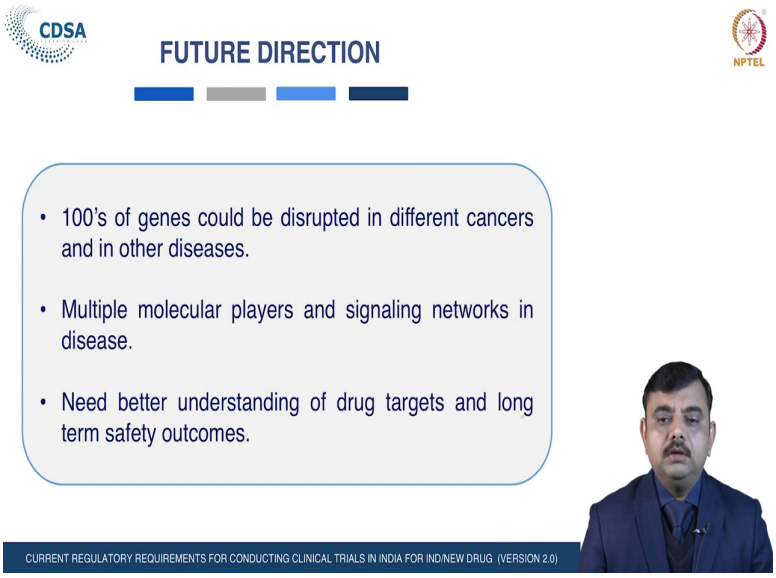

Still we have ineffective therapies with a serious side effects and 100's of gene could be disrupted in different cancer and in other diseases. We have seen this the multiple molecular players and signaling networks in disease. Need to have a better understanding of further drug target and long term safety outcomes. So, this is about the drug discovery and the development.

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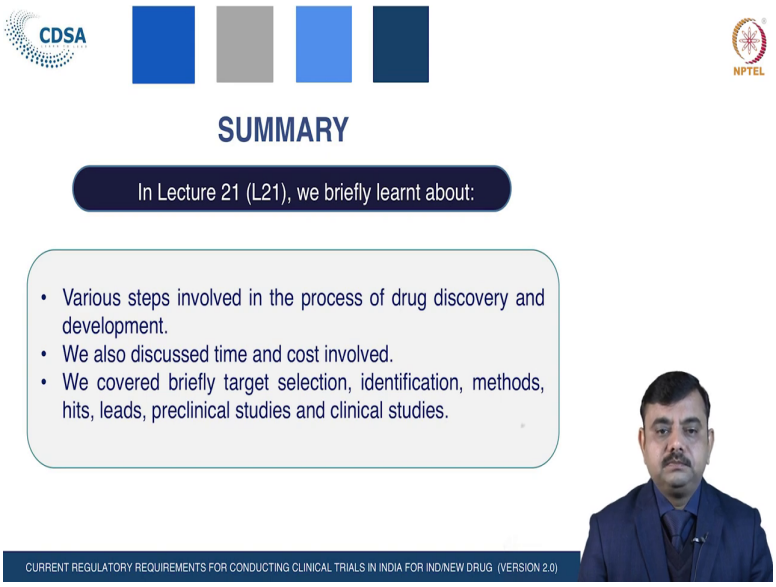

Let us see what we have seen in this lecture. So, in briefly we have seen what are, what is means by drug discovery, what is drug development approximate the time required the cost involved in it, why this is risky pathway and what is target, what is target selection, validation. We have also seen the method for the target identification, then hits then what is leads, lead optimization pre-clinical studies and the clinical studies.

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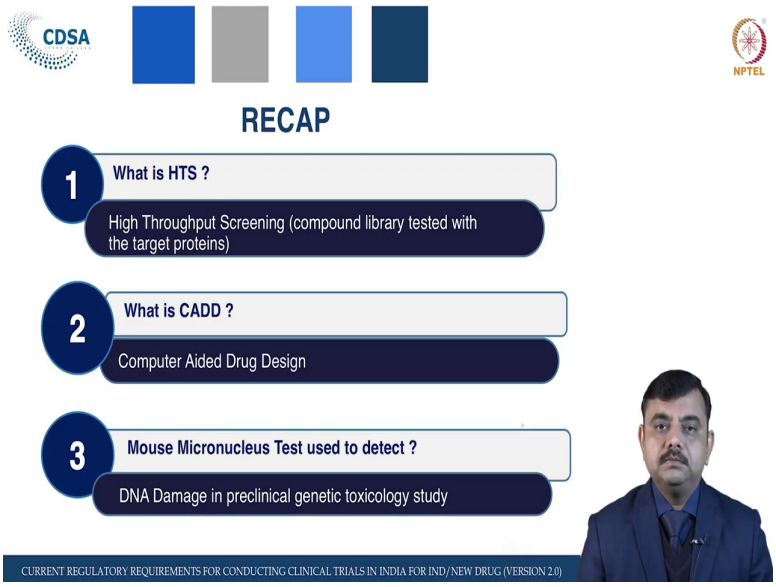

Now, it is your time to see how much you could understood from this lecture. So, the first question for you what is HTS? I have mentioned in my one of the slide, yes this is the High Throughput Screening, it is a compound library tested with the target protein. The next question what is the CADD? This is a Computer Aided Drug Design.

The next question Mouse Micronucleus Test used to detect? You have to answer for what the test is required? This test is to assess the DNA damage in pre-clinical genetic toxic study.

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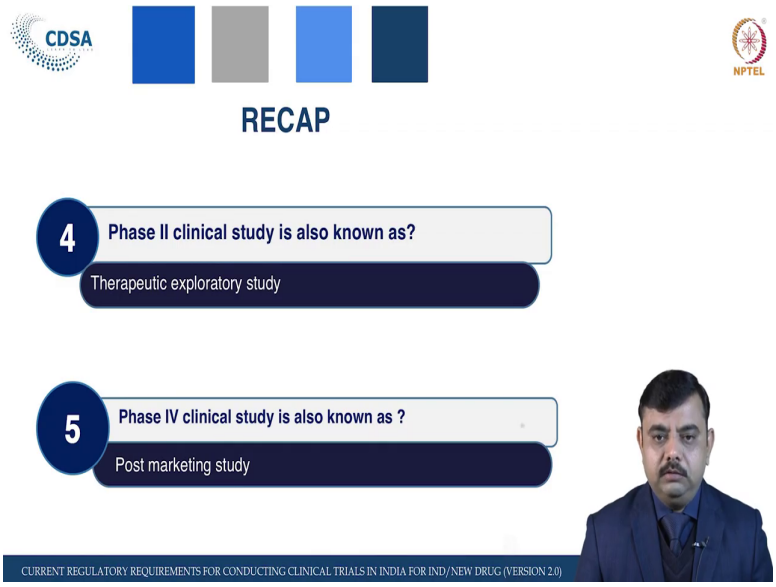

Question 4 phase-II clinical study is also known as? So, this is very simple this is a therapeutic exploratory study. And the last question is also similar like phase-IV clinical study what is means by, what is known as a phase-IV clinical trial study? So, it is a post marketing study.

So, dear friend this is all about our lecture new drug discovery and development, we will see in our next lecture till then you take care bye bye and all the best.

Thank you.