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

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## Lecture – 05
## Pre-Clinical Data Requirements

Hello friends, hope you are doing well. You are once again welcome to the course which is related to the current requirement for conducting clinical trial in India. Dear friend, this course is related to the clinical trial, related provisions in India, but we have seen that in many of the lecture. For example, if you required to submit a protocol for phase three, clinical trial then you required to submit before that preclinical studies.

If the drug has been discovered in India and if applicant in tends to submit a phase one study, then also for the conduct of the phrase one study, he has to shows the preclinical data.

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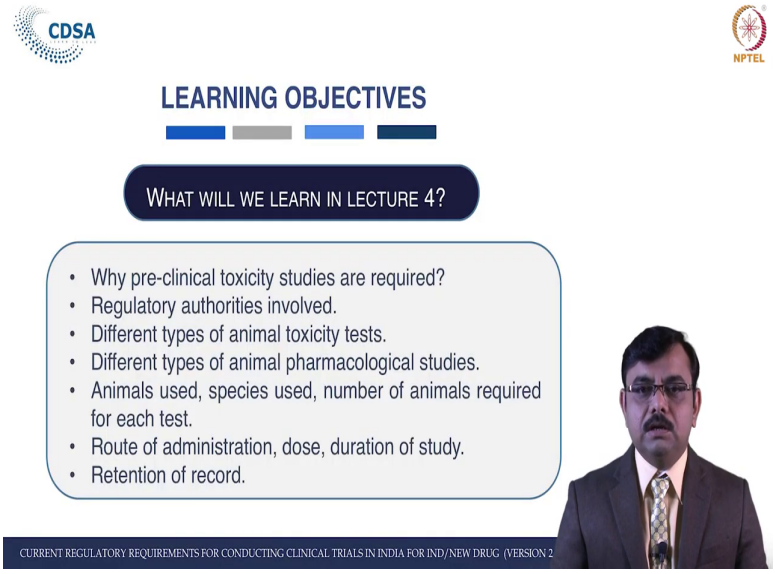


So, here we have given the focus in this lecture to show you the preclinical data requirement, that is why this lecture has been designed. So, this is our lecture 4, which is related to the preclinical data requirement. In this lectures the learners will come to know the why preclinical toxicity studies are required, then what are the regulatory authorities which are involved in giving the permission for use of experimental animals, then what are the different types of preclinical animal toxicity studies and animal pharmacological studies.

Then which are the animals supposed to be used, what species supposed to be used, then for each test how many numbers of the animal should be used, what should be the dosing criteria, what should be the route of administration as compared to the clinical and what should be the duration of the study. So, this we are going to see in this lecture. So, let us start with the purpose of the study why the preclinical studies are required.

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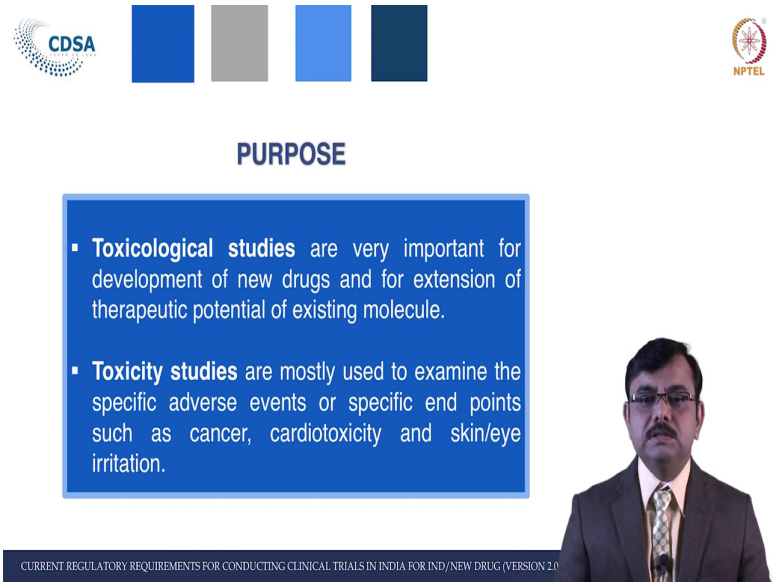


Dear friend, toxicological studies are very important for development of new drug and for extension of the therapeutic potential of that existing molecules. These studies are mostly used to examine the specific adverse event or specific endpoint such as cancer or cardio toxicity, skin, eye irritations.

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This test also help to calculate the NOAEL that is no observer if adverse effect level dose and these are helpful for the clinical trial. Once, this NOAEL has been observed, the dose can be adjusted in the clinical study. Moreover, the as per CDSCO regulation that is a central licensing authority, it is essential to screen new molecule for pharmaceutical activity and toxicity potential in animal as per the New Drug and Clinical Trial Rule 2019, it is mentioned in the second schedule para two and three, if you refer where it is clearly mentioned that the preclinical studies are conducted to define pharmacological and toxicological effect.

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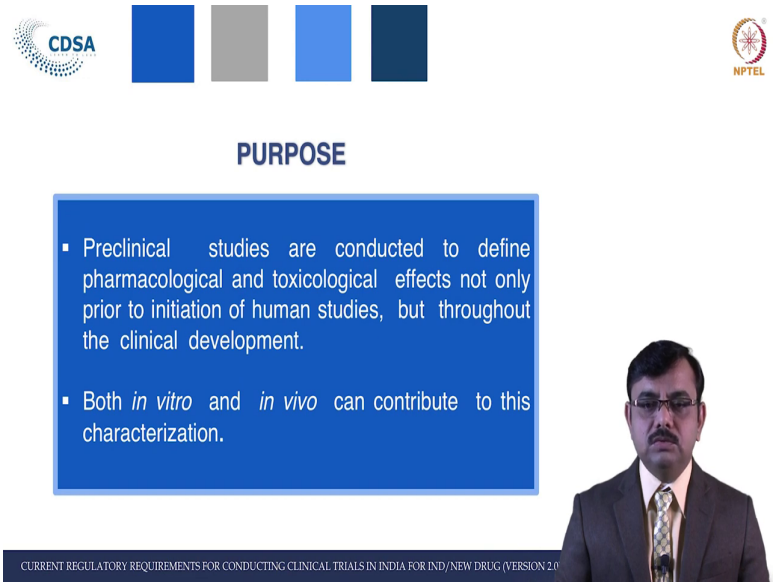


Not only prior to initiation of human studies, but throughout the clinical development and the data with respect to that required to be submitted along with the application. Both in vitro and in vivo can contribute to this characterization. So, in the early stages of the drug development, it is very risky to subject that drug to the clinical status or to try that drug into the human population, that is why the small animals are used to ascertain the safety related issues with that drug. Let us see the regulation in India.

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So, as we have seen the New Drug and Clinical Trial Rule 2019, the second schedule under D and C act and rules there under deals with the preclinical study, then before using the animals, the applicants required to take a permission from these committees like Institute Animal Ethics Committee, we call it as IAEC then CPCSEA, committee which is the committee for the purpose of control and supervision of experiment in animal. So, these committees permission is required before the preclinical studies.

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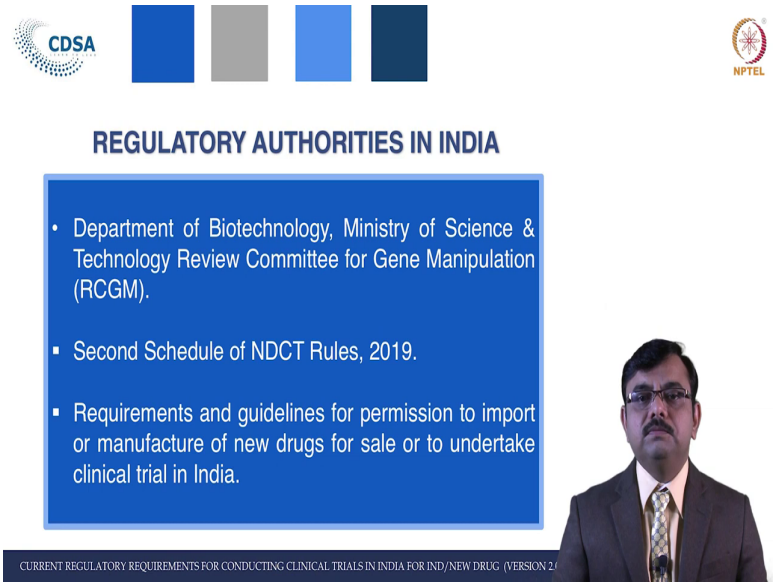


Then one more department that is a Department of Biotechnology, which is under ministry of science and technology. The review committee for gene manipulation, this committee mostly deals with the microorganism if the product is of biotechnology and if there is a problem using the microorganism in the environment, this committee is there to look after such issues. Further, the second schedule of NDCT rules, as I have mentioned requirement and guideline for permission to import or manufacture of new drug for sale or to undertake clinical trial in India, it is mentioned in second schedule.

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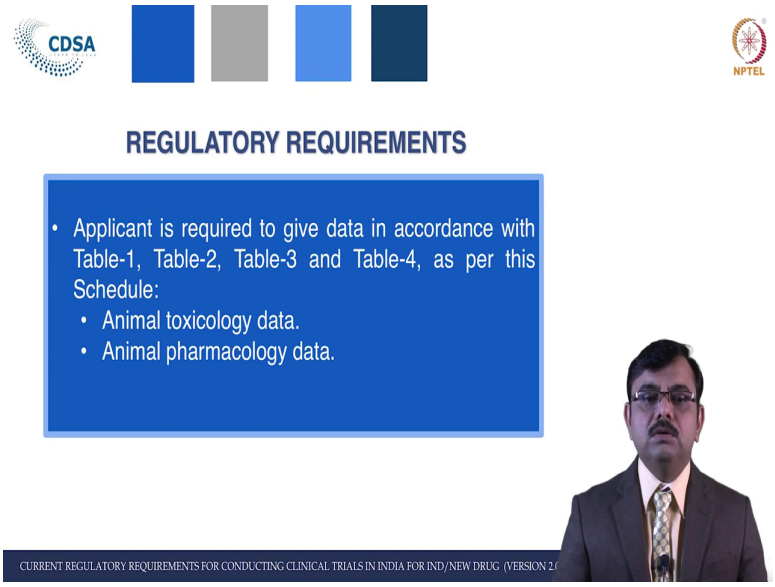


And the applicant is required to give data in accordance with the Table-1, Table-2, 3 and 4 as per these schedules. The animal toxicological data and animal pharmacological data is required. So, this is the mandate of this rule.

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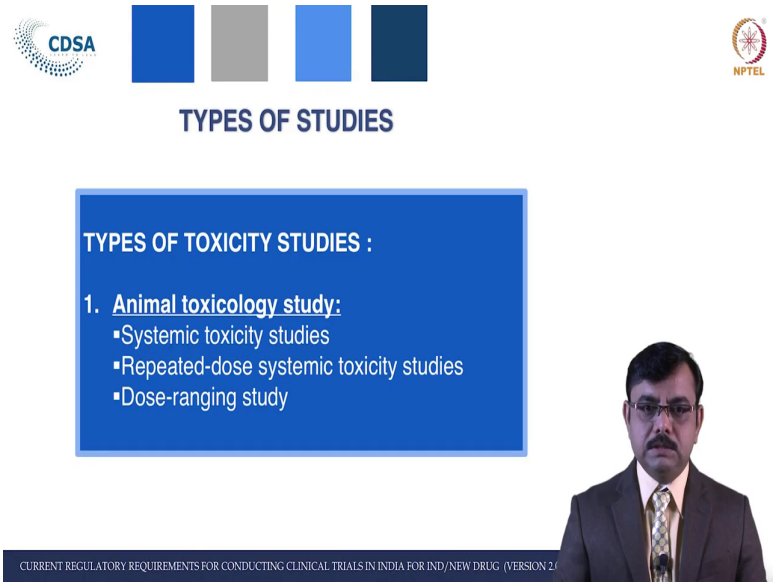


Let us move toward our actual concept what is preclinical study and what are the types of study required to conduct and required to submit the data with respect to that. So, as I have mentioned there are two type of studies; animal toxicology studies and animal pharmacological studies. So, these are the studies which I have mentioned here in this slides, required to be conducted, depending on the nature of the drug and the type of the phase of the clinical trial required to do.

The different types of studies are required. Let us have a look for this animal toxicological studies. So, these are systemic toxicity study, repeat dose toxicity study. In that single dose, multiple dose is also there.

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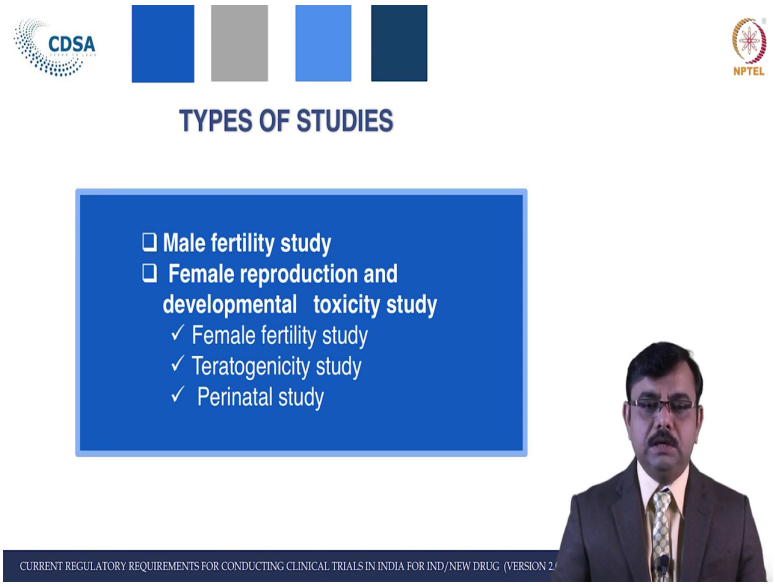


Then dose ranging studies, further male fertility study and female reproduction and developmental toxicity dose study. This is done through female fertility study, teratogenicity study and perinatal studies.

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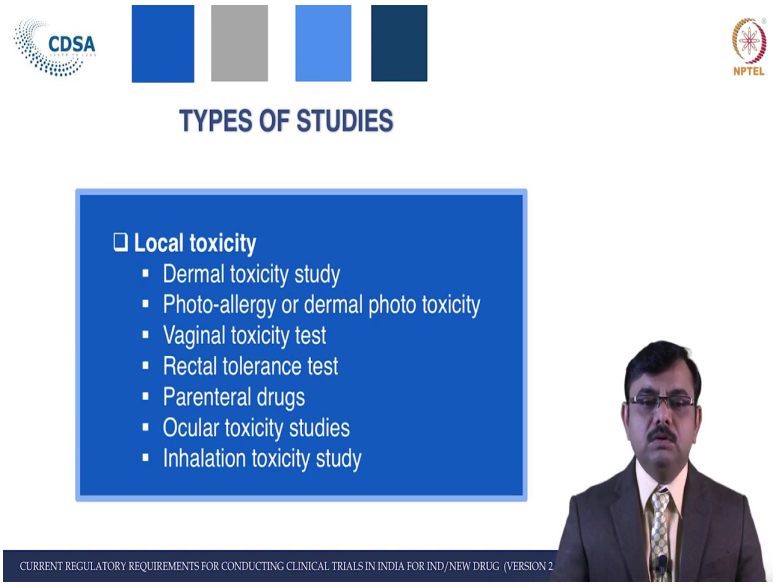


Then the local toxicity study which is mostly required in case of the product if it is applied locally. In these study these sub studies are dermal toxicity study, photo allergy study, dermal photo toxicity study, vaginal toxicity study, rectal tolerance test, parenteral drugs study, then ocular toxicity study, inhalation toxicity study, these are the test to be done, then hypersensitivity or allergenicity test in these are, there are two type of these tests the guinea pig maximization test and LLNA that is a local lymph node as a test. The hyper sensitivity can be determined with these test.

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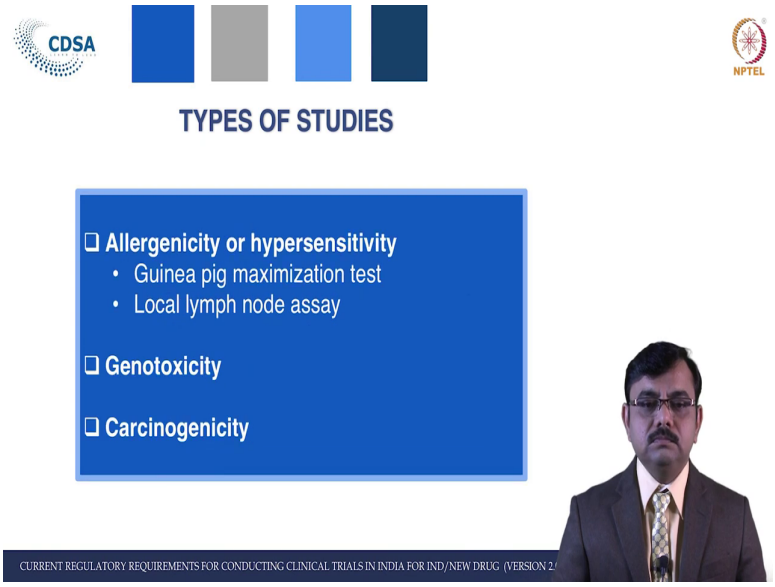


Then two more important tests that are required to be conducted for almost all the drug product is a genotoxicity and carcinogenicity. So, these are the animal toxicological tests.

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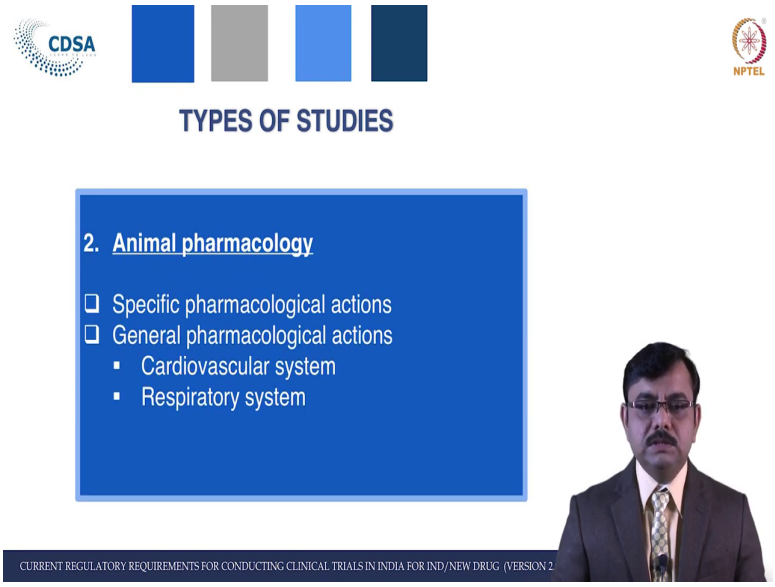


Next, we will see the animal pharmacological test, what is to be consider; what is to be done in the animal pharmacology. So, in this animal pharmacology the data with respect to the, this test has to be submitted the specific pharmacological actions and the general pharmacological actions. So, data related to the specific pharmacological actions, general pharmacological action for example, actions on the cardiovascular system actions of the drug which is given in the animal for and the effect on the respiratory system that is required to be submit.

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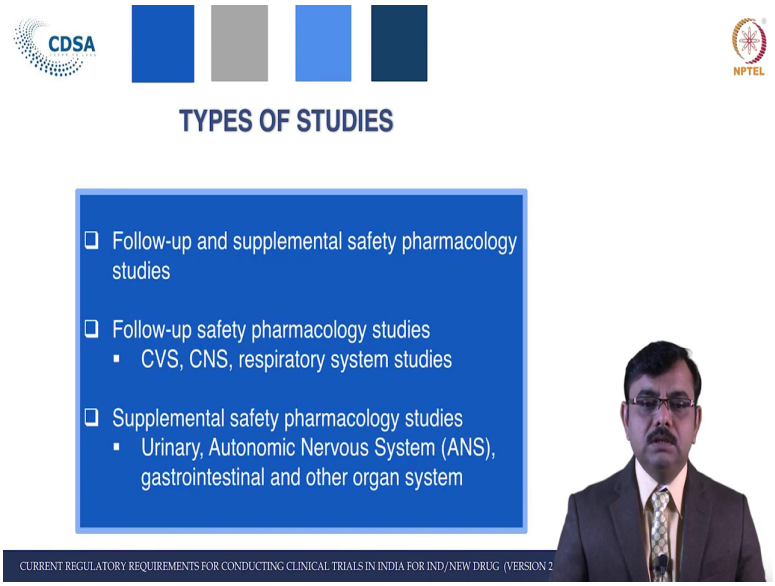


Then after this follow up and supplemental safety pharmacological study follow up safety pharmacological studies in these actually, there are two studies follow up safety pharmacological study and the follow up supplemental safety pharmacology study. In the follow up safety pharmacological studies the effect of the drug on the cardiovascular and CNS, respiratory system, etcetera has to be submitted and in case the supplemental safety pharmacological study the effect of the drug on urinary ANS, GI organ system and the other organ required to be submitted.

Let us see this one by one though, we are not going to be in depth for each test, but the we will, but we will cover the major test, what I have mentioned in the previous slides. So, let us start with the animal toxicology, this is also called as non clinical toxicity studies.

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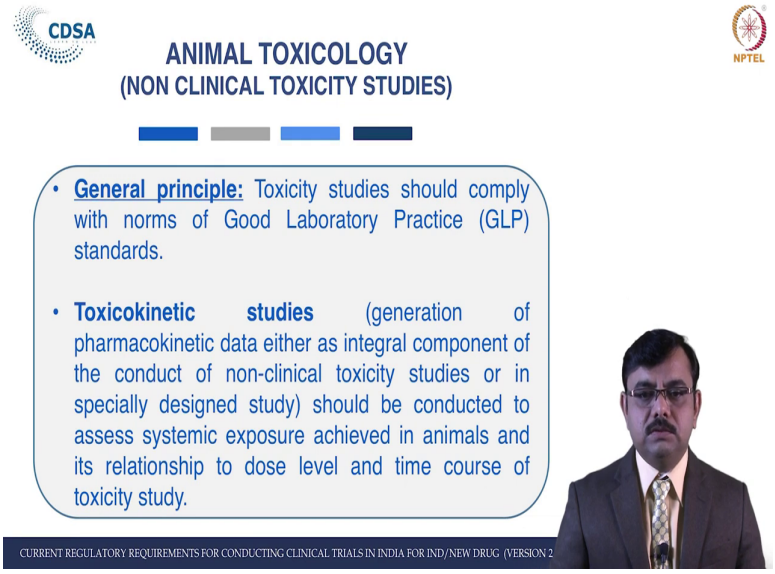


The in the general principle, in the toxicity studies should comply with the norms of the good laboratory practices standard. So, we have seen in our previous lecture from 2005, it has been become mandatory to conduct all this preclinical toxicity states in the laboratory, which is a GLP certified. Toxicokinetic studies, generation of pharmacokinetic data, either as integral component of the conduct of non clinical toxicity study or in special design study. It should be conducted to assess systemic exposure achieved in animals and its relation to dose level and time course of the toxicity study.

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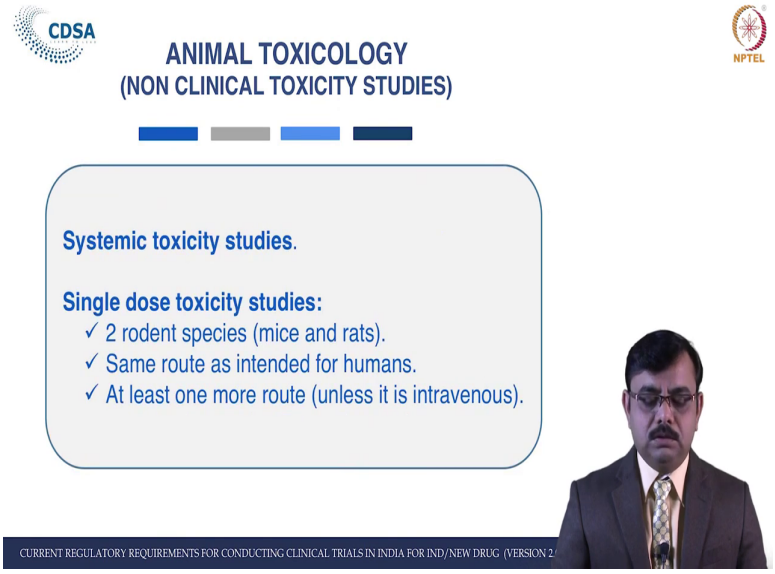


The first is that is a systemic toxicity study. It is the subtest of this, it can be single dose or multiple dose, we will see one by one. The single dose toxicity study, these studies should be carried out in rodent species, at least two rodent species required for this test the rodent species mostly use our mice and rats using the same route as intended for the human.

If the dosage form is intended to be used by the intravenous or oral route, the same route of administration required to be used in the preclinical study. In addition unless the intended route of administration in human is only intravenous, if it is a intravenous then there is no need of using the another route, but if it is not the intravenous route then in that case at least one more root should be used in one of the spaces to ensure the systemic absorption of the drug and this route should depend upon the nature of the drug.

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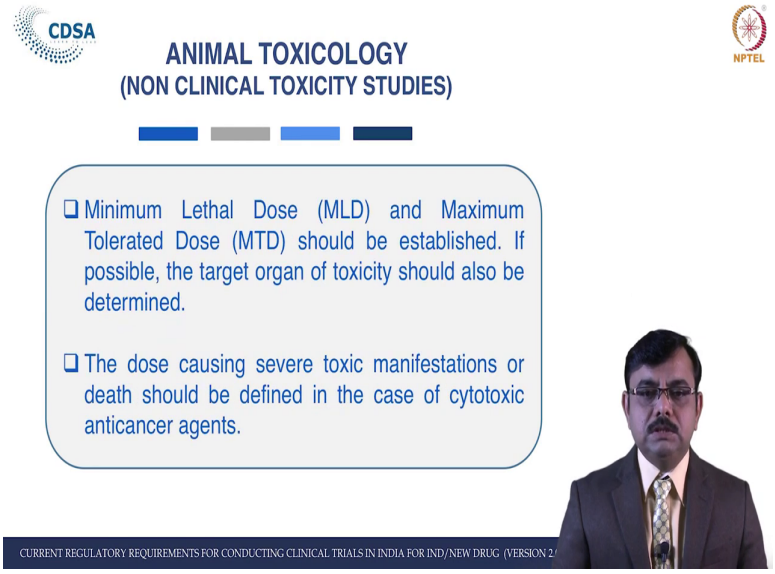


In this toxicity studies the minimum lethal dose and maximum tolerated dose should be established and if possible the target organ of toxicity should also be determined. The dose causing severe toxic manifestation or death should be defined in the case of the cytotoxic or anticancer drug.

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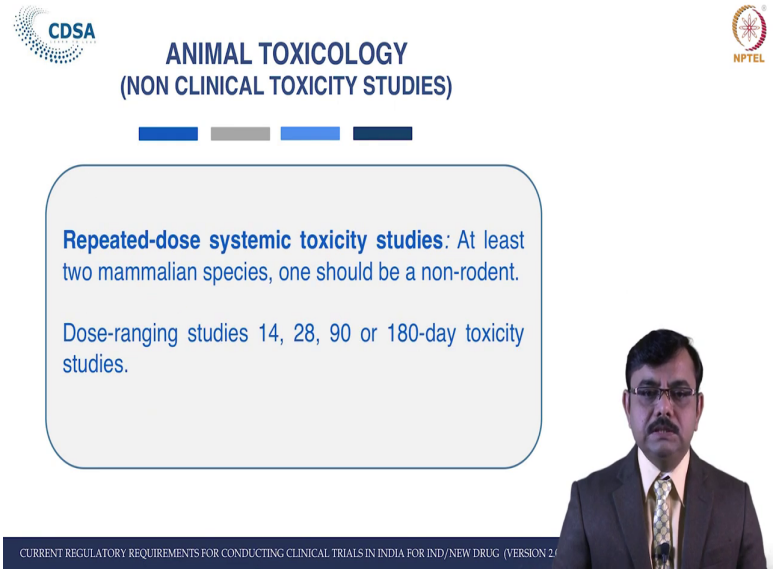


The next is repeated dose systemic toxicity study. This study also required to be carried out in at least two mammalian species of each one should be a non rodent and the dose ranging study should precede the 14 days, 28, 90 days or 180 days, toxicity study depending upon the time of exposure and time of the treatment.

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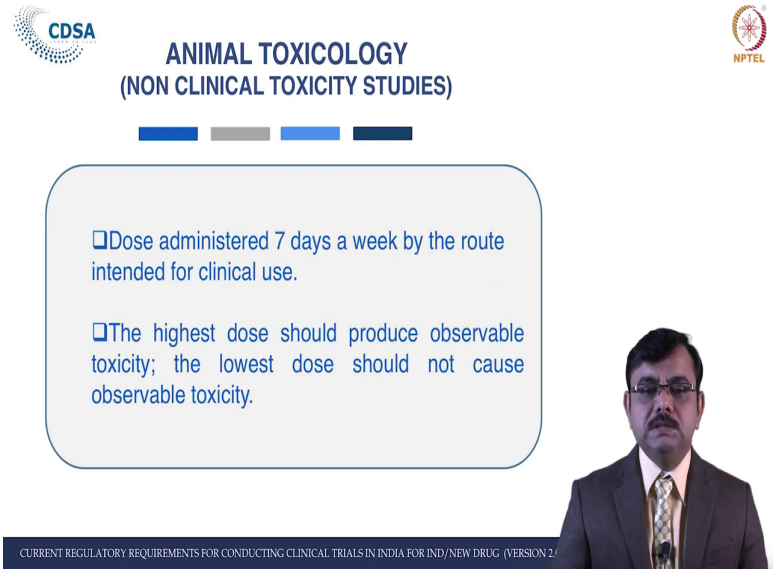


In this repeated dose toxicity study, the drug should be administered 7 days a week by the route intended for the clinical use and wherever applicable a control group of animal given the vehicle alone should be included and three other groups should be given graded dose of the drug. The highest dose should produce observable toxicity and the lowest dose should not cause any observable toxicity.

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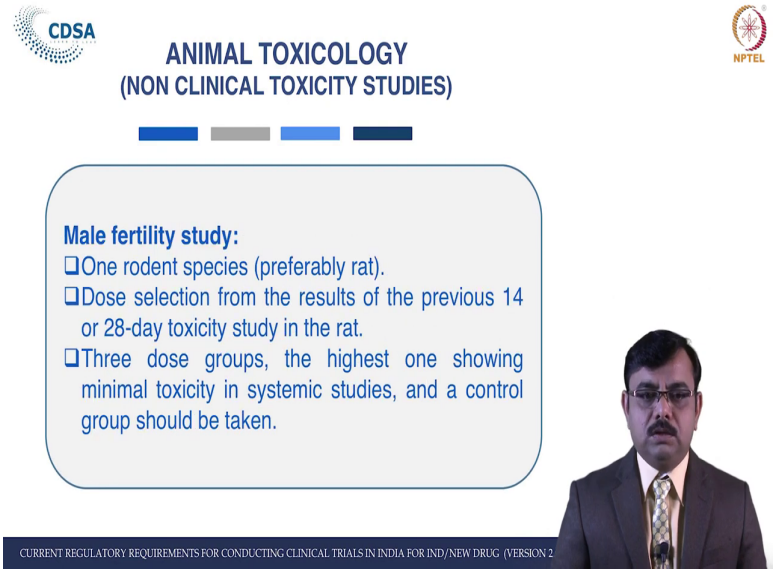


Then the male fertility study; in these studies one rodent species preferably rat should be used and the dose selection should be done from the result the previous 14 or 28 days toxicity studies. Three dose group should be there, then the highest one should show minimal toxicity and systematic studies and the control group should be taken.

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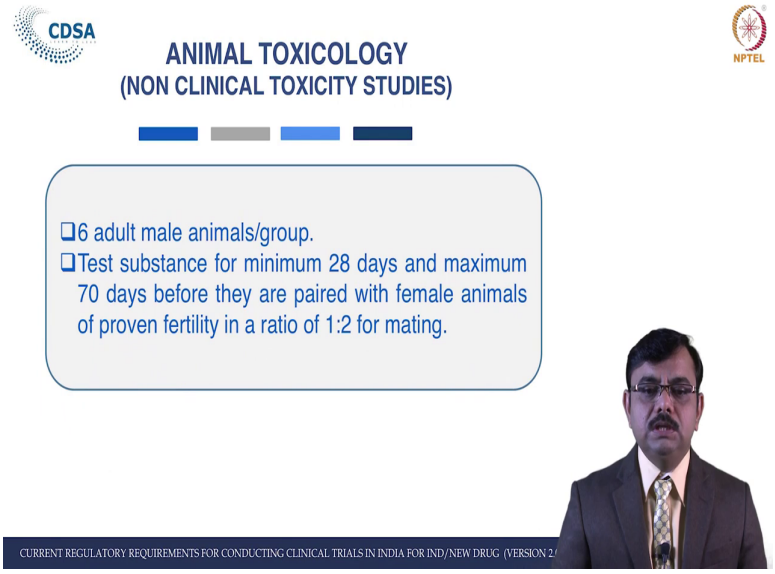


Each group should consist of 6 adult male animals and these animals should be treated with the test substance by the intended route of clinical use for minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in the ratio of 1 is to 2 for mating.

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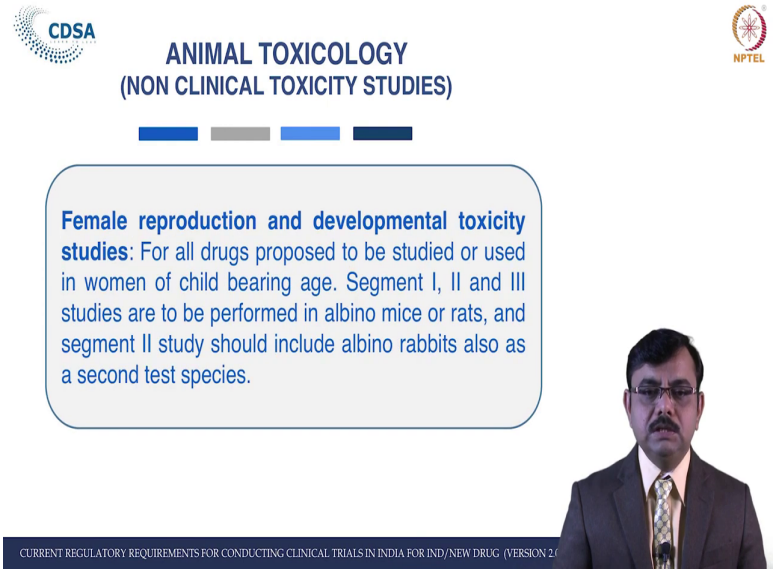


Let us see the female reproduction and developmental toxicity study. These study is need to be carried out. For all drug proposed to be studied or used in women of childbearing age. Segment I, II you have seen I, II and III studies are to be performed in albino mice rat and segment I study which is given in the schedule should include the albino rabbit also as a second test species.

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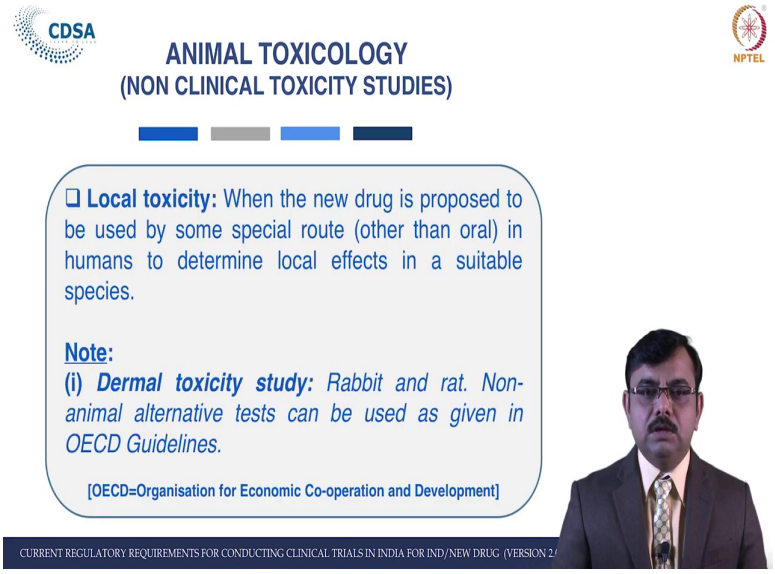


Then local toxicity studies required to be studying. These studies are required when the new drug is proposed to be used by some special route other than the oral route in human. The drug should be applied an appropriate site; example for if it is for the skin purposes or vaginal mucous membrane purposes then the local toxicity is required to determine the local effect in suitable species.

Here, the dermal toxicity study the study may be done in rabbit and rat. The initial toxicity studies shall be carried out by non animal alternative test as given in organization for economic cooperation and development that is OECD guideline to protect the animals and to avoid the unnecessary use of the animals.

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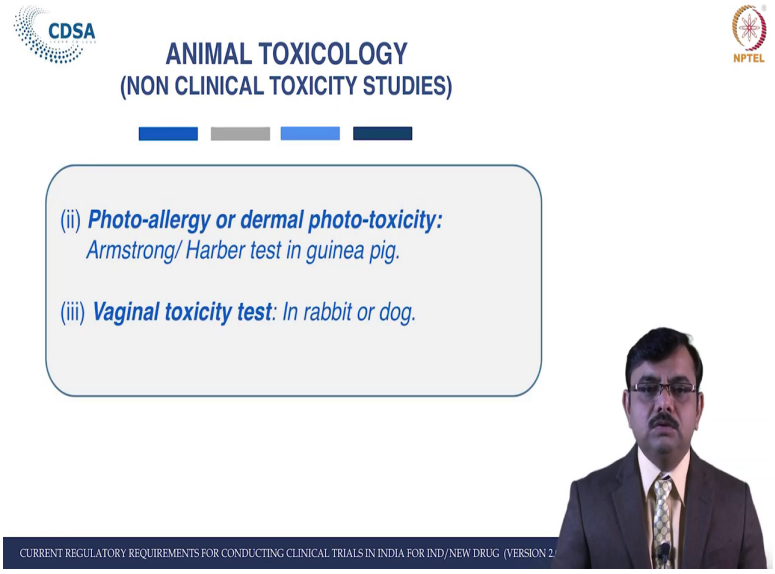


To ascertain this local toxicity study, the various test tests are there like a photo allergy or dermal photo toxicity test. It should be test tested by the Armstrong or Harber test in the guinea pig. The vaginal toxicity test the study is to be done in rabbit or the dog can be used.

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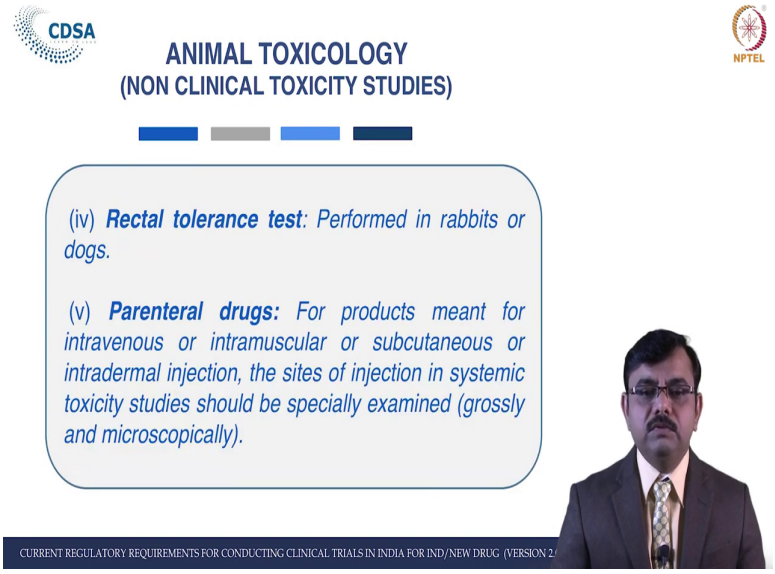


For the rectal tolerance try test for all preparation I mean for rectal administration, this test may be performed in rabbits or the dogs. In case of the parental drugs for product mean for I V or I M or subcutaneous or intradermal injection, the site of injection in systemic of toxicity studies should be specially examine grossly and microscopically.

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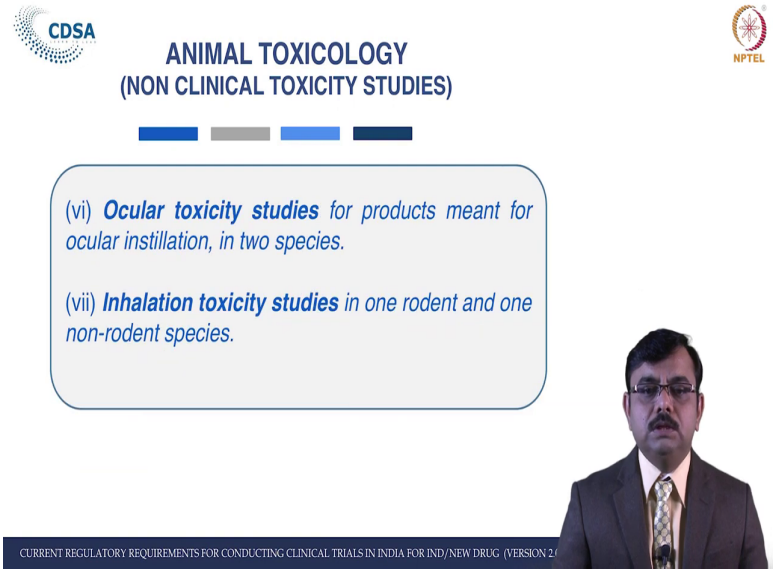


Then the ocular toxicity test for the product meant for ocular installation. If it is ophthalmic preparation then the toxicity in the eyes also required to be conducted. These studies should be carried out also in two spicies. The next test is the inhalation toxicity studies. These studies are to be undertaken in one rodent and one non rodent species, using the formulation that is to be eventually proposed to be marketed. Acute, subacute and chronic toxicity studies should be performed according to the intended duration of human exposure.

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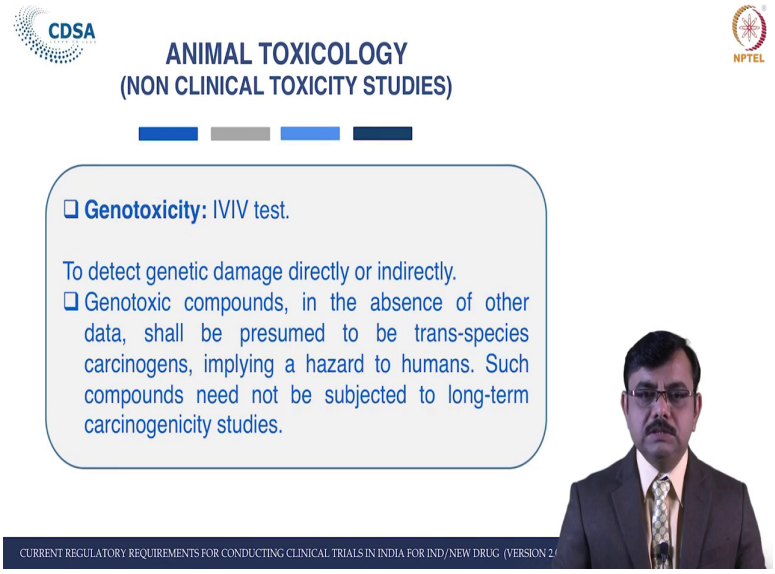


This is one of the important test that is a genotoxicity study. These tests are for the in vitro in vivo tests and conducted to detect the compound, which induce a genetic damage directly or indirectly. So, the chromosomal aberration and the DNA rapture that has to be seen in this test.

The genotoxic compound in the absence of other data shall be presumed to be a trans species carcinogen implying a hazard to human. Such compounds need not be subject to a to a long term carcinogenicity studies. Once, it has been detected that it is carson carcinogenic, then it should not be subjected to a long term application.

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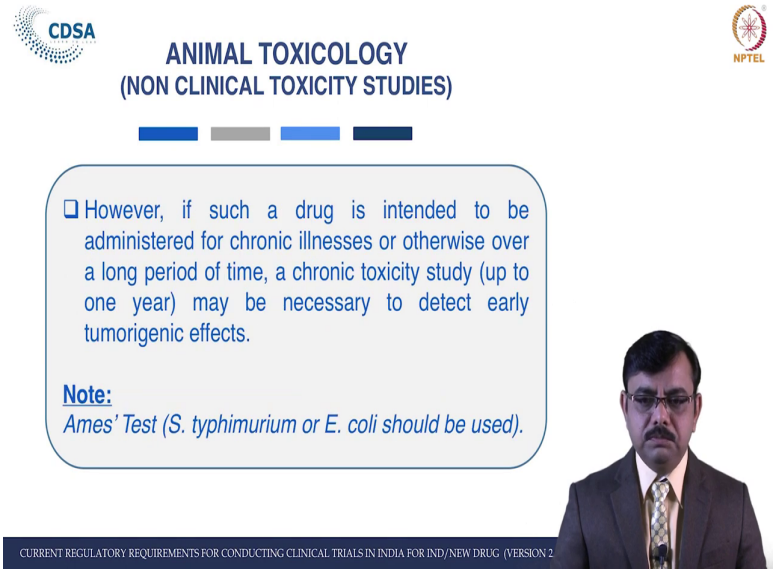


However, if such a drug is intended to be administered for chronic illness or otherwise over long period of time a chronic toxicity study that is the study may continue for up to one year, may be necessary to detect early tumorigenic effect. The test for this as we know the Ames test is there which is also called as the reverse mutation as a in salmonella and the salmonella, typhimurium or E. coli and it is a different kind of strength can be used to conduct this study.

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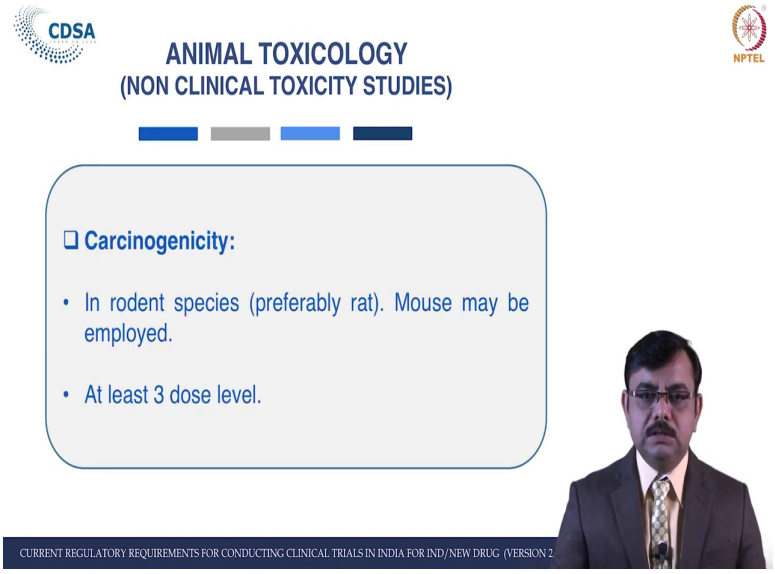


Carcinogenicity study; it is also one of the important study and it should be done in the rodent species, preferably rat. Sometimes mouse may be employed, but the proper scientific justification should be there and this study should be at least three dose level study.

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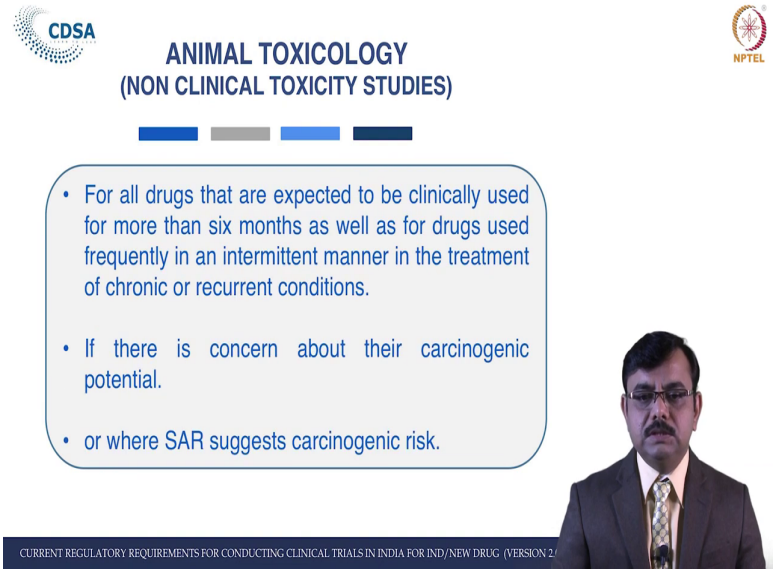


This study should be performed for all drugs that are expected to be clinically used for more than six months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. So, if the drug is to be used for more than six months, this test for the carcinogenicity is mandatory.

This carcinogenicity studies are also to be performed for drug if there is concern about the carcinogenic potential. Emanating from the previous demonstrated of carcinogenic potential in product class that is considered relevant to human or where the SAR that is structure activity relationship suggest that there is a carcinogen carcinogenic risk.

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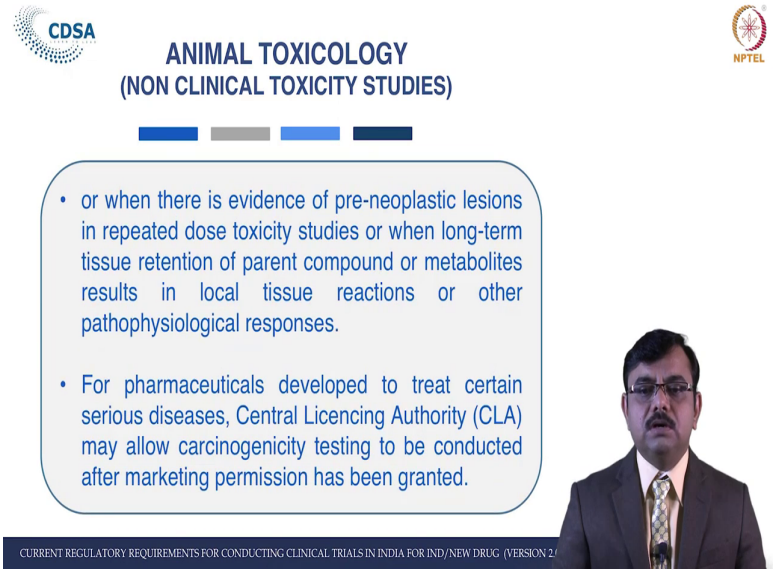


Or when there is evidence of pre neoplastic lesions in repeated dose toxicity study or when the long term tissue retention of parent compound or metabolite result in local tissue reactions or the pathophysiological responses in such cases this test is required. For the pharmaceuticals developed to treat certain serious disease the central licensing authority may allow carcinogenicity testing to be conducted after marketing permission has been granted.

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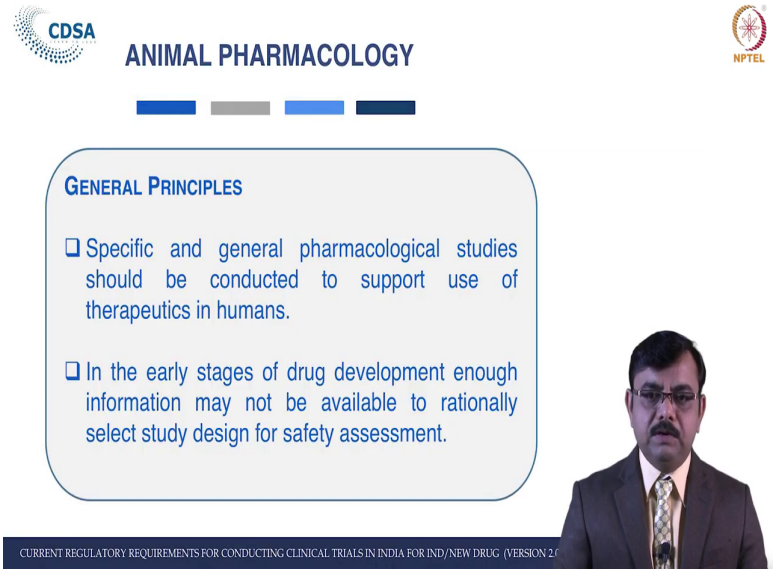


The next part of this lecture is the animal pharmacology study. We have seen in first animal toxygen toxicity study. Now, let us see animal pharmacological studying. So, in the general principle the specific and general pharmacological studies should be conducted to support use of therapeutic in human. In the early stage of drug development enough information may not be available to rationally select study design for safety assessment and in such a situation general approach to safety pharma pharmacology studies can be applied.

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So, the specific pharmacological actions where in specific pharmacological action; those which to demonstrate the therapeutic potential for human has to be conducted and general pharmacological actions need to be conducted to investigate the potential undesirable pharmacodynamic effect of a substance, on physiological function in relation to exposure within therapeutic range and the above.

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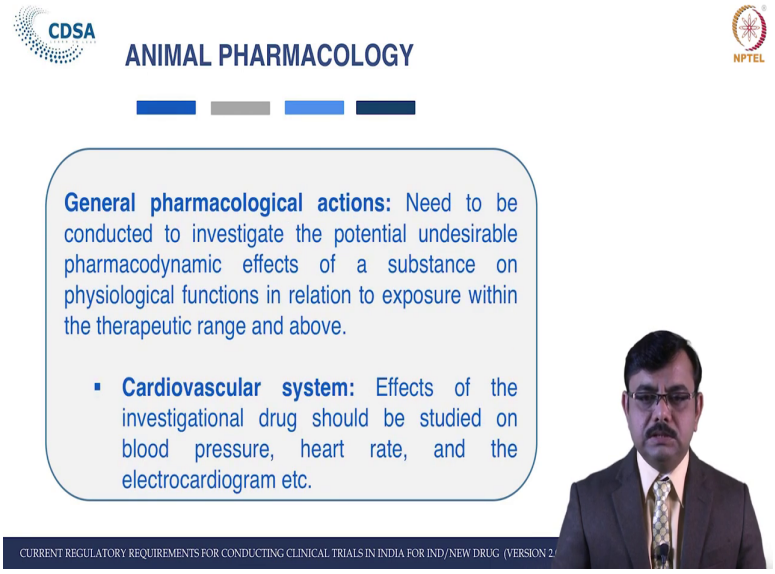


In the general pharmacological actions the effect of the investigational drug should be studied on the cardiovascular system including; blood pressure, heart rate and electrocardiogram, etcetera.

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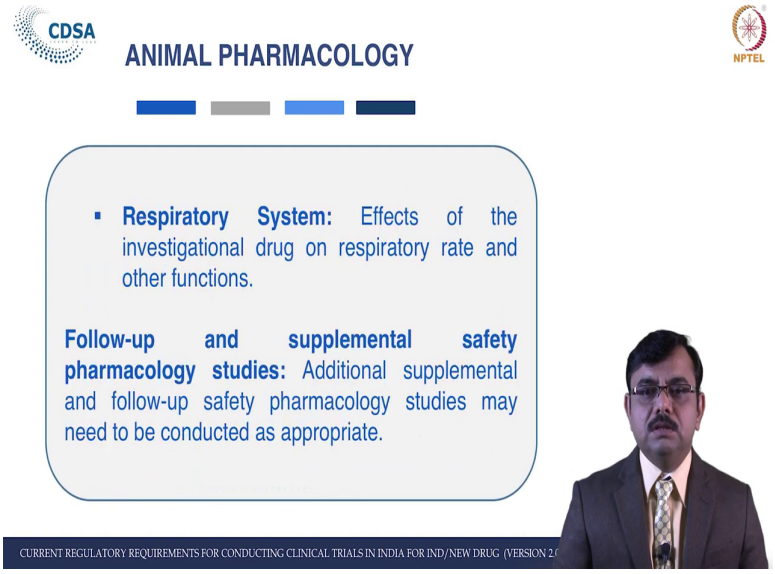


The effect of the drug also required to be seen on the respiratory system and with respect to the respiratory rate and other functions such as tidal volume and haemoglobin, oxygen saturation that should be studied.

The next is the follow up and supplemental safety pharmacological study. So, in addition to the essential safety pharmacological studies what we have seen? The additional supplemental and follow up study which is for the safety pharmacology may be needed to conduct as appropriate and in this follow up safety pharmacological studies the effect of CVS, CNS or respiratory system has to be studied.

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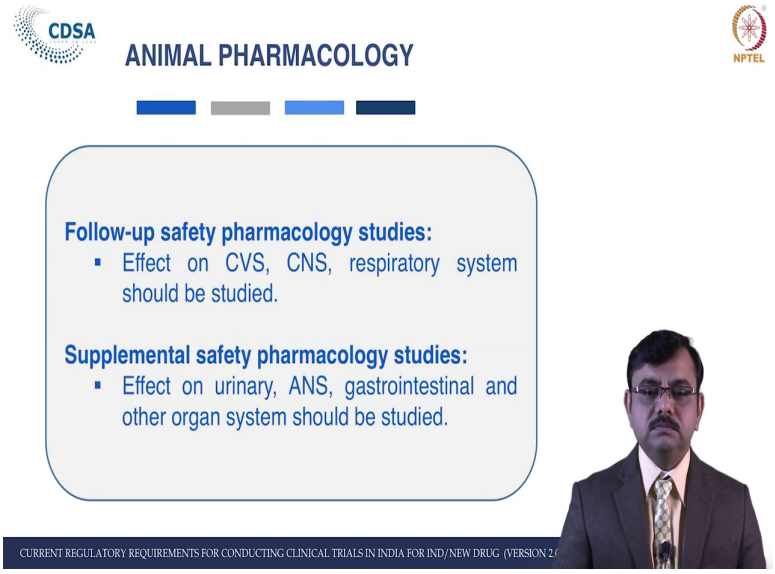


In the supplemental safety pharmacological study effect on urinary, ANS or the gastrointestinal and other organ system, it is required to be studied. The important consideration has to be given.

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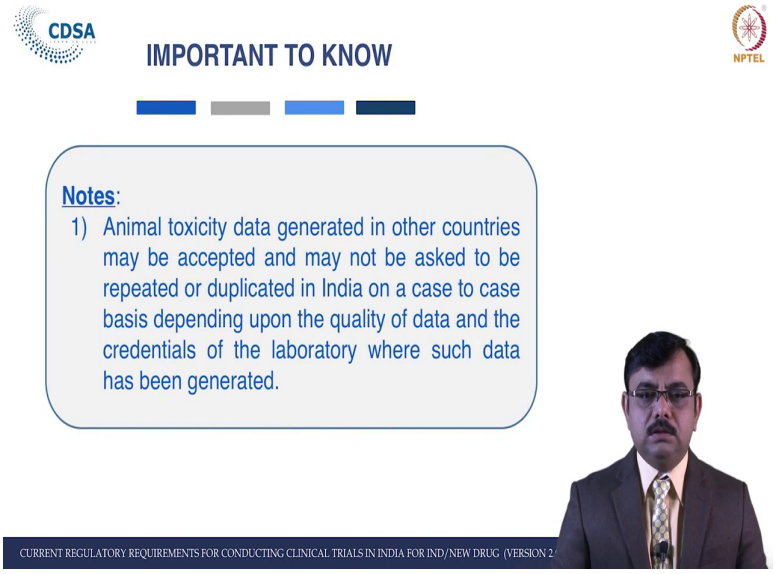


The animal toxicity study data generated in other countries may be accepted and may not be asked to be repeated or duplicated in India on a case to case basis, depending upon the quality of data and the credential of the laboratory where such data has been generated. If the data has already been generated in another countries, then for the approval of that drug that data may not be required to be generated.

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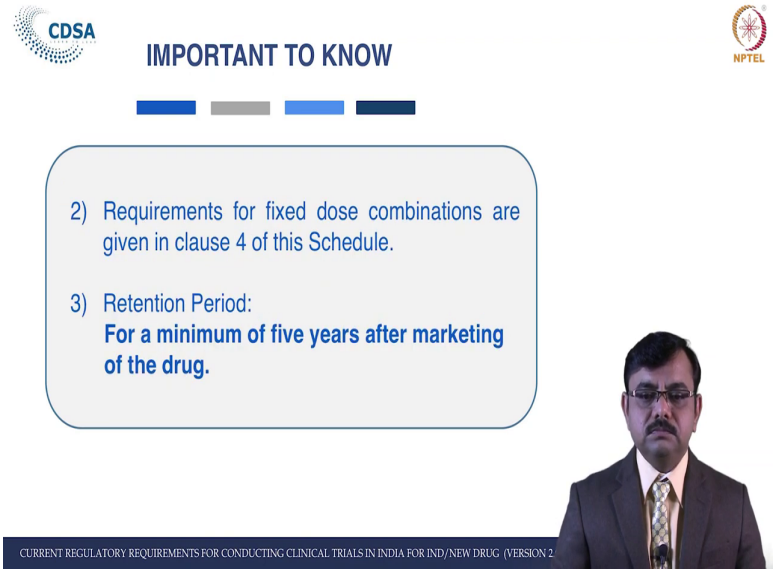


The requirement for fixed dose combination are given in clause 4 of this schedule. So, the FDC requirement has also been given in this clause 4 of this schedule. Once, the study has been conducted and the data has been recorded the all documents belonging to each study including its approval protocol, raw data draft report, then final report, histological slides, paraffin tissue blocks studies, that should be preserved for minimum of a five years after marketing of the drug and whenever the regulatory authorities and, I recommend for this that required to be submitted. So, at the retention period should be at least five years.

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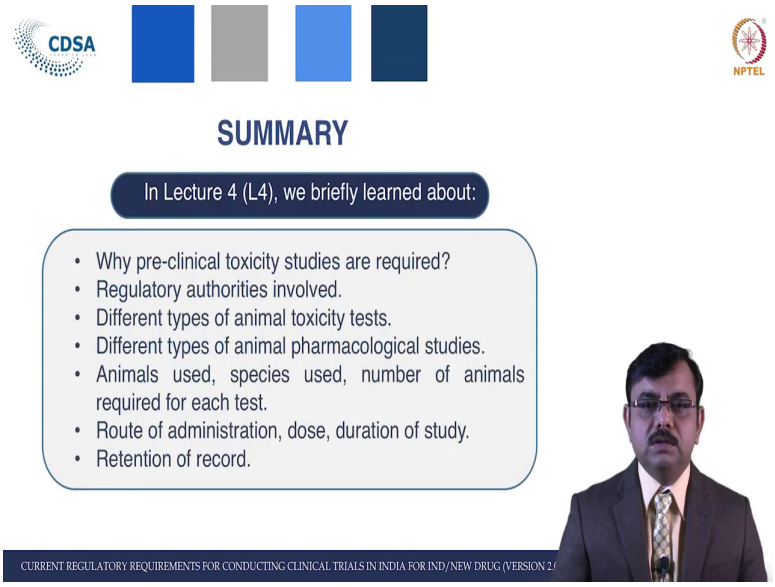


So, this is about the preclinical data requirement as per the New Drug and Clinical Trial Rule 2019. Let us have a look, what we have seen in this lecture. So, in this lectures we have seen the purpose of pre clinical preclinical toxicity testing studies, then why pre preclinical toxicity studies animal pharmacological studies are required, then we have seen the different regulatory authorities which are involved in giving the approval for conducting the preclinical tests and for using the animals, then we have seen different types of animal toxicity stage, animal pharmacological stage.

In that is test we have seen the number of animals to be used, which species required to be used, a rodent where to be used, mouse where to be used. Also, we have seen what should be the route of administration in the dose to be used and retention of the record.

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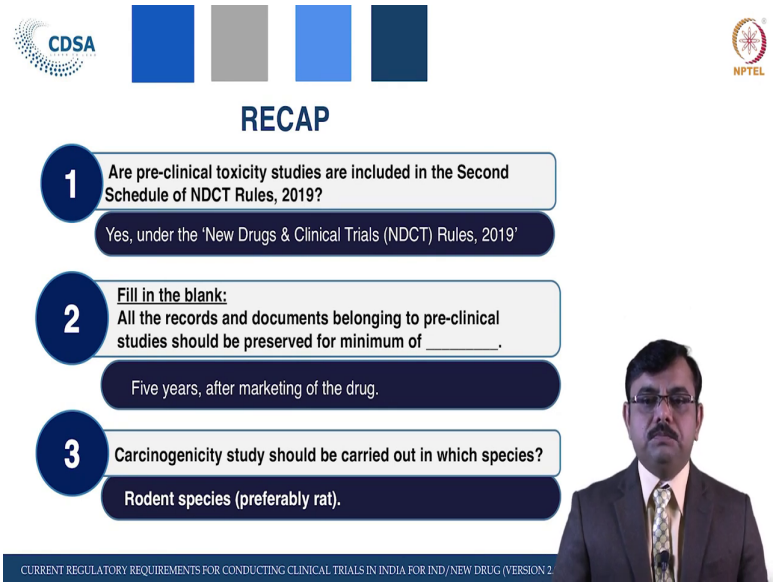


So, this is about the preclinical data requirement. Now, it is a time for your question and answer. So, the first question for you, you have to answer is preclinical toxicity studies are included in the second schedule of New Drug and Clinical Trial Rule 2019? So, this is very simple question, you have to answer yes or no? Yes, under New Drug and Clinical Trial Rule, the preclinical toxicity studies are included.

The question second, you have to fill in the blanks for this question all the record and documents belonging to pre clinical studies should be preserved for minimum of period dash. So, you have to fill in the blanks, the number of year for record keeping. Yes, the answer is five years after marketing of a drug.

The last question it is related to the carcinogenicity study. The study should be done in which species? The study to be done in which species? You have to give the species. So, the study is

required to be conducted in the rodent species and that is also preferably rat we have seen, if the mouse is used then the justification require. So, this is all about the preclinical data requirement we will see in the next lecture.

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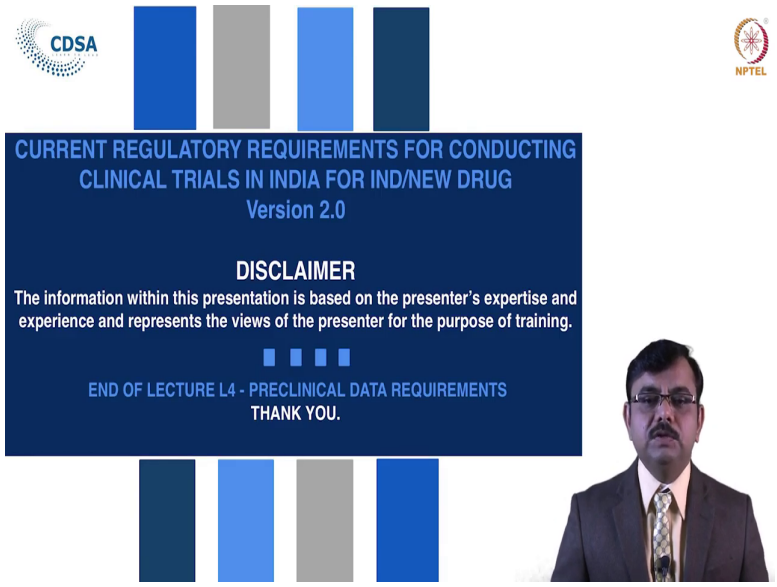


Till then you take you care bye and thank you for paying your attention, watching this video, all the best thank you.